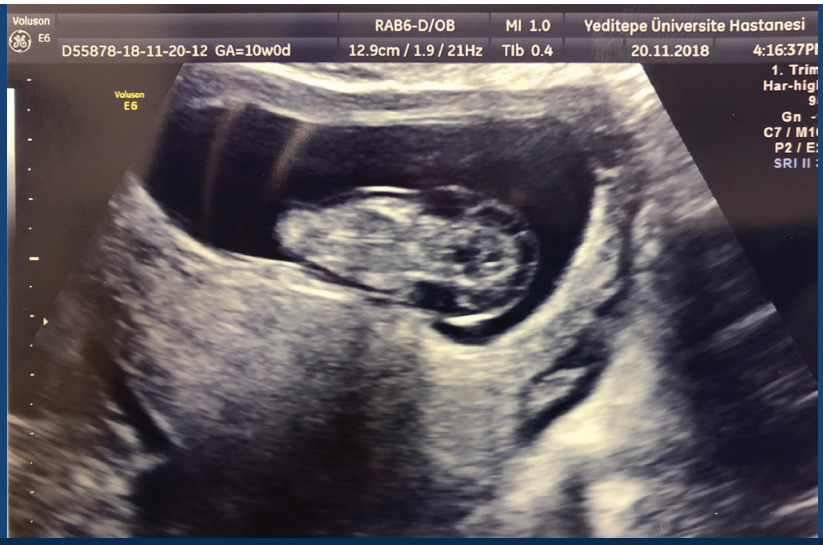
ISSN 1309-0399 • EISSN 1309-0380

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association



Volume 20
Issue 3
September
2019

Cover Picture: Fetal Hidrops in early scan (the courtesy of Gazi Yıldırım)

galenos yayınevi

Official Journal of the Turkish-German Gynecological Education and Research Foundation
www.tajev.org

Official Journal of the Turkish-German Gynecological Association
www.dtgg.de

www.jtgga.org

AŞIRI UTERİN KANAMA'NIN TEDAVİSİNDE*:

FARKLI KADINLAR, FARKLI YAŞAMLAR, FARKLI GEREKSİNİMLER

Oral tedaviyi tercih eden anormal uterin kanamalı kadınlarda[1]

QLAIRISTA® tablet: Her biri 3 mg estradiol valerat içeren 2 adet koyu sarı renkli, 2 mg estradiol valerat ve 2 mg dienogest içeren 5 adet kırmızı renkli, 2 mg estradiol valerat ve 3 mg dienogest içeren 17 adet açık sarı renkli, 1 mg estradiol valerat içeren 2 adet koyu kırmızı renkli, 2 adet beyaz film kaplı (hormon içermeyen) toplam 28 tablet. **Terapötik endikasyonlar:** Oral kontrasepsiyon. Oral kontraseptif kullanmayı tercih eden kadınlarda, organik patoloji olmaksızın gelişen şiddetli menstrüel kanama tedavisi. **Pozolaj/uygulama sıklığı, süresi ve şekli:** Tablet alınma doğal siklusun (menstrüel kanamanın) birinci gününde başlanmalıdır. Tabletler kutunun üzerinde belirtilen sırayla, her gün günün aynı saatinde, yeterli miktarda su ile alınmalıdır. Birbirini izleyen 28 gün boyunca her gün, günde bir tablet alınacaktır. Önceki kutudaki son tabletin alındığı günün ertesi günü, bir sonraki kutuya başlanır. Yan etkiler: Organ sınıfları ve sıklık derecesine göre; Psikiyatrik bozukluklar: Yaygın: Depresyon/Depresif duygudurum (%1.6), emosyonel dengesizlik (%1.4), libido azalması ya da kaybı (%1.1) Sinir sistemi: Yaygın: Migren (%1.9) Kardiovasküler sistem: Seyrek: Venöz ve arteriyel tromboembolik olaylar (<%0.1) Gastrointestinal sistem: Yaygın: Bulantı (%3.1) Ürogenital sistem ve meme: Yaygın: Meme ağrısı (%5.8), düzensiz uterin kanama (%4.4) Yaygın olmayan: Genital sistem kanaması (%0.4) Seyrek kategorisi altında listelenen tüm yan etkiler, sadece 1-2 gönüllü de ortaya çıkmıştır (<%0.1). Etkileşimler: Enzim indükleyicileri ya da inhibitörleri (CYP 3A4): Seks hormonları esas olarak, hem intestinal mukoza hem de karaciğerde bulunan sitokrom P450 3A4 (CYP 3A4) sistemi tarafından metabolize edilirler. Bu nedenle, fenitoin, barbitüratlar, pirimidon, karbamazepin, rifampisin ve muhtemelen okskarbazepin, topiramat, felbamat, griseofulvin, nevirapin ve St. John bitkisi [Hypericum perforatum] gibi CYP 3A4 indükleyicileri ya da azol grubu antifungaller, simetidin, verapamil, makrolidler, diltiazem, proteaz inhibitörleri, antidepresanlar ve greyfurt suyu gibi bilinen inhibitörler ilacın metabolizmasını etkileyebilir. Enzim indüksiyonu nedeniyle seks hormonları klirensinin artması, terapötik etkisini azaltabilir. Enzim inhibisyonuna bağlı olarak seks hormonları klirensinin azalması, indüksiyona bağlı olarak ise artması istenmeyen etkiler ile sonuçlanabilir. Diğer etkileşim şekilleri: Progestagen kullanımı bazı laboratuar testlerinin sonuçlarını etkileyebilir. Pediyatrik popülasyon: Pediyatrik popülasyonda etkileşim çalışması yapılmamıştır. Diğer etkileşim şekilleri: Oral kontraseptifler belirli başka ilaçların (örn. lamotrigin) metabolizmasını etkileyebilir ve sonuçta plazma konsantrasyonlarında yükselme veya azalmaya neden olabilirler. Özel popülasyonlara ilişkin ek bilgiler: Böbrek Yetmezliği: Böbrek yetmezliği olan hastalarda özel olarak çalışılmamıştır. Mevcut veriler bu hasta popülasyonunda tedavi değişikliği yapılmasına ilişkin veri sağlamamıştır. Karaciğer Yetmezliği: Şiddetli karaciğer hastalığı olan kadınlarda kontrendikedir. Pediyatrik popülasyon: Yalnızca menarştan sonra endikedir. Geriyatrik popülasyon: Geriyatrik popülasyonda kullanımı ve menopozdan sonra endikasyonu yoktur. **Kontrendikasyonlar:** Kombine oral kontraseptifler (KOK) aşağıda belirtilen tabloların herhangi birisinin varlığında kullanılmamalıdır. KOK kullanımı sırasında bu tablolardan herhangi biri ilk kez ortaya çıkarsa, ilaç derhal kesilmelidir. Aktif venöz tromboembolik hastalık, arteriyel ve kardiyovasküler hastalık varlığı ya da öyküsü, kontrendikasyon meydana getirebilecek venöz ya da arteryel tromboza yönelik ağır bir risk faktörü veya çok sayıda risk faktörleri, fokal nörolojik semptomlarla birlikte migren öyküsü,vasküler tutulum ile birlikte diabetes mellitus, şiddetli karaciğer hastalığı ve karaciğer fonksiyon testlerinin henüz normale dönmemiş olması, karaciğer tümörü varlığı ya da öyküsü, seks steroidlerinden etkilenen malignitelerin (örn. genital organlarda ya da memelerde) bulunması veya böyle bir malignite kuşkusu, tanısı konulmamış vajinal kanama, Gebelik varlığı veya şüphesi, etken ya da yardımcı maddelere karşı aşırı duyarlılık. **Özel kullanım uyarıları ve önlemleri:** Aşağıda sözü edilen tablolardan/risk faktörlerinden herhangi biri bulunuyorsa, ilaç kullanma kararı verilmeden önce, KOK kullanımının yararları her kadın bireydeki olası risklere karşı tartılmalı ve konu kadın ile de görüşülmelidir. Estradiol/estradiol valerat içeren KOK'ların etkilerine yönelik epidemiyolojik çalışma bulunmamaktadır. Aşağıdaki bütün uyarılar ve önlemler, etinilestradiol içeren KOK'lara ilişkin klinik ve epidemiyolojik verilerden alınmıştır. Bu uyarılar ve önlemlerin QLAIRISTA® için geçerli olup olmadığı bilinmemektedir. Dolaşım bozuklukları: VTE riski güncel olarak bilinmemektedir. Epidemiyolojik çalışmalarda, etinil estradiol içeren KOK kullanımı ile, derin ven trombozu, pulmoner embolizm, miyokard enfarktüsü ve serebrovasküler olay gibi arteryel ve venöz trombotik ve tromboembolik hastalık riskinde artış arasında bir bağıntının varlığı gösterilmiştir. Bu olaylar ender olarak ortaya çıkarlar. Venöz tromboembolizm riski, ilk kullanım yılında en yüksek düzeydedir. Bu risk artışı ilk olarak bir KOK başlanması, aynı KOK ya da farklı bir KOK ile tekrar tedaviye başlanması (en az 4 hafta aradan sonra) sırasında mevcuttur. Geniş ölçekli, prospektif ve 3 kollu çalışma verileri bu risk artışının esas olarak ilk 3 ayda mevcut olduğunu ileri sürmektedir. Düşük doz östrojen (< 50 mg etinilestradiol) içeren KOK kullanılarda toplam venöz tromboembolizm (VTE) riski, gebe olmayan ve KOK kullanmayanlara göre 2-3 kat artmıştır ancak gebelik ve doğum ile ilişkili riskten daha düşüktür. KOK kullananlarda son derecede ender olarak diğer kan damarlarında, örn. hepatik, mezenterik, renal, serebral ya da retinal venler ve arterlerde tromboz oluştuğu bildirilmiştir. Bu olayların KOK kullanımıyla ilişkili olup olmadığı konusunda bir uzlaşı bulunmamaktadır. Tümörler: Serviks kanseri için en önemli risk faktörü, kalıcı HPV enfeksiyonudur. Bazı epidemiyolojik çalışmalarda uzun süreli KOK kullanımının, artmış olan bu riski daha da artırabileceğine işaret edilmiştir; ancak bu bulgunun diğer bazı sonuca ulaşmayı güçleştirici faktörlere (örn. servikal tarama ve bariyer kontraseptiflerin kullanımını da içeren cinsel davranışlar) ne ölçüde bağlı olduğu konusunda tartışmalar devam etmektedir. Elli dört epidemiyolojik çalışma üzerinde yürütülen bir meta analizde, halen KOK kullanan kadınlarda meme kanseri tanısı konulma relatif riskinde hafif bir artış (RR = 1.24) olduğu bildirilmiştir. Bu risk fazlalığı, KOK kullanımı kesildikten sonraki 10 yıl içerisinde aşamalı olarak kaybolmaktadır. Kırk yaş altındaki kadınlarda meme kanseri ender olduğu için, halen KOK kullanmakta olan ya da yakın zamanda kullanmış olan kadınlardaki fazla meme kanseri tanısı sayısı, genel meme kanseri riskine kıyasla küçüktür. Bu çalışmalar nedenselliğe yönelik veri sağlamamaktadır. Gözlenen risk artışı paterni, KOK kullanıcılarında meme kanseri tanısının daha erken konulmasına, KOK'ların biyolojik etkilerine ya da bu ikisinin bir kombinasyonuna bağlı olabilir. Yaşamlarının herhangi bir döneminde KOK kullananlarda tanısı konulan meme kanseri, hiç kullanmamış kadınlarda tanısı konulanlardan, klinik olarak daha az ilerlemiş olma eğilimindedir. KOK kullananlarda ender olgular şeklinde benign karaciğer tümörleri ve çok daha ender olarak malign karaciğer tümörleri bildirilmiştir. **Diğer uyarılar:** Hipertrigliseridemisi olan veya aile özgeçmişinde olan kadınlarda, KOK kullanırken pankreatit riski artabilir. KOK almakta olan çok sayıda kadında kan basıncında küçük artışlar bildirilmiş olmakla birlikte, klinik önem taşıyan artışlar enderdir. Aşağıdaki tabloların hem gebelik hem de KOK kullanımı sırasında ortaya çıktığı ya da kötüleştiği bildirilmiştir, ancak KOK kullanımı ile aradaki ilişkiye yönelik veriler kesin değildir; kolestaza bağlı sarılık ve/veya pruritus, safra taşı oluşumu, porfiri, sistemik lupus erithematozus, hemolitik üremik sendrom, Sydenham koresi, herpes gestasyonis, otoskleroza bağlı işitme kaybı, Herediter anjiyoödemi olan kadınlarda eksojen östrojenler anjiyoödem semptomlarını indükleyebilir veya alevlendirebilir. KOK'lar periferik insülin direnci ve glukoz toleransı üzerinde etkili olabilmekle birlikte, düşük dozlu (<0.05 mg etinilestradiol içeren) KOK kullanan diyabetiklerde terapötik rejimin değiştirilmesi ihtiyacına yönelik kanıt bulunmamaktadır. Ancak diyabetik kadınlar KOK kullanımı sırasında dikkatle gözlenmelidir. Crohn hastalığı ve ülseratif kolit KOK kullanımıyla ilişkili bulunmuştur. Özellikle öyküsünde kloazma gravidarum olan kadınlarda, zaman zaman kloazma ortaya çıkabilir. Kloazma eğilimi taşıyan kadınlar, KOK kullanırken güneşe maruz kalmaktan veya ultraviyole radyasyondan kaçınmalıdır. Unutulan tabletler: Alınması unutulan hormon içermeyen beyaz tablet ise önemsenmeyebilir. Ancak, hormonsuz tablet döneminin istemeden uzatılmasından kaçınmak için, unutulan bu tabletler atılmalıdır. Eğer tablet alınması unutulan süre 12 saatten kısa ise, kontraseptif korunmada azalma söz konusu değildir. Hatırlanır hatırlanmaz tablet alınmalı, ve sonraki tabletler olağan zamanlarında alınmaya devam edilmelidir. Eğer tablet alınması için unutulan süre 12 saatten uzun ise, kontraseptif korunmada azalma olabilir. Aynı anda iki tablet birden alma anlamına gelse bile, hatırlanır hatırlanmaz tablet alınmalıdır. Daha sonraki tabletler ise olağan zamanlarında alınmaya devam edilmelidir. Gastrointestinal rahatsızlıklar durumunda öneriler: Şiddetli gastrointestinal rahatsızlıklar durumunda, emilim tam olmayabilir ve ek kontraseptif önlemlere gerek duyulabilir. Laktoz: QLAIRISTA® ambalajında bulunan 5 farklı formülasyondaki tabletlerin her biri farklı miktarlarda laktoz monohidrat içermektedir; Koyu sarı renkli tabletlerin her biri 48.360 mg, kırmızı renkli tabletlerin her biri 47.360 mg, açık sarı renkli tabletlerin her biri 46.360 mg, koyu kırmızı renkli tabletlerin her biri 50.360 mg, plasebo tabletlerin her biri ise 52.1455 mg laktoz monohidrat içerir. Galaktozemi, kalıtımsal galaktoz intoleransı, Lapp laktoz yetmezliği ya da glukoz galaktoz malabsorpsiyon problemi olan hastaların bu ilacı kullanmaması gerekir. Gebelikte kullanım kontrendike olup gebelik kategorisi X'tir. Kullanımı sırasında gebelik oluşursa, ilaç alımı kesilmelidir. Ancak etinil estradiol içeren KOK'larla yapılan kapsamlı epidemiyolojik çalışmalarda, gebelik öncesinde KOK kullanmış olan kadınların doğurduğu çocuklarda doğum defekti riskinde artış görülmemiştir. Laktasyon döneminde kulanılmamalıdır çünkü bu ajanlar sütün miktarını azaltabilir ve bileşimini değiştirebilir. Araç ve makine kullanma becerileri üzerinde herhangi bir etki gözlenmemiştir. **Doz aşımı ve tedavisi:** Doz aşımı sonucunda, sağlığı bozucu şiddetli etkilerin bildirildiği bir rapor bulunmamaktadır. Hormon içeren film kaplı tabletlerin doz aşımı oluşturacak şekilde alınması sonucunda oluşabilecek semptomlar bulantı, kusma ve genç kızlarda hafif vajinal kanamadır. Antidotu yoktur ve tedavi semptomatik olmalıdır. **Raf ömrü:** 60 ay. Saklamaya yönelik özel tedbirler: 30°C'nin altında, oda sıcaklığında saklanmalıdır. Ambalajın niteliği ve içeriği: Polivinil klorürden yapılı transparan filmler ve sayfa işlenmiş alüminyumdan yapılı metalik folyolardan oluşan blister ambalajda 28 tablet. **Ruhsat sahibi:** Bayer Türk Kimya San. Ltd. Şti., Çakmak Mah. Balkan Cad. No:53 34770 Ümraniye - İstanbul Tel: (0216) 528 36 00 Faks: (0216) 538 36 12 **Ruhsat numarası:**131/95 **İlk ruhsat tarihi:** 17.08.2011 Daha geniş bilgi için firmamıza başvurunuz. **KDV dahil perakende satış fiyatı:** 49.50 TL (19.02.2019).

Rahim içi sistem tercih eden anormal uterin kanamalı kadınlarda[2]

Mirena®
Levonorgestrel

MIRENA® Levonorgestrel rahim içi sistemi **Formülü:** Mirena® rahim içi sistemi, 52 mg levonorgestrel içerir. Başlangıç salım miktarı 20 mikrogram/24 saattir. **Endikasyonları:** Kontrasepsiyon (gebeliğin önlenmesi), İdiyopatik menoraji, Estrogen replasman tedavisi sırasında endometriyal hiperplaziye karşı korunma. **Kontrendikasyonları:** Gebelik veya gebelik şüphesi; Mevcut ya da tekrarlayan pelvik inflamatuvar hastalık; Alt genital kanal enfeksiyonu; Postpartum endometrit; Son 3 ay içinde enfekte düşük; Servisit; Servikal displazi; Rahim ya da serviksin habis tümörleri; Tanı konamayan anormal uterus kanamaları; Rahim boşluğunun biçimini bozan fibroidler de dahil olmak üzere konjenital ya da edinilmiş uterus anomalileri; Artmış enfeksiyon eğilimine yol açan durumlar; Akut karaciğer hastalıkları veya karaciğer tümörü; Mirena®'nın içeriğine karşı olabilecek aşırı duyarlılık durumu. **Uyarılar / Önlemler:** Aşağıdaki durumlardan herhangi biri varsa ya da ilk kez ortaya çıkıyorsa, Mirena® ancak uzman tavsiyesi ve kontrolü dahilinde kullanılmalı ya da sistemin çıkarılması düşünülmelidir: Migren, asimetrik görme kaybıyla seyir eden fokal migren ya da geçici beyin iskemisine yönelik başka belirtiler; alışılmışın dışında şiddetli baş ağrısı; sarılık; belirgin tansiyon yükselmesi; meme kanseri de dahil olmak üzere hormonal bağımlılık gösteren tümör ya da buna ilişkin şüphe; inme ya da miyokard infarktüsü gibi ağır arteriyel hastalıklar. Sadece progestagen içeren haplar kullanan kadınlarda yapılan son epidemiyolojik çalışmalar venöz tromboemboli riskinde hafif bir artış olabileceğini göstermiştir, fakat sonuçlar istatistiksel olarak anlamlı değildir. Ancak, tromboz bulgu ve belirtilerinin olması durumunda derhal uygun tanısal ve terapötik girişimlerde bulunulmalıdır. Varikoz venlerin ve yüzeyel tromboflebitin venöz tromboembolideki olası rolü konusunda görüş birliği yoktur. Mirena® enfekte endokardit riskine yol açan konjenital kalp hastalığı ya da valviüler kalp hastalığı olan kadınlarda dikkatle kullanılmalıdır. Bu hastalarda rahim içi sistem takılır veya çıkartılırken antibiyotik profilaksisi yapılmalıdır. Düşük-doz levonorgestrel glukoz toleransını etkileyebileceğinden, Mirena® kullanan diyabetik kadınlarda kan şekeri izlenmelidir. Düzensiz kanamalar, endometriyum poliplerinin ve kanserinin bazı belirtilerini gizleyebilmektedir. Bu olgularda tanısal girişimlerde bulunulmalıdır. Mirena® genç ve doğum yapmamış kadınlarda ve ileri uterus atrofisi olan postmenopozal kadınlarda ilk seçenek değildir. Uygulama ve çıkarma/tekrar uygulama: Uygulamadan önce, kadın Mirena®'nın etkinliği, riskleri ve yan etkileri hakkında bilgilendirilmelidir. Pelvik muayeneyi ve meme muayenesini içeren bir fizik muayene ve servikal smear yapılmalıdır. Gebelik ve cinsel yolla bulaşan hastalıklar ekarte edilmeli ve genital enfeksiyonlar tamamen tedavi edilmelidir. Uterus pozisyonu ve uterus boşluğunun büyüklüğü belirlenmelidir. Mirena®'nın fundal yerleşimi, progestagenin endometriyuma eşit olarak dağılmasının sağlanması, kazayla çıkmanın önlenmesi ve etkinliğin artırılması açılarından özellikle önem taşır. Bu nedenle uygulama talimatlarına dikkatle uyulmalıdır. Kullanıcı uygulamadan 4-12 hafta sonra tekrar muayene edilmeli ve bundan sonra yılda bir ya da klinik endikasyonu varsa daha sık aralıklarla kontrol edilmelidir. Fertil yaştaki kadınlarda Mirena® uterus boşluğuna menstruasyonun ilk yedi günü içinde yerleştirilmelidir. Mirena® bir yenisiyle sikluson herhangi bir gününde değiştirilebilir. Sistem ilk trimestr düşüklerini takiben hemen uygulanabilir. Postpartum uygulamalar doğum sonrası altıncı haftaya kadar ertelenmelidir. Mirena®'nın post koital bir kontraseptif olarak kullanılması uygun olmayabilir. Estrogen replasman tedavisi sırasında endometriyal koruma için kullanılacaksa, Mirena® amenoreik bir kadına herhangi bir zamanda, ya da menstruasyonun veya çekilme kanamasının son günlerinde takılabilir. Tedavinin ilk aylarında düzensiz kanama ve lekelenme kanamalarının sık görülmesi nedeniyle Mirena® takılmadan önce endometriyal patolojinin ekarte edilmesi önerilir. Mirena® bir forseps yardımıyla ipliklerinden nazikçe çekilerek çıkarılır. Eğer iplikler görülemiyorsa ve sistem uterus boşluğu içindeyse ince bir tenakulum yardımıyla çıkarılabilir. Bu yöntem, servikal kanalın dilatasyonunu gerektirebilir. Sistem beş yıl sonunda çıkarılmalıdır. Eğer kullanıcı aynı yöntemi kullanmaya devam etmek isterse, yeni bir sistem aynı zamanda takılabilir. Eğer gebelik arzu edilmiyorsa, Mirena® fertil yaşlardaki kadınlarda bir sikluson varlığından emin olunması amacıyla menstruasyon sırasında çıkarılmalıdır. Eğer sistem siklus ortasında çıkarıldıysa ve kadın bir hafta içinde ilişkiye girmişse, çıkarılmayı takiben yeni bir sistem takılmadığı takdirde gebelik riski mevcuttur. Uygulama ve çıkarmaya bir miktar ağrı ve kanama eşlik edebilir. Prosedür vazovagal reaksiyonda olduğu gibi bir bayılmaya ya da epileptik bir hastada nöbet geçirmeye yol açabilir. Oligo-/amenore: Mirena® kullanan fertil kadınların %20'sinde zamanla oligomenore ve/veya amenore gelişmektedir. Bir önceki menstruasyonun başlangıcını takiben altı hafta içinde menstruasyon gerçekleşmezse gebelik olasılığı göz önüne alınmalıdır. Amenore gelişen kadınlarda gebeliğin başka belirtileri söz konusu değilse, tekrarlanan gebelik testlerine gerek yoktur. Mirena®'nın kesintisiz estrogen replasman tedavisi ile birlikte kullanıldığı durumlarda, birçok kadında ilk yıl içinde kanamasız bir düzen oluşur. **Pelvik enfeksiyon:** Pelvik enfeksiyonun ciddi sonuçları olabilir, fertiliteye zarar verebilir ve ektopik gebelik riskini artırabilir. Tekrarlanan endometrit veya pelvik enfeksiyonunda ya da tedaviye birkaç gün içinde olumlu yanıt vermeyen veya şiddetli akut bir enfeksiyon durumunda Mirena® çıkarılmalıdır. Enfeksiyon düşündüren en küçük bir belirtide bile bakteriyolojik tetkikler ve izlem önerilir. Yerinden oynama/çıkma: Mirena®, yerinden oynamışsa çıkarılmalıdır. İsteniyorsa o sırada yenisi takılabilir. Kullanıcıya Mirena®'nın ipliklerini nasıl kontrol edeceği öğretilmelidir. **Perforasyon:** Uterusun gövdesinin ya da serviksin bir rahim içi araç tarafından perforasyonu ya da penetrasyonu nadiren görülebilir ve sıklıkla yerleştirme esnasında meydana gelir. Böyle bir durumda sistemin hemen çıkarılması gerekmektedir. **Ektopik gebelik:** Ektopik gebelik, tubal cerrahi veya pelvik enfeksiyon öyküsü olan kadınlar, daha yüksek bir ektopik gebelik riskiyle karşı karşıyadır. İpliklerin görülmemesi: Kontrol muayenelerinde servisde geri çekme iplikleri görülmüyorsa, gebelik ekarte edilmelidir. **Geciken foliküller atrezi:** Mirena®'nın kontraseptif etkisi başlıca lokal etkisine bağlı olduğundan, fertil yaştaki kadınlarda folikül çatlamasının görüldüğü ovulatuar sikluslar sıklıkla gerçekleşir. Bazen folikülün atrezisi gecikir ve folikülogenez devam edebilir. **Yan etkiler/Advers etkiler:** Çok sık (kullanıcıların % 10'undan daha fazlasında) görülen yan etkiler, kanama değişiklikleri ve iyi huylu ovaryal kistlerdir: Farklı kanama değişiklikleri tüm Mirena® kullanıcılarında görülür. İyi huylu ovaryal kist görülme oranı kullanılan tanısal yönteme bağlıdır. Klinik çalışmalarda Mirena® kullanan kadınların %12'sinde büyümüş foliküllere rastlanmıştır. Foliküllerin çoğu asemptomatiktir ve üç ay içinde kaybolur. İstenmeyen etkilerden bazıları: duygu durum değişkenliği, başağrısı, migren, abdominal ağrı, abdominal şişkinlik, akne, saç dökülmesi, hirsutizm, kaşıntı, kızarıklık, ürtiker, sırt ağrısı, pelvik ağrı, dismenore, pelvik enflamatuvar hastalık, uterus perforasyonu, vaginal akıntı, vulvovajinit, servisit, endometrit, memede gerginlik, mastalji, dışarı atılma, uterus perforasyonu. İlaç etkileşmeleri: Progestagenlerin metabolizması, özellikle sitokrom P450 enzimleri gibi ilaçları metabolize eden enzimlerin indüksiyonunu yapan maddeler (fenobarbital, fenitoin, karbamazepin gibi antikonvülsanlar ve rifampisin, rifabutin, nevirapin, efavirenz gibi antiinfektifler) ile birlikte kullanılmaları sonucu artar. Mirena®'nın kontraseptif etkisinin bu tür ilaçlar ile etkileşmi bilinmemektedir, ancak lokal etki mekanizması nedeniyle büyük bir öneme sahip olduğu düşünülmemektedir. Kullanım şekli ve dozu: Mirena® rahim boşluğuna yerleştirilir. Beş yıl boyunca etkilidir. Salım hızı başlangıçta 20 mikrogram/24 saattir. Beş yılın sonunda bu hız 11 mikrogram/24 saate düşer. Beş yıllık kullanım süresi boyunca ortalama salım hızı 14 mikrogram/24 saattir. Hormon replasman tedavisi alan kadınlarda Mirena® progestagen içermeyen oral veya transdermal preparatlarla birlikte kullanılabilir. Mirena® takılacağı zamana kadar açılmamasını gereken steril bir paket halinde sunulmaktadır. Açılmış ürün aseptik koşullara uyularak kullanılmalıdır. Steril paketin ambalajında hasar/açılma mevcutsa, rahim içi sistem tıbbi atık muamelesine tabi tutulmalıdır. Çıkarılmış bir rahim içi sistem de, hormon kalıntıları içerebileceğinden tıbbi atık muamelesine tabi tutulmalıdır. Mirena® aplikatörü hastane atığı, ambalajlar ise evsel atık kabul edilir. Mirena® uygulaması ile ilgili ayrıntılı bilgi "Teknik Bilgiler" bölümünde bulunmaktadır. Daha ayrıntılı bilgi için "Uyarılar / Önlemler" başlığı altındaki "Uygulama ve çıkarma/tekrar uygulama" bölümüne başvurulabilir. Uygulama tekniği diğer rahim içi araçlardan farklı olduğu için, sistemin doğru takılması için eğitime özel önem verilmelidir. **Üretim yeri:** Bayer Schering Pharma Oy, Finlandiya **Ruhsat tarihi:** 13.12.1999 **Ruhsat no:** 106/94. **Ruhsat sahibi:** Bayer Türk Kimya San. Ltd. Şti. İstanbul LM210806 Reçete ile satılır. **Prospektüs onay tarihi:** 14.05.2008 Daha geniş bilgi için firmamıza başvurunuz. **KDV dahil perakende satış fiyatı:** 399.64 TL (19.02.2019).

*Organik patoloji saptanmayan vakalarda

Referanslar: 1. Qlairista Kısa Ürün Bilgisi. **2.** Mirena Kısa Ürün Bilgisi.

Daha fazla bilgi ve Kısa Ürün Bilgileri için https://www.bayer.com.tr/tr/urunler/a-dan-z-ye-urunler/ sayfasını ziyaret edebilirsiniz.

PP-PF-WHC-TR-0126-1

Journal of the
Turkish-German
Gynecological Association

Journal of the
Turkish-German Gynecological Association

Editorial Office

Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı, İstanbul-Turkey
Phone: +90 212 241 45 45
Fax: +90 212 241 44 08
E-mail: tajev@tajev.org

Official Journal of the Turkish-German Gynecological Education and Research Foundation
www.tajev.org

Official Journal of the Turkish-German Gynecological Association
www.dtgg.de

Owned by on behalf of the Turkish German Gynecology Education, Research Foundation / Türk Alman Jinekoloji Eğitim Araştırma ve Hizmet Vakfı adına sahibi: M. Cihat Ünlü
Published by Turkish German Gynecology Education, Research Foundation / Türk Alman Jinekoloji Eğitim Araştırma ve Hizmet Vakfı tarafından yayınlanmaktadır.
Abdi İpekçi Cad. 2/7 34367 Nişantaşı, İstanbul, Turkey

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Turgay Akpınar

Finance Coordinator
Sevinç Çakmak

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Project Coordinators
Eda Kolukısa
Esra Semerci
Günay Selimoğlu
Hatice Balta
Zeynep Altındağ

Project Assistants
Duygu Yıldırım
Gamze Aksoy
Melike Eren
Saliha Tuğçe Güdücü

Research&Development
Mert Can Köse
Mevlüde Özlem Akgüney

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing at: Üniform Basım San. ve Turizm Ltd. Şti. Matbaacılar Sanayi Sitesi 1. Cad. No: 114 34204 Bağcılar, İstanbul, Turkey
Phone: +90 (212) 429 10 00 **Certificate Number:** 42419
Printing Date: August 2019
ISSN: 1309-0399 **E-ISSN:** 1309-0380
International scientific journal published quarterly.

Journal of the
Turkish-German
Gynecological Association

Aims and Scope

Journal of the Turkish-German Gynecological Association is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December. It is an independent peer-reviewed international journal printed in English language. Manuscripts are reviewed in accordance with "double-blind peer review" process for both reviewers and authors.

The target audience of Journal of the Turkish-German Gynecological Association includes gynecologists and primary care physicians interested in gynecology practice. It publishes original works on all aspects of obstertrics and gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor, diagnostic puzzle are also published. Suggestions for new books are also welcomed. Journal of the Turkish-German Gynecological Association does not charge any fee for article submission or processing.

Journal of the Turkish-German Gynecological Association is indexed in PubMed Central, Thomson Reuters – Emerging Sources Citation Index, EMBASE, Scopus, CINAHL, Gale/Cengage Learning, EBSCO, ProQuest, Index Copernicus, ROOT INDEXING, J-GATE, TÜBİTAK ULAKBİM TR Index, Türk Medline, Idealonline and Turkiye Citation Index.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supporting a greater global exchange of knowledge.
Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, is right of authors to retain control over the integrity of their work and the right to be properly acknowledged and cited.

Subscription Information

Journal of the Turkish-German Gynecological Association is distributed free of charge to all physicians, specialists in gynecology field. For subscription please contact Turkish-German Gynecological Education and Research Foundation at www.jtgga.org. The access to tables of contents, abstracts and full texts of all articles published since 2000 are free to all readers via the journal's webpage. Visit the journal's home pages for details of the aims and scope and instruction to authors.

Permission

Permission, required for use any published under CC BY-NC-ND license with commercial purposes (selling, etc.) to protect copyright owner and author rights, may be obtained from the Editorial Office:
Editor: Cihat Ünlü, M.D.
Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı-İstanbul-Turkey
Phone: +90 212 241 45 45 Fax: +90 212 241 44 08
E-mail: tajev@tajev.org

Advertising

Enquiries concerning advertisements should be addressed to Editorial Office:
Editor: Cihat Ünlü, M.D.
Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı-İstanbul-Turkey
Phone: +90 212 241 45 45 Fax: +90 212 241 44 08
E-mail: tajev@tajev.org
Instructions for Authors
Instructions for authors page at the journal is available in the journal content and at www.jtgga.org.

Disclaimer

The statements and opinions contained in the articles of the Journal of the Turkish-German Gynecological Association are solely those of the individual authors and contributors not of the Turkish-German Gynecological Education and Research Foundation, Turkish-German Gynecological Association, Turkish Society of Reproductive Medicine, Editorial Board or Galenos.

The journal is printed on acid-free paper.

OPEN ACCESS

Journal of the
Turkish-German
Gynecological Association

Instructions for Authors

The ''Journal of the Turkish-German Gynecological Association'' (ISSN 1309-0399; Abbreviated as "J Turk Ger Gynecol Assoc") is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and the Turkish-German Gynecological Association. Formerly named "ARTEMIS", the journal is published quarterly (March, June, September, December) in English and publishes original peer-reviewed articles, reviews, and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Case reports are not accepted for publication. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

The "Journal of the Turkish-German Gynecological Association" is a peer reviewed journal and adheres to the highest ethical and editorial standards. The Editorial Board of the journal endorses the editorial policy statements approved by the WAME Board of Directors. The journal is in compliance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals published by the International Committee of Medical Journal Editors (updated December 2016, www.icmje.org). The editors also adhere to the Committee on Publications Ethics (COPE) recommendations (http://publicationethics.org).

Submission of Manuscripts

All manuscripts must be submitted via the self explanatory online submission system which is available through the journal's web page at www.jtgga.org. Manuscripts submitted via any other medium will not be evaluated. During the submission please make sure to provide all requested information to prevent any possible delays in the evaluation process.

The main document and the tables, should be prepared with "Microsoft Office Word software". Times New Roman font (size 12) should be used throughout the main document with 1.5 line spacing. The side margins of the main document should be set at 25 mm from all sides.

The ORCID (Open Researcher and Contributor ID) number of the all authors should be provided while sending the manuscript. A free registration can be done at http://orcid.org.

The figures should be submitted separately through the submission system in .JPG of .TIFF format. Please do not embed the figures in the main document. Make sure that the minimum resolution of each submitted figure is 300 DPI.

A cover letter and a title page should be provided with all submissions. It should be stated in the cover letter that the manuscript was not previously published in any other publication, that it is not accepted for publication in another publication and that it is not under review for possible publication elsewhere.

Before completing your submission, please make sure to check the PDF proof of your manuscript which will be generated by the manuscript submission system and make sure that all items of the submission are displayed correctly.

Authors who have any queries regarding the submission process can contact the journal's editorial office:

Editorial Office:

Abdi İpekçi Caddesi 2/7 Nişantaşı, İstanbul / Turkey

+90 212 217 17 00

scholarone@jtgga.org

Editorial Policies

All manuscripts will be evaluated by the editorial board for their scientific contribution, originality and content. Authors are responsible for the accuracy of the data presented in their manuscript. The journal retains the right to make appropriate changes on the grammar and language of the manuscript when needed. When suitable the manuscript will be send to the corresponding author for revision. The manuscript, if accepted for publication, will become the property of the journal and copyright will be taken out in the name of the journal. All manuscripts submitted to the journal for publication are checked by Crossref Similarity Check powered by iThenticate software for plagiarism. If plagiarism is detected, relevant institutions may be notified. In this case, the authors might be asked to disclose their raw data to relevant institutions.

Peer-Review Process

Each manuscript submitted to Journal of the Turkish-German Gynecological Association is subject to an initial review by the editorial office in order to determine if it is aligned with the journal's aims and scope, and complies with essential requirements. Manuscripts sent for peer review will be assigned to one of the journal's associate editors that has expertise relevant to the manuscript's content. All accepted manuscripts are sent to a statistical and English language editor before publishing. Once papers have been reviewed, the reviewers' comments are sent to the Editor, who will then make a preliminary decision on the paper. At this stage, based on the feedback from reviewers, manuscripts can be accepted, rejected, or revisions can be recommended. Following initial peer-review, articles judged worthy of further consideration often require revision. Revised manuscripts generally must be received within 3 months of the date of the initial decision. Extensions must be requested from the Associate Editor at least 2 weeks before the 3-month revision deadline expires; Journal of the Turkish-German Gynecological Association will reject manuscripts that are not received within the 3-month revision deadline. Manuscripts with extensive revision recommendations will be sent for further review (usually by the same reviewers) upon their re-submission. When a manuscript is finally accepted for publication, the Technical Editor undertakes a final edit and a marked-up copy will be e-mailed to the corresponding author for review and to make any final adjustments.

Journal of the
Turkish-German
Gynecological Association

Instructions for Authors

Full text of all articles can be downloaded at the web site of the journal www.jtgga.org.

Preparation of Manuscripts

The "Journal of the Turkish-German Gynecological Association" follows the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors - http://www.icmje.org/). Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Human and Animal Studies

Manuscripts submitted for publication must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards described in an appropriate version of the 1964 Declaration of Helsinki, as revised in 2013. It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Experimental animal studies should be presented with the disclosure of the appropriateness to the institutional/national/international ethical guides on care and use of laboratory animals.

In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals (http://oacu.od.nih.gov/regs/guide/guide.pdf) and they should obtain animal ethics committee approval.

The editors reserve the right to reject manuscripts that do not comply with the above-mentioned requirements. The author will be held responsible for false statements or for failure to fulfil the above mentioned requirements.

In a cover letter the authors should state if any of the material in the manuscript is submitted or planned for publication elsewhere in any form including electronic media. The cover letter must contain address, telephone, fax and the e-mail address of the corresponding author.

Conflict of Interest

Authors must state whether or not there is the absence or presence of a conflict of interest. They must indicate whether or not they have a financial relationship with the organization that sponsored the research. They should also state that they have had full control of all primary data and that they agree to allow the Journal to review their data if requested. Therefore manuscripts should be accompanied by the "Conflict of Interest Disclosure Form." The form can be obtained from the journal webpage (www.jtgga.org).

Copyright

The author(s) transfer(s) the copyright to his/their article to the Journal of the Turkish-German Gynecological Association effective if and when the article is accepted for publication. The copyright covers the exclusive and unlimited rights to reproduce and distribute the article in any form of reproduction (printing, electronic media or any other form); it also covers translation rights for all languages and countries. For U.S. authors the copyright is transferred to the extent transferable.

Submissions must be accompanied by the "Copyright Transfer Statement". The form is available for download on the journal's manuscript submission and evaluation site. The copyright transfer form should be signed by all contributing authors and a scanned version of the wet signed document should be submitted.

COPYRIGHT TRANSFER FORM

Manuscript Specifications

Submissions should have the following parts.

Title Page

A separate title page should be submitted with all submissions and should include the title of the article, name(s), affiliations and major degree(s) of the author(s) and source(s) of the work or study, a short title (running head) of no more than 50 characters. The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be listed on the title page.

Journal of the
Turkish-German
Gynecological Association

Instructions for Authors

Abstract

All manuscripts should be accompanied by an abstract. A structured abstract is required with original articles and it should include the following subheadings: Objective, Material and Methods, Results and Conclusion. A structured abstract is not required with review articles. The abstract should be limited to 250 words for original articles and review articles.

Keywords

Below the abstract provide 3 to 5 Keywords. Abbreviations should not be used as Keywords. Keywords should be picked from the Medical Subject Headings (MeSH) list (www.nlm.nih.gov/mesh/MBrowser.html).

Original manuscripts should have the following sections.

Introduction

State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

Material and Methods

Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. In addition to the normal peer review procedure, all randomized controlled trials (RCTs) submitted to the journal are sent to members of a team of professional medical statisticians for reviewing.

Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures. Provide information on informed consent and ethics committee approval.

Results

Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

Discussion

State the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with those of others. Provide information on the limitations and strenghts of the study. No new data are to be presented in this section.

Reviews must contain the section with critical evaluation and inefficiacy of evidences and explanations to guide further studies in the end.

References

Number references in Arabic numerals consecutively in the order in which they are mentioned in the text starting with number "1". Use the form of the "Uniform Requirements for Manuscript Submitted to Biomedical Journals" (http://www.amaassn.org/public/peer/wame/uniform.htm). If number of authors exceeds seven, list first 6 authors followed by et al.

Journal titles should conform to the abbreviations used in "Cumulated Index Medicus".

Examples:

Journals;

Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of preeclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol 1996; 7: 182-8.

Book chapter;

Ertan AK, Tanriverdi HA, Schmidt W. Doppler Sonography in Obstetrics. In: Kurjak A, Chervenak FA, editors. Ian Donald School Textbook of Ultrasound in Obstetrics and Gynecology. New Delhi, India: Jaypee Brothers; 2003. p. 395-421.

Book;

Kohler G; Egelkraut H. In Kohler G and Egelkraut H (edts).Munchener Funktionelle Entwicklungsdiagnostik im zweitem und drittem Lebensjahr. Handanweisung. Munchen: Uni Munchen, Institut fur Soziale Paediatrie und Jugendmedizin; 1984.

Review Article: Review articles are comprehensive analyses of specific topics in medicine. All review articles will undergo peer review prior to acceptance. Review articles must not exceed 5000 words for the main text (excluding references, tables, and figure legends) and 400 words for the abstract. A review article can be signed by no more than 5 authors and can have no more than 80 references. Also there should be references to authors' own two works.

Editorial: Editorials are a brief remark on an article published in the journal by the reviewer of the article or by a relevant authority. Most comments are invited by the Editor-in-Chief but spontaneous comments are welcome. It must not exceed 700 words (excluding references). An abstract is not required with this type of manuscripts. It can have no more than 15 references and 1 figure or table.

Letter to the Editor: Letters in reference to a journal article must not exceed 500 words (excluding references). Letters not related to a journal article must also not exceed 500 words (excluding references). An abstract is not required with this type of manuscripts. A letter can be signed by no more than 4 authors and can have no more than 5 references and 1 figure or table.

Tables and Figures

Tables should be included in the main document after the reference list. Color figures or gray-scale images must be at minimum 300 DPI resolution. Figures should be submitted in "*.tiff", "*.jpg" or "*.pdf" format and should not be embedded in the main document. Tables

Instructions for Authors

and figures consecutively in the order they are referred to within the main text. Each table must have a title indicating the purpose or content of the table. Do not use internal horizontal and vertical rules. Place explanatory matter in footnotes, not in the heading. Explain all abbreviations used in each table in footnotes. Each figure must have an accompanying descriptive legend defining abbreviations or symbols found in the figure. If photographs of people are used, the subjects must be unidentifiable and the subjects must have provided written permission to use the photograph. There is no charge for color illustrations.

Units of Measurement and Abbreviations

Units of measurement should be in Systéme International (SI) units. Abbreviations should be avoided in the title. Use only standard abbreviations. If abbreviations are used in the text, they should be defined in the text when first used.

Revisions

Revisions will be sent to the corresponding author. Revisions must be returned as quickly as possible in order not to delay publication. Deadline for the return of revisions is 30 days. The editorial board retains the right to decline manuscripts from review if authors' response delays beyond 30 days. All reviewers' comments should be addressed and a revision note containing the author's responses to the reviewers' comments should be submitted with the revised manuscript. An annotated copy of the main document should be submitted with revisions. The Editors have the right to withdraw or retract the paper from the scientific literature in case of proven allegations of misconduct. The second plagiarism check will be made after revision.

Accepted Articles

Epub Ahead of Print

The abstract of the accepted manuscripts will be shown in PubMed as "Epub ahead of print".

An "Epub ahead of print" signifies that the electronic version of an article has been published online (at PubMed and the journal's website www.jtgga.org), but that the print version of the article has not yet been published.

If an article was published online ahead of print, the date it was published online, along with the digital object identifier (DOI) to ensure that all article versions can be identified, should follow the acceptance date footnote (or, if the journal does not publish the acceptance date, it should be placed first).

Journal and Society Web sites:

www.dtgg.de
(Deutsch-Türkische Gynäkologengeselleschaft)

www.tajev.org
(Turkish-German Gynecological Education and Research Foundation)

www.jtgga.org
(Journal of the Turkish-German Gynecological Association)

- Citation of published manuscripts in J Turk Ger Gynecol Assoc should be as follows: Tews G, Ebner T, Sommergruber M, Marianne M, Omar S. Ectopic Pregnancy in the Assisted Reproduction. J Turk Ger Gynecol Assoc 2004; 5: 59-62.

- The Journal name should be abbreviated as "J Turk Ger Gynecol Assoc"

3 Ovül

Trivag 300 mg/200 mg/100 mg Ovül

Tinidazol
Tiokonazol
Lidokain

Candida albicans'ın oluşturduğu
▶ **Kandidal vulvovajinit**,

Gardnerella vaginalis ve anaerob bakterilerin oluşturduğu
▶ **Bakteriyel vajinozis**,

Trichomonas vaginalis'in oluşturduğu
▶ **Trikomonal vajinit**,

▶ **Mikst vajinal enfeksiyonların**

ampirik tedavisinde tek form ile etkilidir.*

Tedavide rahatlık için*

* Trivag Kısa Ürün Bilgisi
ÜRÜN ADI: TRİVAG 300 mg/200 mg/100 mg ovül FORMÜLÜ: Her bir ovül 300 mg tinidazol, 200 mg tiokonazol, 100 mg lidokain içerir. TERAPÖTİK ENDİKASYONLAR: Candida albicans'ın oluşturduğu kandidal vulvovajinit; Gardnerella vaginalis ve anaerob bakterilerin oluşturduğu bakteriyel vajinoz ve Trichomonas vaginalis'in oluşturduğu trikomonal vajinit ile mikst vajinal enfeksiyonların tedavisinde kullanılır. KULLANIM ŞEKLİ VE DOZU: Gece yatmadan önce bir ovül, 3 gün süreyle uygulanır. TRİVAG sırtüstü yatar pozisyonda, paketin içindeki parmaklıkların yardımı ile vajen derinliğine uygulanmalıdır. İSTENMEYEN ETKİLER: Güçsüzlük, bitkinlik, halsizlik, baş ağrısı, baş dönmesi, ağızda metalik/acı tat, mide bulantısı, anoreksi, iştahsızlık, midede gaz toplanması, dispepsi, abdominal kramp, epigastrik rahatsızlık, kusma, konstipasyon, idrar renginde koyulaşma. GEBELİK VE LAKTASYON: Gebelik kategorisi C'dir. Tinidazol anne sütüne geçtiğinden emzirme döneminde tedavi sırasında bebek sütten kesilmelidir, tedavi bittikten 72 saat sonra emzirmeye devam edilmelidir. DİĞER TIBBİ ÜRÜNLERLE ETKİLEŞİMLER VE DİĞER ETKİLEŞİM ŞEKİLLERİ: Birlikte kullanıldığında tinidazolün emilmesine bağlı olarak etkileşim görülebilir; asenokumarol, anisindion, dikumarol, fenindion, fenprokumon, varfarin, kolestiramin, simetidin, siklosporin, disülfiram, fluorourasil, fosfenitoin, ketokonazol, lityum, fenobarbital, fenitoin, rifampin, takrolimus, CYP3A4 indükleyicileri/inhibitörleri. Tiokonazolün emilmesine bağlı olarak etkileşim görülebilir; oksikodon. Lidokainin emilmesine bağlı olarak etkileşim görülebilir; propranolol, simetidin, antiaritmik ürünler, fenitoin veya barbitüratlar. KONTRENDİKASYONLARI: Bileşimindeki etkin maddelere veya bunların türevlerine karşı aşırı duyarlılığı bulunanlarda, gebeliğin ilk üç ayında, emzirme döneminde, organik nörolojik bozukluğu bulunanlarda, kan diskrazisi tablosu veya geçmişi bulunan hastalarda. ÖZEL KULLANIM UYARILARI VE ÖNLEMLERİ: Vajinal yoldan kullanılmalıdır. Geçici lökopeni ve nötropeni gelişebilir. Tedavi süresince ve tedavi bittikten 3 gün sonrasına kadar alkol alınmamalıdır. Cinsel olgunluğa erişmemiş kız çocuklarında ve bakirelerde kullanılmamalıdır. Kardiyovasküler hastalıkları olanlarda dikkatli kullanılmalıdır. Kontraseptif diyafram ve prezervatifle temas etmemelidir. Lidokain özellikle yüksek dozda ve geniş deri yüzeylerine, bilhassa da oklüzyon altında uygulandığında kalp ritm bozuklukları, nefes alma zorluğu, koma ve hatta ölüme yol açabilmektedir. Spermisidler, vajinal duşlar veya vajinal yoldan uygulanan diğer ürünlerle birlikte kullanılmamalıdır. Trikomonal vajinit vakalarında eş tedavisi de gereklidir. TİCARİ TAKDİM ŞEKLİ VE FİYATI: Trivag ovül (Ruhsat tarihi ve no: 29.09.2017-2017/742) 16,53 TL. (Fiyat Tarihi: Mayıs 2018) Ruhsat Sahibi: Bilim İlaç San. ve Tic. A.Ş. Son Güncelleme: Mayıs 2018. Reçeteli satılır. Daha geniş bilgi için "BİLİM İLAÇ SAN. ve TİC A.Ş. 34440 Beyoğlu-İSTANBUL" adresine başvurunuz. Ürünlerimiz ile ilgili advers olayları PHARMACOVIGILANCE@bilimilac.com adresine e-posta göndererek veya 0 212 365 1717 iletişim numarasını arayarak ürün güvenliliği sorumlusuna bildirebilirsiniz.

BİL 5646 TRİV 07

bilim İLAÇ

Journal of the
Turkish-German
Gynecological Association

Contents

Journal of the
Turkish-German
Gynecological Association

Editorial

Dear Colleagues,

It is my great pleasure to present you the third issue of Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc) in the publishing year of 2019. We have the policy of Open Access publications. Open access (also known as open-access publishing and free online scholarship) is an ongoing publication practice which differs in the way traditional methods of publishing papers to the public get submitted, reviewed, authenticated and finally published. It proposes a new business model for academic publishing that enables immediate, worldwide, barrier-free, open access to the full text of research articles for the best interests of the scientific community.

Some important tips and clues were given by me with every issues. As the field of medicine becomes more competitive some may feel that research is becoming a compulsory component of the training. Research learning outcomes are essential for OB&GYN specialist training programs. The process of undertaking a research project teaches trainees valuable lessons in reading and critically appraising research literature, creating a hypothesis, understanding ethical issues in research, learning about data acquisition and cleaning, and data analysis. We have a good platform that encouraging young researcher for writing and publishing their work in our journal.

For the young researchers, to actually enjoy training and be productive, follow the tips described below.

1. **Make an outline of your plans and goals**
2. **Work on your time-management skills**
3. **Combine both intellectual and physical work**
4. **Ask your chiefs or mentors and residents**
5. **Don't be afraid to make mistakes**
6. **Read papers/articles and do not stick to old textbook**
7. **Be a reviewer (we have an open invitation for you)**
8. **Write papers and ask help from someone who has experiences for this.**

Writing reviews is a good way to get published - especially for people who are in the early stages of their career. It's a chance to practice at writing a piece for publication, and get a free copy of a book that you want. We publish more reviews than papers so we're constantly looking for reviewers. Some journals, including ours, publish replies to papers that have been published in the same journal. Editors quite like to publish replies to previous papers because it stimulates discussion.

Journal of the
Turkish-German
Gynecological Association

Editorial

Dear Researchers,

We have a very interesting and astonishing issue. There are several well written manuscript from all over the world. I would like to wish a successful working period to all colleagues. We are looking forward to receiving your valuable submissions and thank you in advance for your contributions.

Have a nice and productive academic year!

Best regards,

Prof. Cihat Ünlü, M.D.
Editor in Chief of *J Turk Ger Gynecol Assoc*
President of TGGF

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the
Turkish-German
Gynecological Association

MOST CITED AND MOST VIEWED ARTICLES

Dear Readers,
We would like to present our most cited and most viewed articles on different platforms, like our website, Web of Science, Scopus and PubMed.

Website

Frozen embryo transfer prevents the detrimental effect of high estrogen on endometrium receptivity by
Aynur Adeviye Erşahin, Mustafa Acet, Suat Süphan Erşahin, Nur Dokuzeylül Güngör

Web of Science

Impact of obesity on infertility in women by
Zeynep Özcan Dağ, Berna Dilbaz

Scopus

Impact of obesity on infertility in women by
Zeynep Özcan Dağ, Berna Dilbaz

PubMed

Placental location and pregnancy outcome by
Shumaila Zia

http://www.jtgga.org/

VIDEO ARTICLE

Our journal started to accept video articles for evaluation. Video articles are a new method for science, a visualisation helps authors to present their work effectively and can be submitted to submission system. For detailed information, please check our journal's webpage.

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the

Turkish-German Gynecological Association


TGGF
TURKISH - GERMAN GYNECOLOGICAL
EDUCATION and RESEARCH FOUNDATION
XIII
TURKISH GERMAN
GYNECOLOGIC
CONGRESS
WWW.TAJEV2021.ORG
May 19-23, 2021
Titanic Mardan Palace,
Antalya, Turkey
www.tajev2021.org

Clinical characteristics and location of lesions in patients with deep infiltrating endometriosis using the revised Enzian classification

Fred Morgan-Ortiz[1], Manuel Antonio López-de la Torre[1], Marco Antonio López-Zepeda[2], Fred Valentín Morgan-Ruiz[1], José Cándido Ortiz-Bojórquez[3], Martín Adrián Bolívar-Rodríguez[3]

[1]Department of Obstetrics and Gynecology, Civil Hospital of Culiacán, Center for Research and Training in Health Sciences, Autonomous University of Sinaloa, Culiacán, Sinaloa, Mexico

[2]Center of Excellence in Endometriosis, San Javier Hospital, Guadalajara, Mexico

[3]Department of General Surgery, Civil Hospital of Culiacán, Center for Research and Training in Health Sciences, Autonomous University of Sinaloa, Culiacán, Sinaloa, Mexico

Abstract

Objective: To describe the clinical characteristics and location of lesions in patients with deeply infiltrating endometriosis using the revised Enzian (rEnzian) classification.

Material and Methods: The clinical records of 60 patients undergoing laparoscopy for deeply infiltrating endometriosis at Hospital Civil de Culiacán, Sinaloa and Hospital San Javier, Jalisco, Mexico, were reviewed. Age, body mass index (BMI), number of pregnancies, childbearing, previous abortions, laparoscopic suggestion (pelvic pain, bleeding, infertility), and size and location of the lesions were assessed according to the rEnzian classification.

Results: The mean age of the patients was 30.5 years. The mean BMI was 25.6 kg/m^2. Sixty-eight percent were nulliparous and 13% had at least one birth. Eighty-five percent had pelvic pain and 8.3% had infertility. Seventy percent (n=42) of the women had ovarian endometriomas (middle compartment); uterosacral and the torus uterinus ligaments were affected in 23.3%, rectum and sigmoid colon in 35% (posterior compartment), and the appendix and small intestine in 3.3%. According to the rEnzian classification, the most affected compartment was C2 (rectum and sigmoid colon with 1-3 cm lesions).

Conclusion: Pelvic pain was the main symptom of patients with deeply infiltrating endometriosis, mainly in nulliparous women. According to the rEnzian classification, the C2 compartment was the most affected (rectum and sigmoid colon). (J Turk Ger Gynecol Assoc 2019; 20: 133-7)

Keywords: Endometriosis, clinical characteristics, surgical findings, deeply infiltrating endometriosis, Enzian classification

Received: 19 September, 2018 **Accepted:** 13 December, 2018

Introduction

Endometriosis is one of the main causes of pain and infertility in women. It can be classified as peritoneal, ovarian, and deep, and affects mostly reproductive-age women (25-35 years), with a rate of 10-15% (1). It is unusual in pre or postmenarcheal women and rare in postmenopausal women (2,3).

The main symptoms reported by patients who are diagnosed as having endometriosis are dysmenorrhea (79%), pelvic pain (69%), dyspareunia (45%), modified gut transit (constipation, diarrhea in 36%), intestinal pain (29%), infertility (26%), ovarian mass (20%), dysuria (10%), and other urinary disorders (6%) (4,5).

Different classifications for endometriosis staging have been proposed based on anatomic location and disease severity. The American Society for Reproductive Medicine (ASRM) score is the most commonly used; it is easily applied and understood by physicians and patients and classifies disease severity in stages I to IV. Among its disadvantages are that staging is not fully correlated with morphologic affection of organs, poor prediction of pregnancy success after treatment, limited reproducibility, and neither retroperitoneal affection nor deeply infiltrating endometriosis are included. Moreover, pain and infertility are poorly correlated with the duration of the disease (6,7).

Address for Correspondence: *Fred Morgan-Ortiz*
e.mail: frnorganortiz@hotmail.com ORCID: orcid.org/0000-0002-6072-3636

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2018.2018.0120

For this reason, in Austria in 2005, a working group meeting was held with the purpose of forming new classification that included retroperitoneal affection, mainly deeply infiltrating endometriosis (DIE), which was finally designated the Enzian classification (8). However, it is currently not well-known and has a poor level of international acceptance, it is mainly used in German-speaking countries. This first Enzian classification was difficult to use and included anterior, medial, and posterior compartments (8). Then, in 2011, a review of this classification clarified the findings, combining morphologic structures in compartments as with its predecessor, but only considering the posterior portion of the uterus as compartment A (rectovaginal septum and vagina), B (sacrouterine ligaments and pelvic wall), and C (sigmoid colon and rectum), and set the severity of the lesions according to their size as: grade 1 (invasion <1 cm), grade 2 (invasion 1-3 cm) and grade 3 (invasion >3 cm) (9). Invasion to other organs of the lesser pelvis and distance are also considered in this new classification as FA for adenomyosis, FB for bladder involvement, FU for intrinsic ureter involvement, FI for intestinal involvement, and FO for involvement of other organs or structures, such as the abdominal wall. This reviewed version of the classification (2011) was more feasible, useful, and easy to understand by physicians (9).

Several studies have evaluated Enzian classification in relation to its correlation with clinical symptoms and the rASRM classification, reporting that the Enzian classification was partially related to clinical symptoms and severity grades, but significantly correlated with pain and dysmenorrhea, thus, it could be recommended as a complement to the rASRM classification in order to better morphologically describe DIE lesions, even though it requires improvement (10-12).

The aim of the present study was to describe the clinical and sociodemographic characteristics, as well as the distribution of lesions according to the revised Enzian (rEnzian) classification in patients with deeply infiltrating endometriosis as observed during laparoscopy.

Material and Methods

Previously approved by the Ethics and Research Committee, an observational, descriptive, and retrospective study was conducted in patients who were diagnosed and treated for DIE with histopathologic study. Sixty clinical records of patients undergoing laparoscopic surgery from Hospital Civil de Culiacán, Culiacán, Sinaloa and Clínica de Excelencia en Endometriosis, Hospital San Javier, Guadalajara, Jalisco, Mexico, were assessed from July 2010 to July 2016. All patients were diagnosed as having DIE before surgical treatment by a multidisciplinary team that included a gynecologist, coloproctologist, urologist, psychologist, and experts in ultrasound and magnetic resonance imaging.

The Enzian classification (2005) and rEnzian classification (2011) were used to assess the disease (12). The latter version only evaluates DIE location, mainly in the posterior portion of the uterus as described previously.

Analyzed variables were as follows: age, body mass index (BMI), number of pregnancies, childbearing, previous abortions, laparoscopic suggestion (pelvic pain, bleeding or infertility) as well as medical sessions previous to the diagnostic of endometriosis. Surgical findings included number and location of the lesions: anterior compartment (bladder and vesical peritoneum), medium compartment (uterus and ovaries), posterior compartment (rectovaginal septum, uterosacral ligaments (USL), and rectum sigmoid colon) and other locations (e.g. ureter, small gut, appendix), as well as their size. In addition, a description of surgical findings in patients with DIE was reported according to the rEnzian classification related to the distribution and severity of the lesions in compartments A, B, C, FA, FB, FI, and FO.

Statistical analyses included mean and standard deviations for numeric variables, and frequencies and percentages for categorical variables. In addition, 95% confidence intervals (CI) were calculated for each estimate. The SPSS statistical package version 22.0 was used for statistical analyses.

Results

Mean age of the patients was 30.5 years (95% CI: 28.6-32.3). The mean BMI was 25.7 kg/m^{2}SC (95% CI: 24.8-26.5). The mean number of medical sessions prior to the diagnosis of endometriosis was 7 (95% CI: 5.9-8.0). Regarding the gyneco-obstetric characteristics, 68% of the women were never-pregnant (95% CI: 55.0-79.7), with at least one childbirth 13% (95% CI: 5.9-24.5), at least one cesarean 18% (n=11/60; 95% CI: 9.52-30.43), and at least one abortion 13% (n=8/60; 95% CI: 5.9-24.5). The first symptom to proceed with a diagnostic/surgical laparoscopic procedure was pain in 85% (95% CI: 73.4-92.9), infertility in 8.3% (95% CI: 2.7-18.3), and abnormal genital bleeding in 6.7% (95% CI: 1.8-16.1) (Table 1).

DIE lesions were very commonly found in the medial compartment, in 80% of the subjects (95% CI: 69.5-90.4) (Table 2).

Analysis of DIE lesions by compartment were found in the anterior portion and commonly in the vesical floor (6.6%), with 1-3 cm size in 3.3%, and more than 3 cm in 3.3%. In the medial compartment, the most affected organ was the ovary in 70% (95% CI: 58.4-81.5). The right ovary was the most influenced in 26.6% of the women (95% CI: 16.1-39.6). The size of the lesions most commonly found in this compartment were larger than 3 cm in 45% (95% CI: 32.4-57.6). Related to the posterior compartment, DIE lesions were more frequent in the rectum and sigmoid colon (35%; 95% CI: 22.9-47.1), the most common

lesions being 1-3 cm (33.3%; 95% CI: 21.4-45.2). Other unusual lesions were found in the bowel, appendix, and abdominal wall (Table 3).

In regard to the distribution and severity of the lesions according to the rEnzian classification, which does not consider ovaries affection; type C2 (affection to rectum and sigmoid colon with 1-3 cm lesions) was the most commonly found in 23.3%, followed by type B3 (uterus sacral ligaments with lesions larger than 3 cm) in 10% (Table 4).

Discussion

Infiltrating lesions from DIE are defined as solid focused lesions that invade 5 mm deep or more of organ serosa (13). Some reports indicate that 95% of the lesions involve serosa and muscularis propria, only 38% affect the submucosa and 6% affect the mucosa (14).

DIE is a usual cause of chronic pelvic pain in reproductive-age women. In general, it is associated with anatomic location and the invasion degree of the lesions (>5 mm), (15-17) which agrees with the findings in this case series where chronic pelvic pain was the most frequent indication for surgery.

Many endometriosis symptoms are masked by other medical conditions, delaying diagnosis for about 5-10 years when patients have had, on average, 7 medical sessions without a correct diagnosis due to disease unawareness from the first contact with a physician and the patients themselves, who consider the symptoms as normal (18).

The importance of a classification to describe a disease relies on understanding its limits, using the same language when reporting the clinical entity, and reproducing the study within the same terms.

In this trial of 60 cases using the Enzian Classification (2005), the medial compartment was found as the most affected area in 80% of the cases (mainly ovarian endometriomas), followed by the posterior compartment in 65% (mainly rectum and sigmoid colon), and less frequently, the anterior compartment (vesical affection).

Related to the anatomic distribution of endometriosis lesions and a probable physiopathogenic implication, a study revealed

Table 1. General characteristics of the studied population

Characteristics	Mean or frequency (%)	95% CI
Age (years)	30.5	28.6-32.3
BMI (kg/m^2)	25.7	24.8-26.5
Nulliparous	68.3% (n=41)	55.0-79.7
One or more pregnancies	31.7% (n=19)	20-43.4
One or more cesareans	18.3% (n=11)	9.5-30.4
One or more abortions	13.3% (n=8)	5.93-24.5
Number of previous medical visits to diagnostic of the disease	7	5.97-8.03
Main symptoms		
Pain	85% (n=51)	73.4-92.9
Infertility	8.3% (n=5)	2.7-18.3
Bleeding	6.6% (n=4)	1.8-16.1

Table 2. Location of deep infiltrating lesions by compartment

Compartment	Frequency (%)	95% CI[a]
Anterior	6.6 (n=4)	1.8-16.1
Medial	80 (n=48)	69.5-90.4
Posterior	65.0 (n=39)	32.1-58.3
[a]95% CI: Confidence interval of 95%		

Table 3. Distribution and size of deep infiltrating lesions by compartment

Compartment	Frequency (n)	95% CI
Anterior		
Vesical wall	6.6 (n=4)	1.8-16.1
Size of the lesion		
Nodule 1-3 cm	3.3 (n=2)	0.40-11.5
Nodule >3 cm	3.3 (n=2)	0.40-11.5
Medial		
Uterus	**10 (n=6)**	**3.7-20.5**
Ovaries	**70 (n=42)**	**58.4-81.5**
Right ovary	26.6 (n=16)	16.1-39.6
Left ovary	21.6 (n=13)	12.1-34.2
Both ovaries	21.6 (n=13)	12.1-34.2
Size of the lesion		
1-3 cm	25.0 (n=15)	14.7-37.8
>3 cm	45.0 (n=27)	32.4-57.6
Posterior		
A) Recto-vaginal septum and vagina	6.6 (n=4)	0.31-12.8
B) Uterosacral and torus uterinus ligaments	23.3 (n=14)	12.6-33.9
C) Rectum and sigmoid colon	35.0 (n=21)	22.9-47.1
Size of the lesion		
<1 cm	11.7 (n=7)	3.5-19.8
1-3 cm	33.3 (n=20)	21.4-45.2
>3 cm	20.0 (n=12)	9.8-30.1
Other locations		
FA	16.6 (n=10)	7.2-26.0
FI	3.3 (n=2)	0.40-11.5
FO	5.0 (n=3)	0.51-10.5
FA: Adenomyosis, FI: Intestinal, FO: Appendix (n=2) and abdominal wall (n=1)		

Table 4. Distribution and severity of deeply infiltrating endometriosis in agreement with the revised Enzian classification (2011)

Severity	Location % (n)						
	A	B	C	FV	FA	FI	FO
Grade 1 (<1 cm)	0	8.3 (5)	3.3 (2)	0	0	3.3 (2)	3.3 (2)
Grade 2 (1-3 cm)	5.0 (3)	5.0 (3)	23.3 (14)	1.7 (1)	10.0 (6)	0	0
Grade 3 (>3 cm)	1.7 (1)	10.0 (6)	8.3 (5)	0	6.6 (4)	0	1.7 (1)

A: Rectovaginal septum and vagina, B: Uterosacral ligaments and pelvic wall, C: Rectum and sigmoid colon, FV: Vesical, FA: Adenomyosis, FI: Intestinal, FO: Appendix and abdominal wall

that the most affected compartment was the posterior compartment (93.4%), and mainly the left side (67.8%); less frequently, the anterior compartment with vesical affection (6%) (13). This vesical affection report (anterior compartment) is in agreement with the findings in our series of 60 cases where 6.6% was shown; nevertheless, it differs with other reported studies in which 85% were in the bladder, 10% in the ureter, and 4% were found in kidney lesions (19).

Therefore, it could be concluded that DIE is an entity that affects the female pelvis asymmetrically, being more common in the posterior portion and left side of the uterus. This might be explained by the presence of the rectum and sigmoid colon in that side of the pelvis, modifying peritoneal flux in both hemipelvis, thus, blood drops retrogradely during menstruation and accumulates in this area of the pelvis, leading to implantation of endometrial cells and disease development (13).

The presence of endometriomas (medial compartment) could be a marker of endometriosis severity, mainly DIE. In the present series of 60 cases with DIE, 70% of the patients showed an endometrioma more often on the right than on the left side, in disagreement with a previous study hypothesis proposing anatomic distribution of the pelvis. This frequency is similar to 77% of endometriomas in patients with DIE (rectum and sigmoid colon involvement) compared with 21% without endometrioma (risk ratio: 6.96; 95% CI: 4.04-12.00) (20).

It is important to mention that ovarian endometriosis is a marker of spread pelvic disease, and associated with cul-de-sac obliteration involving the rectum, sigmoid colon, and the seromuscular layer of the bowel, which should be treated if surgery favors the patient, even when ovarian affection absence does not discard DIE as a possibility (21). Moreover, USL affection could be a marker of ureteral involvement by DIE (22,23). In a study with 463 patients DIE with presurgical transvaginal ultrasound, 111 patients showed USL involvement. Ureter affection was associated with ovarian mobility, ureteral changes on the right side, nodule size of USLs, and endometrioma on the left side, particularly when USLs were 1.75-1.95 cm, in the right and left sides, respectively (22).

The Enzian classification in 2005 was poorly accepted due to its complex clinical application, so it was revised and modified in 2011 (rEnzian) (8,9). This 2005 review only included affection of endometriosis from the posterior compartment. In the revised classification, posterior compartment of the uterus was divided in three as A, B, C and F, and severity goes with nodule size (G1, G2, and G3) in such a way that tumor, node, metastasis staging could be used as in malignant diseases; therefore, a presurgical description of involved organs using the compartment and severity of the lesion is possible. For example, a presurgical patient with DIE using the Enzian classification would be A0 B1 C2 F (with no lesions in the rectovaginal septum and vagina, with less than 1 cm lesions in the USLs and pelvic wall, and 1-3 cm lesions in the sigmoid colon).

In the present case series, the most affected compartment was C with 21 cases, 14 of which were grade 2. Thus, to describe this lesion it should be classified as C2, which means that the most affected sites in the patients of this trial were the rectum and sigmoid colon with infiltrative lesions from 1-3 cm. This implies that patients would require a discoid or segmental resection of those organs, the surgeon should then anticipate instrumental provisions, surgical time and, most importantly, a multidisciplinary team to continue the procedure. In Mexico and other countries around the world, there is little knowledge of DIE treatment as a multidisciplinary disease, where imaging experts and surgeons work together with a close communication to handle patients with DIE.

One of the biggest problems for physicians is having presurgical diagnostic confidence of the disease relying on cost/benefit and less invasive techniques such as ultrasound, which in skilled experts has an excellent sensitivity and specificity to diagnose DIE, even similar to magnetic resonance (24,25). Unfortunately, most centers in Mexico lack trained personnel to diagnose DIE because they have never faced this problem in the past or do not know about its existence.

The same happens with DIE surgical treatment as a multidisciplinary entity; few groups at national level work on integral DIE treatment; however, with that goal, an accurate diagnostic of involved organs is required in order to anticipate the needs for a correct management, as mentioned.

Accordingly, the rEnzian classification becomes useful as in the present study where, even with a small sample, the frequency of affected organs was described clearly and could simplify pre and post-surgical reports.

Synopsis: Deeply infiltrating endometriosis occurs mainly in young women with pelvic pain and lesions that are often located in the C2 compartment according to the rEnzian classification.

Ethics Committee Approval: *Previously approved by Ethic and Research Committee an observational, descriptive and retrospective study was carried out in patients diagnosed and treated for deeply infiltrating endometriosis (DIE) with histopathologic study*

Informed Consent: *It was taken.*

Peer-review: *Internally and externally peer-reviewed.*

Author Contributions: *Concept: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.; Design: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.; Supervision: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.; Materials: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.; Data Collection and/or Processing: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.; Analysis and/or Interpretation: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.; Writer: F.M.O., M.A.L.T., M.A.L.Z., F.V.M.R., J.C.O.B., M.A.B.R.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Wang G, Tokushige N, Markham R, Fraser IS. Rich innervation of deep infiltrating endometriosis. Hum Reprod. 2009; 24: 827-34. Available from: https://academic.oup.com/humrep/article/24/4/827/632224
2. Sangi-Haghpeykar H, Poindexter AN. Epidemiology of endometriosis among parous women. Obstet Gynecol 1995; 85: 983-92.
3. Steele RW, Dmowski WP, Marmer DJ. Immunologic Aspects of Human Endometriosis. Am J Reprod Immunol 1984; 6: 33-6.
4. Sinaii N, Plumb K, Cotton L, Lambert A, Kennedy S, Zondervan K, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. Fertil Steril 2008; 89: 538-45.
5. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014; 29: 400-12.
6. No authors listed. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997; 67: 817-21.
7. Haas D, Shebl O, Shamiyeh A, Oppelt P. The rASRM score and the Enzian classification for endometriosis: their strengths and weaknesses. Acta Obstet Gynecol Scand 2013; 92: 3-7.
8. Tuttlies F, Keckstein J, Ulrich U, Possover M, Schweppe KW, Wustlich M, et al. ENZIAN-score, a classification of deep infiltrating endometriosis. Zentralbl Gynakol 2005; 127: 275-81.
9. Stiftung Endometriose Forschung. The revised Enzian classification. Consensus meeting, 7th Conference of the Stiftung Endometriose Forschung (SEF) (Foundation for Endometriosis Research), Hotel Enzian, Weissensee, Austria, February 25-27, 2011. Weissensee, Austria, 2011.
10. Haas D, Oppelt P, Shebl O, Shamiyeh A, Schimetta W, Mayer R. Enzian classification: does it correlate with clinical symptoms and the rASRM score? Acta Obstet Gynecol Scand 2013; 92: 562-6.
11. Haas D, Chvatal R, Habelsberger A, Wurm P, Schimetta W, Oppelt P. Comparison of revised American Fertility Society and ENZIAN staging: a critical evaluation of classifications of endometriosis on the basis of our patient population. Fertil Steril 2011; 95: 1574-8.
12. Haas D, Wurm P, Shamiyeh A, Shebl O, Chvatal R, Oppelt P. Efficacy of the revised Enzian classification: a retrospective analysis. Does the revised Enzian classification solve the problem of duplicate classification in rASRM and Enzian? Arch Gynecol Obstet 2013; 287: 941-5.
13. Chapron C, Chopin N, Borghese B, Foulot H, Dousset B, Vacher-Lavenu MC, et al. Deeply infiltrating endometriosis: pathogenetic implications of the anatomical distribution. Human Reprod 2006; 21: 1839-45.
14. De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. Bowel resection for deep endometriosis: a systematic review. BJOG 2011; 118: 285-91.
15. Abrao MS, Podgaec S, Dias JA Jr, Averbach M, Silva LF, Marino de Carvalho F. Endometriosis Lesions That Compromise the Rectum Deeper than the Inner Muscularis Layer Have More Than 40% of the Circumference of the Rectum Affected by the Disease. J Minim Invasive Gynecol 2008; 15: 280-5.
16. Donnez J, Squifflet J. Laparoscopic excision of deep endometriosis. Obstet Gynecol Clin Nort Am 2004; 31: 567-80.
17. Howard FM. The role of laparoscopy in the evaluation of chronic pelvic pain: Pitfalls with a negative laparoscopy. J Am Assoc Gynecol Laparosc 1996; 4: 85-94.
18. Ballard K, Lowton K, Wright J. What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. Fertil Steril 2006; 86: 1296-301.
19. Yohannes P. Ureteral Endometriosis. J Urol 2003; 170: 20-5.
20. Banerjee SK, Ballard KD, Wright JT. Endometriomas as a Marker of Disease Severity. J Minim Invasive Gynecol 2008; 15: 538-40.
21. Redwine DB, Wright JT. Laparoscopic treatment of complete obliteration of the cul-de-sac associated with endometriosis: long-term follow-up of en bloc resection. Fertil Steril 2001; 76: 358-65.
22. Lima R, Abdalla-Ribeiro H, Nicola AL, Eras A, Lobao A, Ribeiro PA. Endometriosis on the uterosacral ligament: a marker of ureteral involvement. Fertil Steril 2017; 107: 1348-54.
23. Carfagna P, De Cicco Nardone C, De Cicco Nardone A, Testa AC, Scambia G, Marana R, et al. Role of transvaginal ultrasound in evaluation of ureteral involvement in deep infiltrating endometriosis. Ultrasound Obstet Gynecol 2017; 51: 550-5.
24. Turocy JM, Benacerraf BR. Transvaginal sonography in the diagnosis of deep infiltrating endometriosis: A review. J Clin Ultrasound 2017; 45: 313-8.
25. Exacoustos C, Lazzeri L, Zupi E. Expert sonographers and surgeons are needed to manage deep infiltrating endometriosis. Ultrasound Obstet Gynecol 2017; 49: 417.

The effect of gender-role orientation on attitudes towards menstruation in a sample of female university students

Ashraf Ghiasi

Student Research Committee, School of Nursing and Midwifery, Shahroud University of Medical Sciences, Shahroud, Iran

Abstract

Objective: To examine the effect of gender role orientation on attitudes towards menstruation in a sample of Iranian female students of medical sciences.

Material and Methods: Three hundred female university students (94%; response rate: 282) were enrolled in the study via stratified random sampling. Data were collected using a demographic questionnaire, the Menstrual Attitude Questionnaire (MAQ), and the short version of the Bem Sex Role Inventory (BSRI). Data were analyzed using SPSS v.18. Analyses were performed using the Kruskal-Wallis test and the Mann-Whitney U test.

Results: The mean scores of the MAQ subscales ranged from 3.7±1.35 to 5.6±1.3, indicating that most of the respondents had natural to moderate attitudes toward menstruation. When participants were classified into one of four gender-role categories of BSRI, the results showed that the undifferentiated group with 33.7% was higher than other gender-role groups. The undifferentiated group was significantly less likely than the other groups to perceive "menstruation as a natural event".

Conclusion: The study shows an association between gender-role orientation and attitudes toward menstruation in female university students. However, further research is still necessary in this issue. (J Turk Ger Gynecol Assoc 2019; 20: 138-41)

Keywords: Attitudes, Bem Sex Role Inventory, female students, gender-role orientation, menstruation

Received: 3 October, 2018 **Accepted:** 11 November, 2018

Introduction

Menstruation, the cyclical shedding of blood and endometrium from the uterine cavity, is a physiologic process that occurs throughout a woman's reproductive years (1). Although menstruation is a natural/biologic event, perimenstrual symptoms (immediately before and during menstruation), including anxiety, depression, irritability, tension, mood swings, fatigue, skin disorders, breast tenderness, swelling, weight gain, cramps, and backache affect a significant percentage of women (2,3). Evidence suggests that attitudes toward menstruation can influence the reporting of perimenstrual symptoms (4). For example, Lu (5) found a significant association between negative attitudes toward menstruation and the experience of perimenstrual symptoms in Taiwanese women. Studies have also demonstrated that a woman's beliefs about and attitudes toward menstruation were influenced by socio-cultural factors and family environments (6-8). For example, Hoerster et al. (9) compared Indian and American women's attitudes toward menstruation. They found that menstruation was perceived as significantly more debilitating and a less natural event by American women compared with Indian women (9). A few studies investigated the effect of gender-role orientation – the extent to which a person believes or perceives that she/he possesses gender-typed characteristics – on attitudes toward menstruation (10,11). Chrisler (11) showed that undifferentiated and feminine college students were more likely than androgynous and masculine students to perceive menstruation as a bothersome event; undifferentiated and masculine college students were more likely than

Address for Correspondence: *Ashraf Ghiasi*
e.mail: a.ghiasi25@gmail.com ORCID: orcid.org/0000-0002-4918-3210

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2018.2018.0122

androgynous and feminine students to perceive menstruation as a debilitating event. The effect of gender-role orientation on menstrual attitudes is not entirely clear. Hence, in the present study, the Menstrual Attitude Questionnaire (MAQ) and Bem Sex Role Inventory (BSRI) were administered to a sample of female students with the aim of examining the impact of gender-role orientation on attitudes toward menstruation.

Material and Methods

Participants

In the academic year 2015/16, there were nearly 900 female students at 4 schools of Shahroud University of Medical Sciences. Thus, the sample size was estimated as 269 using a Krejcie & Morgan table. After adding a 10% non-response rate, the final sample size for this cross-sectional study became 300. Stratified random sampling was used to choose the study participants. The inclusion criteria in this study were as follows: Iranian nationality, aged between 18 and 30 years, and no history of polycystic ovary syndrome or mental disorders.

Instruments

Data were collected using a demographic questionnaire, the 30-item version of the BSRI, and the MAQ.

The demographic questionnaire included questions about menstrual status (age at first menstruation, menstrual cycle length, menstrual frequency, and regulation of menstruation), age, and marital status.

The original (BSRI Bem, 1974) includes 20 masculine, 20 feminine, and 20 neutral items, each item ranges from 1 'never/almost never true' to 7 'always/almost always true'. It was designed to categorize subjects into four groups: Masculine (high masculine, low feminine), feminine (high feminine, low masculine), androgynous (high masculine, high feminine), and undifferentiated (low masculine, low feminine) (12). In this study, the short 30-item version of the BSRI was used. The validity and reliability of the Persian version of this questionnaire were confirmed in previous studies (13). In the present study, the internal consistency coefficient of the femininity and masculinity subscales were 0.76 and 0.84, respectively.

The MAQ comprises 33-items divided into five subscales: (1) menstruation as a deliberating event (12 items), (2) menstruation as a bothersome event (6 items), (3) menstruation as a natural event (4 items), (4) anticipation and prediction of the onset of menstruation (4 items), and (5) denial of any effects of menstruation (7 items). The items are scored on a Likert scale (1: strongly disagree to 7: strongly agree) (14). In the current study, the alpha coefficient values of the five subscales ranged between 0.77 and 0.85.

Statistical analysis

Data were analyzed using SPSS v.18. Descriptive statistics were calculated where appropriate for each variable. The Kruskal-Wallis test and Mann-Whitney U test were used to examine the impact of gender-role orientation on the female university students' attitudes toward menstruation. $P<0.05$ was considered statistically significant.

Results

Eighteen recruited participants for the study were excluded because of failure to complete the questionnaire, resulting in a response rate of 94%. The participants' mean age was 21.8 (±2.2) years. The mean age at onset of menstruation was 12.81 (±1.49) years, the mean length of menstrual cycle was 6.43 (±1.39) days, and the mean menstrual frequency was 28.87 (±4.4) days. Most (71.6%) study participants had a regular menstrual pattern and the majority (88.3%) was single.

The mean scores on the MAQ subscales ranged from 3.7±1.35 to 5.6±1.3, indicating that most of the participants had natural to moderate attitudes toward menstruation (Table 1).

In order to determine the gender roles of feminine, masculine, androgynous and undifferentiated, masculine and feminine median scores were calculated. Median masculinity score was M: 5.36 and the median femininity score was F: 5.6.

In this study, 16.6% (n=47) of the participants were in the feminine gender role group, 16.6% (n=47) were masculine, 33.7% (n=95) were undifferentiated, and 33% (n=93) of the participants were in the androgynous gender role group.

There was a significant difference in the "menstruation as a natural event" subscale of the MAQ among the participants based on the BSRI – masculine, feminine, undifferentiated, and androgynous – ($p<0.05$) (Table 2).

As seen in Table 3, the undifferentiated group was significantly ($p<0.05$) less likely to perceive menstruation as a natural event than the androgynous, feminine, and masculine groups.

Discussion

The current study investigated the effect of gender-role orientation on attitudes toward menstruation in a sample

Table 1. Mean and standard deviation scores on the subscales of menstrual attitude questionnaire

Subscales	Mean	Standard deviation
Debilitating	4.7	1.3
Bothersome	4.1	1.53
Natural	5.4	1.07
Predictable	5.6	1.3
Denial	3.7	1.35

Table 2. Differences in attitudes toward menstruation based on gender role orientation

	Masculine	Feminine	Androgynous	Undifferentiated	Kruskal-Wallis	
MAQ subscales	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**	**χ^2, df=3**	**p value**
Debilitating	130.46	136.81	117.87	126.93	2.42	0.448
Bothersome	107.04	128.7	124.75	134.8	4.35	0.225
Natural	129.5	134.9	141.37	103.63	14.1	*0.003
Predictable	117	135.15	135.19	115.29	4.97	0.174
Denial	127.25	127.76	125.38	125.21	0.58	0.996

*Statistical significance, p<0.05; MAQ: Menstrual attitude questionnaire

Table 3. The Post-Hoc Mann-Whitney U test results

MAQ subscale	Gender-role types	Mann-Whitney U	Z	p value
Menstruation as a natural event	Feminine-masculine	747.000	-0.342	0.732
	Feminine-androgyny	1586.000	-0.633	0.527
	Masculine-androgyny	1490.000	-0.941	0.347
	Androgyny-undifferentiated	2587.000	-3.468	0.001*
	Feminine-undifferentiated	1263.000	-2.564	0.01*
	Masculine-undifferentiated	1321.000	-2.024	0.043*

*Statistical significance, p<0.05; MAQ: Menstrual attitude questionnaire

of female university students. When analyzing attitudes toward menstruation, the results showed that the highest and lowest mean scores on the MAQ subscales among the participants were the anticipation and prediction of the onset of menstruation and the denial of any effects of menstruation, respectively. This result is consistent with a previous study among women in the United States military (15). In another study by Guvenc et al. (16) among Turkish nursing students, the highest and lowest mean scores on the MAQ subscales were menstruation as a natural event and denial of any effects of menstruation, respectively. When participants were classified into one of four gender-role categories of BSRI, masculine, feminine, androgynous, or undifferentiated, results show that the percentage of the undifferentiated group was higher than other gender-role groups.

In a study by Mullis and McKinley (10), masculine was the most frequent gender-role type among a sample of female adolescents. These differences between studies could be due to different cultural, social, or religious backgrounds (13,17). In the present study, there was a significant difference in only one of the five subscales of the MAQ based on four gender-role categories of BSRI. Undifferentiated individuals were significantly less likely to perceive menstruation as a natural event than the other gender role types. This indicates that gender-role orientation is a small to moderate contributor to women's attitude toward menstruation.

A previous study by Chrisler (11) was conducted on two samples. Sample A included 11 men, aged 28-39 years, and 20 women, aged 30-45 years. Sample B comprised 19 men, aged 18-22 years, and 37 women, aged 18-23 years. The results showed that in sample A, gender orientation had no significant effect on attitudes toward menstruation. However, in sample B, undifferentiated and feminine college students were more likely to perceive menstruation as a bothersome event than the androgynous and masculine students; undifferentiated and masculine college students were more likely to perceive menstruation as a debilitating event than the androgynous and feminine students.

Several limitations in the study ought to be considered. This research was conducted among female students of medical sciences; the findings may not be same for other segments of the female population. Also, because the study has a cross-sectional design, it can only illuminate the current situation of the participants. Furthermore, this study relied on self-reports of gender-role orientation, and these reports may not have always been accurate.

In conclusion, in this study there was a significant difference in the “menstruation as a natural event” subscale of the MAQ among female university students based on four categories of BSRI (androgynous, undifferentiated, masculine, and feminine). The undifferentiated group was significantly less likely to perceive menstruation as a natural event than the other groups.

Ethics Committee Approval: *The ethics committee of Shahroud University of Medical Sciences.*

Informed Consent: *All students participating in the study signed informed consent forms.*

Peer-review: *Externally peer-reviewed.*

Financial Disclosure: *This work was supported by a grant (Grant No 9464) from Shahroud University of Medical Sciences.*

References

1. Verma P, Ahmad S, Srivastava RK. Knowledge and Practices about menstrual hygiene among higher secondary school girls. Indian Journal of Community Health 2013; 25: 265-71.
2. Negriff S, Dorn LD, Hillman JB, Huang B. The measurement of menstrual symptoms: factor structure of the menstrual symptom questionnaire in adolescent girls. J Health Psychol 2009; 14: 899-908.
3. Ghiasi A, Keramat A, Mollaahmadi L. The relationship between attitudes toward menstruation and perimenstrual symptoms among female students of Shahroud University of Medical Sciences, Northeast Iran. Shiraz E-Med J 2018; 19: 65714.
4. Chandra PS, Chaturvedi SK. Cultural Variations in Attitudes toward Menstruation. Can J Psychiatry 1992; 37: 196-8.
5. Lu ZJ. The relationship between menstrual attitudes and menstrual symptoms among Taiwanese women. J Adv Nurs 2001; 33: 621-8.
6. Chaturvedi SK, Chandra PS. Sociocultural aspects of menstrual attitudes and premenstrual experiences in India. Soc Sci Med 1991; 32: 349-51.
7. Brooks J, Ruble D, Clark A. College women's attitudes and expectations concerning menstrual related changes. Psychosom Med 1977; 39: 288-98.
8. Firat M, Kulakaç O, Oncel S, Akcan A. Menstrual Attitude Questionnaire: confirmatory and exploratory factor analysis with Turkish samples. J Adv Nurs 2009; 65: 652-62.
9. Hoerster KD, Chrisler JC, Rose JG. Attitudes toward and experience with menstruation in the US and India. Women Health 2003; 38: 77-95.
10. Mullis RL, McKinley K. Gender-Role Orientation of Adolescent Females: Effects on Self-Esteem and Locus of Control. J Adolesc Res 1989; 4: 506-16.
11. Chrisler JC. Age, gender-role orientation, and attitudes toward menstruation. Psychol Rep 1988; 63: 827-34.
12. Bem SL. The measurement of psychological androgyny. J Consult Clin Psychol 1974; 42: 155-62.
13. Aliakbari Dehkordi M. Gender type in Iranian women and the comparison of Their Emotional Intelligence and Mental Health International. Journal of Psychology 2012; 6: 119-43.
14. Brooks-Gunn J, Ruble DN. Men's and women's attitudes and beliefs about the menstrual cycle. Sex Roles 1986; 14: 287-99.
15. Trego LL, Jordan PJ. Military women's attitudes toward menstruation and menstrual suppression in relation to the deployed environment: development and testing of the MWATMS-9 (short form). Womens Health Issues 2010; 20: 287-93.
16. Guvenc G, Kilic A, Akyuz A, Ustunsoz A. Premenstrual syndrome and attitudes toward menstruation in a sample of nursing students. J Psychosom Obstet Gynaecol 2012; 33: 106-11.
17. Eswi AS, Elarousy W. Menstrual attitude and knowledge among Egyptian female adolescents. Journal of American Science 2012; 8: 555-65.

Does minimally invasive surgery reduce anxiety?

Evrim Bostancı Ergen[1], Yaşam Kemal Akpak[2], Çetin Kılıççı[1], Çiğdem Abide Yayla[1], Selçuk Ayas[1]

[1]Clinic of Gynecology Obstetrics and Reproductive Medicine, İstanbul Zeynep Kamil Woman and Child Diseases Training and Research Hospital, İstanbul, Turkey

[2]Clinic of Gynecology Obstetrics and Gynecology, University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Turkey

Abstract

Objective: To evaluate whether there were any differences in preoperative and postoperative anxiety in patients who underwent total laparoscopic hysterectomy (TLH) (n=37) and total abdominal hysterectomy (TAH) (n=37).

Material and Methods: All premenopausal patients who underwent TLH or TAH because of benign uterine disorders were enrolled. Anxiety status was assessed 6 hours before and after the operation using standardized validated questionnaires: State-Trait Anxiety Inventory.

Results: In the TAH group, the state anxiety level of the patients significantly increased, whereas there was a significant decrease in the TLH group. For the trait anxiety level, there was a statistically significant increase in the TAH group postoperatively. In the TLH group, trait anxiety levels decreased postoperatively. In the analysis of between-group differences, pre and postoperative the state anxiety level was higher in the TAH group. A statistically significant difference was determined between the groups in respect of the postoperative state anxiety levels ($p<0.05$), but not in the preoperative state anxiety levels ($p>0.05$). Statistically significant differences were determined between the groups in respect of education, occupation, and curettage rates ($p<0.05$).

Conclusion: Women undergoing TLH for benign uterine disease may have lower levels of preoperative and postoperative anxiety than women undergoing TAH. (J Turk Ger Gynecol Assoc 2019; 20: 142-6)

Keywords: Preoperative, postoperative, anxiety, total abdominal hysterectomy, total laparoscopic hysterectomy

Received: 22 May, 2018 **Accepted:** 6 July, 2018

Introduction

Hysterectomy is the second most common major surgical procedure applied to women of reproductive age and 90% of the procedures are for benign causes (1). It is known that most patients experience anxiety and fear at different levels before surgery and that anxiety increases during the operation (2,3). However, gynaecologic operations are specific to women, who are more sensitive and emotional so they constitute a specific study group. In this situation, patients fear that their body image will be destroyed, there are concerns related to sexuality, they are anxious about pain, there is the fear of not waking from anaesthesia, and a concern of loss of function (2). Just as much as the effect of anxiety on the patient's emotional state, anaesthesia complications such as nausea and vomiting have a negative effect on postoperative healing and length of hospital stay (4).

As the measurement and evaluation of anxiety is a difficult subject, it has been halted by many obstructions. Anxiety is a personal issue, so generalization could perpetuate an error and although it can be measured with questions and surveys in patients who are conscious, in those who are unconscious, even if it can be evaluated metabolically, it may not always be possible to reveal objective data (5). The most widely used test in medicine for the measurement of anxiety is the State-Trait Anxiety Inventory (STAI), which was developed by Spielberger et al. (6) and Öner (7).

Although abdominal and vaginal hysterectomies have been performed for many years, laparoscopic hysterectomy was first reported in 1989 (8). There has been increasing interest in

Address for Correspondence: *Evrim Bostancı Ergen*
e.mail: evrimbostanc6666@gmail.com ORCID: orcid.org/0000-0002-1634-6781

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2018.2018.0073

more minimally invasive surgical procedures during the past 20 years. In comparison with laparotomy, laparoscopic surgery has some advantages including lower rates of wound infections, shorter hospital stay, and a rapid return to work (9). There are studies comparing psychological well-being, sexuality, and quality of life after laparoscopic and abdominal hysterectomy (10-12), and there are studies comparing preoperative and postoperative anxiety in surgeries (13,14). However, to the best of our knowledge, there are no data showing how laparoscopic and abdominal hysterectomy affects pre and postoperative anxiety.

The aim of this study was to evaluate the effect of the type of surgery on the level of anxiety of the patient, through measurements of preoperative and postoperative anxiety levels and an evaluation of the factors affecting these levels.

Material and Methods

In this prospective comparative study, a total of 74 hysterectomies were performed on patients who met the study inclusion criteria between January 1st, 2013, and October 31st, 2016. Approval for the study was granted by the Local Ethics Committee.

This study was registered with the www.clinicaltrials.gov protocol registration system (NCT02938845). The patients were classified in two groups; group 1 included patients who underwent total laparoscopic hysterectomy (TLH) (n=37) and group 2 comprised patients who underwent total abdominal hysterectomy (TAH) surgery (n=37). The technical aspects of both types of hysterectomy were discussed with each patient, and the appropriate hysterectomy type was selected through mutual discussion. Anxiety was measured using the STAI questionnaire. The study was designed with 2 assessment points: 6 hours before surgery and 6 hours after surgery. All questionnaires were coded with an identifying number, and the respondents could not view their previous answers. Sample size calculation determined that 33 participants in each group would be sufficient to detect a significant difference on the STAI-TX2, when the mean STAI was set at 37 in the TAH group and at 37 in the TLH group, with an effect size of 0.309 for STAI, difference between standard deviations was 0.19, and difference between means was 0.91.

All hysterectomies were performed for benign reasons. Patients with malignancy, chronic opioid or non-steroidal anti-inflammatory drug use, or chronic pain conditions, a history of two or more caesarean sections, a history of abdominal surgery, autoimmune disease, a history of psychiatric disease, coagulation disorders, the presence of any known systemic or psychiatric disease, those receiving any regular sedative medication at the time of the procedure, those with intraoperatively diagnosed adnexal pathology requiring subsequent unilateral or bilateral oophorectomy, those taking preoperative or postoperative hormone-therapy, and those who were not able to communicate in Turkish were excluded from the study.

Preoperatively, all patients underwent gynecologic examination, medical histories were obtained, and transvaginal ultrasound and routine laboratory tests were performed. All procedures were performed by the same two equally skilled and experienced surgeons (>100 TLH and TAH surgeries) using an identical technique. Informed consent was obtained and all patients were admitted to hospital 1 day preoperatively. General anesthesia was used in all cases and all patients received preoperative antibiotic prophylaxis and anticoagulants during immobilization. All the patients were administered with the same postoperative analgesic procedure (Diclofenac 75 mg/3 mL solution for injection).

The STAI measures both state and trait anxiety. State anxiety (STAI-S) refers to a temporary emotional state related to a specific situation, whereas trait anxiety (STAI-T) represents anxiety as a relatively stable personality characteristic. Each scale has values ranging from 20 to 80, with higher scores representing more severe anxiety. The STAI has no established categories, but a cut-off score of 40 has been used to identify patients with high/very high anxiety. Validity and reliability studies of the Turkish versions of these instruments have been performed (7).

Statistical analysis

All statistical procedures were performed using SPSS 17.0 for Windows and Microsoft Excel 2010 software. The baseline characteristics of the participants are described with frequency analysis, where scale means are stated as mean ± standard deviation. The chi-square test was used to assess differences between demographic parameters. The Kolmogorov-Smirnov test was used to test the normality of distribution of data in the parameters. Between-group comparisons were made using the independent samples t-test, and the paired-samples t-test was used for within-group differences (pre-after tests). In the evaluation of demographic group- based differences, the independent samples t-test was used for two groups, and one-way ANOVA for more than two groups. The Levene test was used to define the homogeneity of variances. In cases where there was no homogenous variance, robust tests (Welch) were applied. A value of $p<0.05$ was accepted as statistically significant.

Results

The baseline characteristics of the TLH and TAH groups are shown in Table 1. Statistically significant differences were

determined between the groups in respect of education, occupation, and curettage rates ($p<0.05$).

Between and within-group differences in the preoperative and postoperative state and trait anxiety values are shown in Table 2. The within-group comparisons showed statistically significant differences in the mean TX1 values of both groups ($p<0.05$). In the TAH group, the state anxiety level (STAI-TX1) significantly increased, and in the TLH group, there was a significant decrease. The trait anxiety level (STAI-TX2) showed a statistically significant increase postoperatively in the TAH group and a decrease in the TLH group. However, this decrease was not statistically significant ($p>0.05$). In the between-group differences, it was found that the state anxiety level was higher in the TAH group both preoperatively and postoperatively. The postoperative STAI-TX1 differences were found to be statistically significant ($p<0.05$), but not the preoperative state anxiety differences ($p>0.05$). In the comparison of STAI-TX2 levels, the preoperative anxiety level was higher in the TLH group, and the postoperative STAI-TX1 level was higher in the TAH group. No statistically significantly difference was determined between the groups in respect of either the preoperative or postoperative STAI-TX2 levels ($p>0.05$) (Figure 1).

The preoperative state anxiety levels in the TAH group showed statistically significant differences based on occupation and income level of the patient ($p<0.05$). The postoperative state anxiety levels in the TAH group showed statistically significant differences based on income and the patients' place of residence ($p<0.05$). The preoperative trait anxiety level in the TAH group showed statistically significant differences based

Table 1. Baseline characteristics of the TAH and TLH groups

Parameters	TAH (n=37)	TLH (n=37)	p
Age (years)			
<45	11 (29.7)	13 (35.1)	0.595[b]
45-49	13 (35.1)	15 (40.5)	
>50	13 (35.1)	9 (24.3)	
Marital status			
Single	-	6 (16.2)	0.066[a]
Married	35 (94.6)	24 (64.9)	
Divorced	2 (5.4)	7 (18.9)	
Education			
Primary school	22 (59.5)	19 (51.4)	**0.010[b]**
High school	14 (37.8)	8 (21.6)	
University graduate	1 (2.7)	10 (27.0)	
Occupation			
Housewife	32 (86.5)	25 (67.6)	
Domestic worker	1 (2.7)	1 (2.7)	**0.041[a]**
Worker	3 (8.1)	7 (18.9)	
Other	1 (2.7)	4 (10.8)	
Income			
<2000 TL	13 (35.1)	19 (51.4)	0.460[a]
2001-3000 TL	22 (59.5)	14 (37.8)	
>3000 TL	2 (5.4)	4 (10.8)	
Place of residence			
Town	20 (54.1)	12 (32.4)	0.051[b]
Village	4 (10.8)	4 (10.8)	
City	13 (35.1)	21 (56.8)	
Curettage			
No	12 (32.4)	35 (94.6)	**<0.05[b]**
Yes	25 (67.6)	2 (5.4)	
Abortion			
No	18 (48.6)	23 (62.2)	0.242[b]
Yes	19 (51.4)	14 (37.8)	

[a]Chi-square test (Linear association); [b]Chi-square test; TLH: Total laparoscopic hysterectomy; TAH: Total abdominal hysterectomy

Table 2. Preop-postop state and trait anxiety levels between and within group differences

Parameters	TAH (n=37)	TLH (n=37)	p[a]
Preop STAI-TX1	44.95±4.83	43.57±4.49	0.208[c]
Postop STAI-TX1	48.81±5.64	39.62±5.44	**<0.05[c]**
p[b]	**<0.05[d]**	**<0.05[d]**	
Preop STAI-TX2	49.76±5.87	51.24±7.44	0.343[c]
Postop STAI TX2	51.97±5.84	50.84±7.13	0.456[c]
p[b]	**<0.05[d]**	0.242[d]	

[a]Between groups (TAH-TLH); [b]Within groups (preop-postop); [c]Independent sample t-test; [d]Paired-sample t-test; TLH: Total laparoscopic hysterectomy; TAH: Total abdominal hysterectomy; STAI-X1: State anxiety scale; STAI-X2: Trait anxiety scale

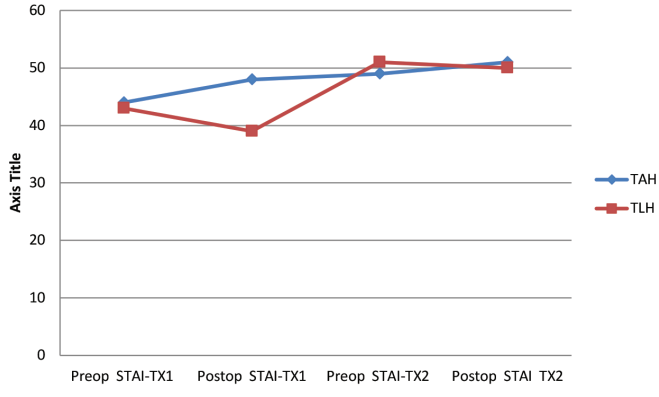


Figure 1. The graph shows the Preop-Postop state and trait anxiety levels between and within TAH and TLH groups

TLH: Total laparoscopic hysterectomy; TAH: Total abdominal hysterectomy; STAI-X1: State anxiety scale; STAI-X2: Trait anxiety scale

on income and the patients' place of residence ($p<0.05$). The trait anxiety levels in the TLH group showed no statistically significant differences based on the analyzed demographic parameters ($p>0.05$). The state anxiety levels in the TLH group showed statistically significant differences based on education, marital status, curettage and abortion history of the patients ($p<0.05$).

Discussion

In the last decade in particular, TAH and TLH operations have been compared in terms of many factors such as operating time, blood loss during surgery, complication rates, inflammatory response, febrile morbidity, length of stay in hospital, and the requirement for analgesia, but there has been insufficient evaluation in respect of preoperative and postoperative anxiety scores (15). In the current study, although the postoperative patient status (temporary state) and anxiety (general state) were observed to be greater than preoperatively following TAH procedures, a decrease was seen in the postoperative anxiety following TLH procedures compared with the preoperative score. When the postoperative scores were evaluated, a lower anxiety score was determined in the TLH group than in the TAH group. The demographic characteristics were determined to have had a lower effect on TAH procedures than on TLH procedures. It was observed in the TAH group that a higher occupation and income group reduced state anxiety and older age and a rural place of residence reduced trait anxiety. In the TLH group, no factor was observed that affected trait anxiety, but the marital status of the patient, low education levels, and no history of miscarriage or curettage were seen to reduce the level of preoperative state anxiety.

Apart from the several benefits of TLH (e.g., shorter hospital stay, better status on discharge, lower level of postoperative pain) previous studies have not been effective in researching psychological well-being (10,11). In a study that used a visual analogue scale rather than psychometric tests, evaluation was made of scores given from 1-100 daily from preoperative to 35 days postoperatively. From the results obtained, it was determined that there was no superiority of TLH over TAH in respect of patient well-being and mood (16). A meta-analysis conducted in 2014 reported results that were not consistent with the findings of the current study. It was stated that there was no relationship between depression, anxiety, and hysterectomies performed for benign gynaecologic reasons, and it was even reported that hysterectomy reduced symptoms of depression. It was concluded that the type of hysterectomy and surgical technique did not contribute to any psychological effects (17). The main problem of studies in general is the selection of heterogenous patient groups. The current study focussed more on the data of actual anxiety in the short-term, whereas the above-mentioned review evaluated the long-term relief of patients from pain, bleeding, and other symptoms. In the normal female population, the mean anxiety questionnaire evaluation points have been measured as 36.85 (18). The points in the current study were determined to be above this average. However, following TLH, the mean value of the tests evaluating general anxiety was found to be close to this reported average (39.62 ± 5.44).

In a study that researched preoperative risk factors, a history of psychiatric disease, previous diagnosis of cancer, presence of depressive symptoms, history of cigarettte smoking, type of operation, female sex, high level of education, and a history of surgery were evaluated as risk factors for preoperative anxiety (19). Similarly, in the current study, a low education level and no history of curettage were seen to cause a decrease in the preoperative anxiety scores of patients undergoing TLH.

The relationship between age and anxiety has been clearly proven, as it has been demonstrated that younger patients undergoing hysterectomy require more help and experience worse pathologic trauma (20). In the current study, older age was determined as a parameter that reduced trait anxiety in TAH procedures. Other previous studies have observed that married patients felt less anxiety post-hysterectomy due to the support of their husband (21). In the current study, although not at a statistically significant level, this was observed in the scores of the TAH group, whereas the opposite was determined in the TLH group.

A study that was conducted related to previous gynaecologic operations reported that anxiety was increased in patients who had previously felt pain (4), and in the current study, preoperative anxiety was reduced most notably in the TLH group in patients who had not previously undergone curettage. The main reasons for preoperative anxiety were found to be female sex and no history of surgery in studies that researched the reasons for preoperative anxiety in elective surgery (5). However, in contrast to the results of that review, which was conducted on general operations, in the current study of gynaecologic procedures in particular, no history of dilatation and curettage was evaluated as a reason for reduced anxiety.

That the anxiety scores in the preoperative patient group were determined to be higher than the average of the normal population can be attributed to a more unstable psychological structure in gynaecology patients, despite reports stating the opposite and this renders the selection of surgical method more important (2,17). If the type of procedure is evaluated regarding parameters other than psychometric tests, a study in Denmark reported that the hysterectomy type and histopathologic diagnosis had no affect on the prevalence of chronic pelvic

pain and this was found to be related more to the personal perception of pain from neurologic nerve damage (22). In a prospective, randomized, multicentre study, laparoscopically assisted vaginal hysterectomy was found to be statistically significantly superior to TAH in respect of early postoperative pain, length of stay in hospital, and patient satisfaction (23).

In a prospective study of 119 patients, a difference was determined between TLH and TAH in respect of psychometric evaluations conducted 5 weeks and 6 months postoperatively. In the same study, in contrast to general evidence, less anxiety and better emotional well-being was observed compared with the preoperative status at the same time points (11). In the current study, the patients were examined in a more acute phase and at close time points and lower anxiety scores were determined in the TLH group than in the TAH group when the postoperative scores were evaluated. Postoperative anxiety scores were also determined to be lower than the preoperative scores in the TLH group.

It can be concluded that laparoscopic surgery should be applied to selected patients because it has positive effects on reducing postoperative anxiety. There is a need for further, prospective studies of larger patient groups to determine which type of hysterectomy causes the least preoperative and postoperative anxiety.

Ethics Committee Approval: *Approved by Zeynep Kamil Ethics Commitee on 25/01/2013-025.*

Informed Consent: *Taken from all participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices - S.A.; Concept - S.A.; Design - E.B.E., S.A.; Data Collection or Processing - Ç.K., Ç.A.Y.; Analysis or Interpretation - E.B.E.; Literature Search - E.B.E.; Writing - Y.K.A., E.B.E.*

Conflict of Interest: *No conflict of interest was declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Keshavarz H, Hillis S, Kieke BA, Marchbanks AP. Hysterectomy surveillance - United States, 1994-1999. MMWR 2002; 51: 1-8.
2. Kürek Eken M, İlhan G, Temizkan O, Çelik EE, Herkiloğlu D, Karateke A. The impact of abdominal and laparoscopic hysterectomies on women's sexuality and psychological condition. Turk J Obstet Gynecol 2016; 13: 196-202.
3. Cheung LH, Callaghan P, Chang AM. A controlled trial of psycho-educational interventions in preparing Chinese women for elective hysterectomy. Int J Nurs Stud 2003; 40: 207-16.
4. Carr E, Brockbank K, Allen S, Strike P. Patterns and frequency of anxiety in women undergoing gynaecological surgery. J Clin Nurs 2006; 15: 341-52.
5. Mitchell M. Patient anxiety and modern elective surgery: a literature review. J Clin Nurs 2003; 12: 806-15.
6. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.
7. Öner N. Le Compte A: A handbook of State Trait Anxiety Inventory. Boğaziçi Üniversitesi, Istanbul: 1985.
8. Reich H, DeCaprio J, McGlynn F. Laparoscopic hysterectomy. J Gynecol Surg 2009; 5: 213-6.
9. Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2009: CD003677.
10. Ellström MA, Aström M, Möller A, Olsson JH, Hahlin M. A randomized trial comparing changes in psychological well-being and sexuality after laparoscopic and abdominal hysterectomy. Acta Obstet Gynecol Scand 2003; 82: 871-5.
11. Persson P, Wijma K, Hammar M, Kjølhede P. Psychological wellbeing after laparoscopic and abdominal hysterectomy a randomised controlled multicentre study. BJOG 2006; 113: 1023-30.
12. Nieboer TE, Hendriks JC, Bongers MY, Vierhout ME, Kluivers KB. Quality of life after laparoscopic and abdominal hysterectomy: a randomized controlled trial. Obstet Gynecol 2012; 119: 85-91.
13. Fathi M, Alavi SM, Joudi M, Joudi M, Mahdikhani H, Ferasatkish R, et al. Preoperative anxiety in candidates for heart surgery. Iran J Psychiatry Behav Sci 2014; 8: 90-6.
14. Hepp P, Hagenbeck C, Burghardt B, Jaeger B, Wolf OT, Fehm T, et al. Measuring the course of anxiety in women giving birth by caesarean section: a prospective study. BMC Pregnancy Childbirth 2016; 16: 113.
15. Clayton RD. Hysterectomy. Best Pract Res Clin Obstet Gynaecol 2006; 20: 73-87.
16. Persson P, Kjølhede P. Factors associated with postoperative recovery after laparoscopic and abdominal hysterectomy. Eur J Obstet Gynecol Reprod Biol 2008; 140: 108-13.
17. Darwish M, Atlantis E, Mohamed-Taysir T. Psychological outcomes after hysterectomy for benign conditions: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2014; 174: 5-19.
18. Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. Br J Clin Psychol 1983; 22: 245-9.
19. Caumo W, Schmidt AP, Schneider CN, Bergmann J, Iwamoto CW, Bandeira D, et al. Risk factors for preoperative anxiety in adults. Acta Anaesthesiol Scand 2001; 45: 298-307.
20. Cooper R, Mishra G, Hardy R, Kuh D. Hysterectomy and subsequent psychological health: findings from a British birth cohort study. J Affect Disord 2009; 115: 122-30.
21. Wang XQ, Lambert CE, Lambert VA. Anxiety, depression and coping strategies in post-hysterectomy Chinese women prior to discharge. Int Nurs Rev 2007; 54: 271-9.
22. Brandsborg B. Pain following hysterectomy: epidemiological and clinical aspects. Dan Med J 2012; 59: 4374.
23. Marana R, Busacca M, Zupie E, Garcea N, Paparella P, Catalano GF. Laparoscopically assisted vaginal hysterectomy versus total abdominal hysterectomy: a prospective, randomized, multicenter study. Am J Obstet Gynecol 1999; 180: 270-5.

Assesment of pregnancy outcomes among twin pregnancies with single fetal demise regarding chorionicity and fetal death time

Sevcan Arzu Arınkan, Resul Arısoy, Murat Api

Department of Obstetrics and Gynecology, İstanbul Zeynep Kamil Maternity and Pediatric Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: The objective of this study was to assess maternal and perinatal outcomes of twin pregnancies with single fetal demise in terms of chorionicity and fetal death time.

Material and Methods: All deliveries between January 2008 and July 2015 were reviewed retrospectively and 85 twin pregnancies with single fetal demise were included. These cases were grouped according to chorionicity and fetal death time.

Results: The incidence of single fetal demise was 4.7%. The mean delivery week was later in the dichorionic group (34.16±4.65) than in the monochorionic group (31.1±3.83). The ratios of deliveries before the 34th gestational week were 71.4% in monochorionics and 35% in dichorionics. Monochorionics had a 13 times greater risk for having delivery before the 37th gestational week and a 4 times greater risk for having delivery before the 34th gestational week compared with dichorionics. Furthermore, monochorionics had a 7 times greater risk for having abruptio placenta compared with dichorionics. The newborn intensive care unit admission ratios were 61.3% in dichorionics and 85.7% in monochorionics. Also, monochorionics had a 3.7 times greater risk for admission to newborn intensive care unit compared with dichorionics.

Conclusion: We recommend follow-up of twin pregnancies with single fetal demise in terms of premature birth, regardless of chorionicity. Also, close monitoring is recommended for monochorionic twin pregnancies with single fetal demise in terms of premature birth before 34 weeks of gestation, abruptio placenta, the need for neonatal intensive care, and respiratory distress syndrome. (J Turk Ger Gynecol Assoc 2019; 20: 147-53)

Keywords: Single twin demise, intrauterine death, twin pregnancy, perinatal outcomes, pregnancy outcomes

Received: 30 April, 2018 **Accepted:** 20 July, 2018

Introduction

In monozygotic twins compared with dizygotic twins pregnancy, the relative risks of exitus of two fetuses, single fetal demise, and neonatal exitus of a living fetus were reported as 20, 1.63, and 2.26, respectively (1). The incidence of single fetal demise after the 20th week among all twin pregnancies ranges from 2.6% to 6.2% (2). Chorionicity is an important factor in the ratio of intrauterine loss; the risk of fetal demise is greater in monochorionic twin pregnancies compared with dichorionic twin pregnancies (3). One of the main reasons for this situation is anastomoses of placental circulation and twin-to-twin transfusion syndrome risk (4). Intrauterine death of one fetus significantly increases the risk of mortality and morbidity of the living fetus (4). The management after single fetal demise is considered according to chorionicity and gestational age. The decision for delivery should be given by considering prematurity-related complications or morbidity and mortality that may be seen in the living fetus. If there are no other obstetric causes, delivery of dichorionic twin pregnancies with single fetus demise is not recommended before the 38th week (4). However, regular monitoring of living twin growth and follow-up in terms of hypertension, preeclampsia, and coagulopathy is recommended (5,6). In monochorionic

Address for Correspondence: *Sevcan Arzu Arınkan*
e.mail: pataraa96@gmail.com ORCID: orcid.org/0000-0002-0034-372X

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2018.2018.0053

twin pregnancies with single fetal demise, premature birth, intrauterin exitus or ischemic brain injury risks are present for the living twin (5,6). Ischaemic brain damage is considered to occur during or immediately after single fetal demise (6). For this reason, follow-up is recommended to avoid prematurity-related complications before 34 weeks in monochorionic pregnancies after single fetal demise (5). Barigye et al. (6) reported that the risk of fetal loss in the third trimester was also high in uncomplicated monochorionic pregnancies. They calculated that 23 cases in the 32nd week and 30 cases in 34th week should be delivered to save one fetus (7).

The objective of this study was to assess maternal and perinatal outcomes of twin pregnancies with single fetal demise in terms of chorionicity and fetal death time.

Material and Methods

All the deliveries between January 2008 and July 2015 were reviewed retrospectively and 85 twin pregnancies with single fetal demise were included in the study. Monoamniotic pregnancies, pregnancies with both fetal demises, singleton gestations, higher-order multiple gestations, pregnancies discontinued antenatal surveillance, and cases which chorinocity that was not exactly determined were excluded. Only pregnancies with complete outcome information were included. These cases were grouped according to chorionicity and fetal death time (0-13, 14-28, 29-34 gestational weeks). Chorionicity was determined using the earliest available ultrasound or confirmed by pathology. Gestational age was determined by the first day of a woman's last menstrual period and with the earliest ultrasound. Data were controlled for gestational age at delivery. Antenatal steroids and tocolitics were administered between 24 and 34 weeks if delivery was expected within 7 days. The criteria for deliveries were spontaneous preterm delivery, preeclampsia, deterioration of Doppler, and non-reassuring cardiotocography. Dichorionic diamniotic pregnancies were compared with monochorionic diamniotics regarding to preeclampsia, gestational diabetes (GDM), abruptio placenta, preterm delivery (34 and 37 gestational weeks), premature rupture of membranes (PROM), intrauterine growth retardation (IUGR). IUGR was diagnosed when esimated fetal weight was below the 10th percentile for gestational age. A 50 g oral glucose test was performed to all patients. If the screening test was positive (>140 mg/dL), a 3 hours' glucose tolerance test was performed. GDM diagnosis was confirmed with any two abnormal values (≥95-180-155-140 mg/dL). Also, intensive care unit admission, intracranial hemorrhage, phototherapy, polycythemia, respiratory distress syndrome (RDS), sepsis, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), and twin-to-twin syndrome (TTTS) were also studied. Capillary hematocrit was sampled at 12 hours after birth. Venous hematocrit was obtained from those with hematocrits more than 70%. Venous hematocrits more than 65% were accepted as polycythemic.

The study was approved by the Ethics and Clinical Investigation Committee. The Statistical Package for the Social Sciences (SPSS; Version 20.0, Chicago, IL, USA) was used for statistical analyses. Descriptive statistics are presented as mean ± standard deviation for normally distributed data, and as numbers and percentages for categorical data. The relationship between the categorical variables was examined using the chi-square test and Fisher's exact test. The results were evaluated with a confidence interval of 95%, and $p<0.05$ / $p<0.01$ was considered statistically significant. The Kolmogorov-Smirnov test was used for the assessment of the normality of data. The Mann-Whitney U test was used for data that were not normally distributed.

Results

Between January 2008 and July 2015, 1808 of a total of 77,204 deliveries were twins (2.34%); 85 twin pregnancies with single fetal demise were included in the study. Single fetal demise was seen in about 4.7% of pregnancies. The average age of patients participating in the study was 29±6 years. Seventy-four percent of cases (n=64) were diamniotic dichorionic twin pregnancies, and 26% (n=21) were diamniotic monochorionic twin pregnancies. In addition, 19% (n=16), 40% (n=34), and 41.2% (n=35) of fetal demise occured in the first, second, and third trimesters, respectively. The average gestational week for delivery was 34 weeks and birth weight was 2099±795 g.

The average gestational age for delivery in dichorionic twin pregnancies (34.3±4.6 weeks), which was higher than the average gestational age in monochorionics (32±4 weeks, p=0.009). The average birthweight was 2.222±835 g in dichorionic twin pregnancies and 1.836±627 g in monochorionic twin pregnancies (p=0.052).

Preeclampsia was observed in 27.4% (n=17) of the dichorionic twin pregnancy group and 28.6% (n=6) monochorionic twin pregnancies (p=0.919). The distribution of patients with preeclampsia in the dichorionic group was 35.3%, 41.2%, and 23.5% in that single fetal demise was seen in the first, second, and third trimesters, respectively. Monochorionic and dichorionic groups were compared according to preeclampsia and fetal death time and there was no statistically significant difference (p>0.05) (Table 1).

The incidence of abruptio placenta was higher in monochorionic twin pregnancies (19%) compared with dichorionic twin pregnancies (3.2%) and the incidence of abruptio placenta was 7 times higher in monochorionic twin

pregnancies compared with dichorionic twin pregnancies [odds ratio (OR): 7.05; p=0.033]. The distribution of pregnancy complications according to chorionicity is shown in Table 1.

Premature rupture of membranes was seen in 16.1% (n=10) of cases in the dichorionic group and in 9.5% (n=2) of cases in the monochorionic group. The incidence of IUGR was 11.3% (n=7) in the dichorionic group and 14.3% (n=3) in the monochorionic group. There was no statistically significant difference between monochorionic and dichorionic twin pregnancies in terms of the incidence of premature rupture of membranes, IUGR, and oligohydramnios (p>0.05). There was no statistically significant difference between the monochorionic and dichorionic groups according to the fetal death time in terms of incidence of IUGR and PROM (p>0.05). The distribution of pregnancy complications according to chorionicity and fetal death time are shown in Table 2.

The frequency of deliveries before the 37th gestational week after the death of one twin was found to be 13 times higher in monochorionic twin pregnancies than in dichorionics (OR: 13.33, p=0.002). The frequency of delivery before the 34th gestational week after the death of one twin was found to be 4 times higher in monochorionic twin pregnancies than in dichorionics (OR: 4.64, p=0.005). In the dichorionic group, there was a statistically significant difference in terms of time of fetal demise (34th week and 37th week) (p=0.012, p=0.002). In the dichorionic group, the rate of giving birth before the 37th gestational week was found to be higher in those with single fetal demise in the second trimester (81%) compared with the third trimester (59%) and first trimester (38%) (p=0.041) (Table 2).

The ratio of newborns whose 1-minute APGAR score was less than 7 was found higher in the monochorionic group (74%) compared with the dichorionic group (51%). Similarly, the ratio of patients whose 5-minute APGAR score was less than 7 was found higher in the monochorionic group (47.1%) compared with the dichorionic group (13.7%). Although the 5-minute APGAR score showed statistically significant differences according to chorionicity, there was no statistically significant difference for the 1-minute APGAR score (p=0.007 and p=0.086).

The need for neonatal intensive care was 61.3% in the dichorionic group and this ratio was 86% in the monochorionic group. The incidence of RDS was 25% and 47% in the dichorionic and monochorionic groups, respectively (p=0.095) (Table 3). The need for neonatal intensive care was 3.7 times greater in monochorionic pregnancies compared with dichorionic pregnancies (OR: 3.78, p=0.039).

The incidence of sepsis was 17.6% (n=6) in the dichorionic group, and 35.7% (n=5) in the monochorionic group. However, there was no statistically significant difference between the groups according to chorionicity in terms of sepsis, hypoglycemia

Table 1. Obstetric outcomes regarding chorionicity

Variables		n	%	OR	p
<37 week delivery, DC	-	24	40	13.33	0.002[b]**
	+	36	60		
<37 week delivery, MC	-	1	4.8		
	+	20	95.2		
Preeclampsia, DC	-	45	72.6		0.919[a]
	+	17	27.4		
Preeclampsia, MC	-	15	71.4		
	+	6	28.6		
Abruptio placenta DC	-	60	96.8	7.05	0.033[b]*
	+	2	3.2		
Abruptio olacenta, MC	-	17	81		
	+	4	19		
<34 week delivery, DC	-	39	65	8.36	0.005**[b]
	+	21	35		
<34 week delivery, MC	-	6	28.6		
	+	15	71.4		

[a]: Chi-square test, [b]: Fisher's exact test, DC: Dichorionic, MC: Monochorionic, OR: Odds ratio, *p<0.05, **p<0.01

Table 2. Obstetric outcomes regarding chorionicity and fetal death time

		Fetal death time			Test
		1st trimester	2nd trimester	3rd trimester	p[a]
		n	n	n	
<37 weeks delivery, DC	-	10	4	10	0.012*
	+	5	18	13	
<37 weeks delivery, MC	-	0	1	0	0.497
	+	1	8	11	
IUGR, DC	-	14	21	20	0.808
	+	1	3	3	
IUGR, MC	-	1	8	9	0.828
	+	0	1	2	
Preeclampsia, DC	-	9	17	19	0.302
	+	6	7	4	
Preeclampsia, MC	-	1	6	8	0.775
	+	0	3	3	
PROM, DC	-	12	20	20	0.847
	+	3	4	3	
PROM, MC	-	1	7	11	0.229
	+	0	2	0	

[a]: Chi-square test, DC: Dichorionic, IUGR: Intrauterine growth retardation, MC: Monochorionic, PROM: Premature rupture of membranes, *p<0.05

development, and phototherapy (p>0.05). The comparison of neonatal complications by chorionicities is shown in Table 3.

In the dichorionic group, the distribution of patients with neonatal intensive care needs was as follows: 52.6%, 34.2%, and 13.2% in the group with single fetal demise in the second, third, and first trimesters, respectively. In the monochorionic group, 55.6% of patients requiring neonatal intensive care were in the group with single fetal demise in the third trimester. There were statistically significant differences between the dichorionic and monochorionic groups accrding to time of single fetal demise in terms of frequency of neonatal intensive care need (p=0.006 and p=0.043). Neonatal outcomes and the distributions of pregnancies by time of fetal demise are shown in Table 4.

In the dichorionic group, 91% of patients with RDS were in the group with single fetal demise in the second trimester. In the monochorionic group, the distribution of patients with RDS was 75% and 25% in the group with single fetal demise in the second and third trimesters, respectively. There were statistically significant differences in terms of RDS according to fetal death time in the dichorionic and monochorionic groups (p=0.001 and p=0.008) (Table 4).

In the dichorionic group, the distribution of 21 patients who underwent phototherapy was as follows: 62% and 24% were in the group with single fetal demise in the second and third trimesters, respectively. This difference was statistically significant (p=0.005) (Table 4).

The mean hemoglobin level in fetuses after delivery was 49.83 g/dL. Polycythemia was identified in 6 patients. There was no statistically significant difference in terms of incidence of polycythemia by chorionicity. Three and one of four patients in the dichorionic group were in the group of single fetal demise in the first and third trimesters, respectively. This difference was found statistically significant (p=0.005).

BPD was monitored in a total of 4 newborns, 3 and 1 of the patients were dichorionic and monochorionic twin pregnancies, respectively. PDA was seen in 6 neonates (5 dichorionic, 1 monochorionic). Intracranial hemorrhage was detected in 5 patients including 3 and 2 patients in dichorionic and monochorionic groups, respectively. There was no significant difference between the groups in terms of intracranial hemorrhage, BPD, and PDA regarding chorionicity and fetal demise time (p>0.05). TTTS was identified in a total of 7 patients, 6 of them stage 1, and 1 one was stage 3. Laser ablation was performed to one patient.

Consumption coagulopathy was observed in no cases.

Table 3. Fetal outcomes regarding chorionicity

Variables		n	%	OR	p
NICU, DC	-	24	38.7	3.78	0.039[a]
	+	38	61.3		
NICU, MC	-	3	14.3		
	+	18	85.7		
Hypoglycemia, DC	-	47	85.5		0.314[a]
	+	8	14.5		
Hypoglycemia, MC	-	17	94.4		
	+	1	5.6		
Phototherapy, DC	-	33	61.1		0.677[a]
	+	21	38.9		
Phototherapy, MC	-	10	55.6		
	+	8	44.4		
RDS, DC	-	33	75		0.095[a]
	+	11	25		
RDS, MC	-	9	52.9		
	+	8	47.1		
Sepsis, DC	-	28	82.4		0.176[a]
	+	6	17.6		
Sepsis, MC	-	9	64.3		
	+	5	35.7		

[a]: Chi-square test, DC: Dichorionic, MC: Monochorionic, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome, *p<0.05

Table 4. Fetal outcomes regarding chorionicity and fetal death time

		Fetal death time			Test
		1st trimester	2nd trimester	3rd trimester	p[a]
Variables		n	n	n	
NICU, DC	-	10	4	10	0.006*
	+	5	20	13	
NICU, MC	-	1	1	1	0.043*
	+	0	8	10	
Phototherapy, DC	-	11	6	16	0.005*
	+	3	13	5	
Phototherapy, MC	-	1	3	6	0.512
	+	0	4	4	
RDS, DC	-	7	9	17	0.001**
	+	1	10	0	
RDS, MC	-	0	1	8	0.008*
	+	0	6	2	
Sepsis, DC	-	5	12	11	0.518
	+	1	4	1	
Sepsis, MC	-	0	1	8	0.052*
	+	0	3	2	

[a]: Chi-square test, DC: Dichorionic, MC: Monochorionic, NICU: Neonatal intensive care unit, RDS: Respiratory distress syndrome, *p<0.05, **p<0.01

Discussion

The risk of morbidity and mortality in living fetuses can be explained by hemodynamic temporary fluctuations between twins and the theories of embolism and coagulopathy between the chorions (8). It is proposed that this coagulopathy in the living twin can lead to infarctions, and cystic changes in renal, pulmonary, hepatic, splenic and neurologic systems (7). Single fetal demise in the second and third trimester was seen in approximately 0.5-6% of twin pregnancies (8). Consistent with the literature, in our study, single fetal demise was seen in approximately 4.9% of twin pregnancies, single fetal demise after the first trimester was seen in 4.01%. Although there are insufficient data about the adverse effects for the living twin after single fetal demise in the first trimester, this subject is still controversial. Sun et al. (9) detected lower birthweight in pregnancies with vanishing twin syndrome compared with single pregnancies in their. In addition, brain abnormalities have been shown in the living twin in monochorionic twins with single fetal demise in the first trimester (10,11).

Ong et al. (2) detected preterm birth before 34 weeks as 68% in monochorionic twins with single fetal demise and 57% in dichorionics in their systematic review. In addition, it has been reported that premature birth before 34 weeks was more common in monochorionic twin pregnancies with single fetal demise, but this difference was not statistically significant (2). Aslan et al. (12) reported without distinction of chorionicity the premature birth rate as 81.3% and 41.6% for the 37th and 32nd gestational weeks, respectively.

Frequency of preterm delivery as 46% and 43% among monochorionic and dichorionic twin pregnancies, respectively. They concluded that the difference between the groups was not statistically significant, but noted a negative correlation between the mean gestational week of fetal death and the mean gestational week at delivery. Furthermore, no significant correlation was found between the mean gestational week of fetal death and mean fibrinogen levels.

Giwnewer et al. (13) reported the rate of premature birth before the 37th and 34th weeks in diamniotic pregnancies with single fetal demise as 73.3% and 38.8%, respectively. Unlike in our study, we found a higher birth rate before 34 weeks in the monochorionic group. In addition, we detected that the frequency of deliveries before 37 weeks was 11 times greater in monochorionic twin pregnancies after single fetal demise than in dichorionics, and the frequency of delivery before 34 weeks was 4 times greater. In addition, we found the frequency of deliveries before 37 weeks of dichorionic twin pregnancies with single fetal demise in the second trimester (81%) higher than the third and first trimesters. Different from the literature, we found differences in the frequency of deliveries before both the 37th and 34th weeks according to chorionicity. Also, in addition to the information in the literature, we found the frequency of deliveries before 37 weeks in dichorionic pregnancies with single fetal demise in the second trimester was higher than pregnancies with single fetal demise in the third (28-34th gestational weeks) and first trimesters.

Giwnewer et al. (13) detected premature rupture of membranes as 6% in diamniotic twin pregnancies with single fetal demise in their study performed without discriminating chorionicity. Fichera et al. (14) reported PPROM in one patient in their dichorionic group at the 33rd gestational week. We found no statistically significant difference in terms of incidence of PROM by chorionicity.

Fichera et al. (14) detected preeclampsia in their study consisting of 23 cases of single fetal demise in the second and third trimesters in one (7.7%) patient in the monochorionics group, which consisted of 13 patients, and two (20%) in the dichorionic group of 10 patients. Aslan et al. (12) found preeclampsia in 3 (9.4%) of 32 cases in their study, which was performed without chorionicity discrimination. In the study conducted by Giwnewer et al. (13), mild and severe preeclampsia rates were detected as 8.6% and 5.2%, respectively, in diamniotic pregnancies with single fetal demise. In our study, the incidence of preeclampsia was higher in contrast to the literature. We observed no differences in terms of incidence of preeclampsia by chorionicity. Deveer et al. (15) detected preeclampsia in 2 patients, one of them was in the first trimester group and the other was in the group of first trimester and after the first trimester. In our study, we found no statistically significant difference in terms of incidence preeclampsia and PROM by fetal death time in monochorionic and dichorionic groups.

In the study conducted by Giwnewer et al. (13) abruptio placenta was detected as 0.09% in diamniotic pregnancies with single fetal demise, and 1.9% in the control group, which comprised diamniotic twin pregnancies. This difference was not statistically significant. In our study different from Giwnewer et al. (13), abruptio placenta rate was detected as 3.6% (n=2) in dichorionic twin pregnancies and 20% (n=4) in the monochorionic group. In addition, the incidence of abruptio placenta was more than 6 times higher in monochorionic twin pregnancies than in dichorionic twin pregnancies.

In the study conducted by Giwnewer et al. (13) intrauterine growth retardation was detected in 3.4% of fetuses in diamniotic pregnancies with single fetal demise and postpartum death was detected in 9.5% of diamniotic pregnancies with single fetal demise. Chelli et al. (16) assessed 33 cases with single fetal demise after the 26th gestational week, postpartum death was detected in 6 patients.

Giwnewer et al. (13) detected the average birthweight of diamniotic pregnancies with single fetal demise as 1953 g and the proportion of those with low birthweight (<2500 g) as 71.6%. In addition, the proportion of patients with 1-minute APGAR score less than 7 and 5-minute APGAR score less than 7 was found as 30% and 6.9%, respectively. In our study, the proportion of patients with 1-minute APGAR scores less than 7 in the dichorionic group (47.9%) was found to be lower than the monochorionic group (72.2%). In addition, the proportion of patients with 5-minute APGAR scores less than 7 in dichorionic group (15.2%) was found to be lower than the monochorionic group (43.8%). In our study, there was a statistically significantly difference in terms of 1-minute APGAR scores by chorionicity, but there was no statistically significantly difference in terms of 5-minute APGAR scores.

Deveer et al. (15) reported the need for neonatal intensive care in 5 of 38 patients in their study. All of these patients were in the group with single fetal demise after the first trimester. In our study, the risk of need for neonatal intensive care was 3.4 times higher in monochorionic pregnancies than in dichorionic pregnancies. Similar to the study conducted by Deveer et al. (15), we also found that 48,6%, 37.1%, and 14.3% of cases requiring neonatal intensive care in the dichorionic group were in the groups with single fetal demise in the second, third, and first trimesters, respectively. There was a statistically significant difference between the dichorionic and monochorionic groups in terms of the frequency of need for neonatal intensive care by fetal death time.

Reported that severe cerebral injury was diagnosed in 13 (26%) of 50 co-twins. They concluded that cerebral injury was due to hypoxic-ischemic injury resulting in cystic PVL, middle cerebral artery infarction or injury to basal ganglia, thalamus and/or cortex.

One of the most important outcome of fetuses in twin pregnancy with one IUFD is the neurologic condition of the surviving fetus, especially in monochorionic twins. Data about the MCA Doppler in the surviving fetus after one IUFD were not collected by chart reviews because only pregnancies with complete outcome information were included. This manuscript does not discuss these problems.

In our study, delivery before 37 and 34 weeks was found to be more frequent in monochorionic twin pregnancies with single fetal demise than in dichorionics. Furthermore, abruptio placenta, need for neonatal intensive care, and incidence of RDS were found to be higher in monochorionic twin pregnancies with single fetal demise than in dichorionic twin pregnancies with single fetal demise. We found the average gestational age at delivery as 34 weeks. We recommend follow-up of twin pregnancies with single fetal demise in terms of premature birth, regardless of chorionicity. Also, close monitoring is recommended for monochorionic twin pregnancies with single fetal demise in terms of premature birth before 34 weeks of gestation, abruptio placenta, the need for neonatal intensive care, and RDS.

Ethics Committee Approval: *İstanbul Zeynep Kamil Maternity and Pediatric Training and Research Hospital (Approval Number: 19.09.2014/164).*

Informed Consent: *Because this study is retrospective, informed consent was not taken.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – R.A.; Design – R.A.; Supervision – M.A.; Materials – S.A.A.; Writer - S.A.A.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. West CR, Adi Y, Pharoah PO. Fetal and infant death in mono- and dizygotic twins in England and Wales 1982-91. Arc Dis Childhood Fetal Neonatal Ed 1999; 80: 217-20.
2. Ong SS, Zamora J, Khan KS, Kilby MD. Prognosis for the co-twin following single-twin death: a systematic review. BJOG 2006; 113: 992-8.
3. Walker MC, Murphy KE, Pan S, Yang Q, Wen SW. Adverse maternal outcomes in multifetal pregnancies. BJOG 2004; 111: 1294-6.
4. Chauhan SP, Scardo JA, Hayes E, Abuhamad AZ, Berghella V. Twins: prevalence, problems, and preterm births. Am J Obstet Gynecol 2010; 203: 305-15.
5. Hillman SC, Morris RK, Kilby MD. Single twin demise: consequence for survivors. Semin Fetal Neonatal Med 2010; 15: 319-26.
6. Barigye O, Pasquini L, Galea P, Chambers H, Chappell L, Fisk NM. High risk of unexpected late fetal death in monochorionic twins despite intensive ultrasound surveillance: a cohort study. PLoS Med 2005; 2: 172.
7. Cunningham FG WJ. Williams Obstetrics. 23rd ed. New York: McGraw-Hill Medical; 2010.
8. Cleary-Goldman J, D'Alton M. Management of single fetal demise in a multiple gestation. Obstet Gynecol Surv 2004; 59: 285-98.
9. Sun L, Chen Z, Liu J, Fu J. Obstetric and neonatal outcomes of vanishing twin syndrome. Nan fang yi Ke SD Xue Xue Bao 2014; 34: 1537-40.
10. Takahashi H, Baba Y, Matsubara S. Brain damage of surviving co-twin following single fetal death in monochorionic diamniotic twin pregnancy at 8-9 weeks' gestation. Acta Obstet Gynecol Scand 2014; 93: 1336.
11. Weiss JL, Cleary-Goldman J, Tanji K, Budorick N, D'Alton ME. Multicystic encephalomalacia after first-trimester intrauterine fetal death in monochorionic twins. Am J Obstet Gynecol 2004; 190: 563-5.
12. Aslan H, Gul A, Cebeci A, Polat I, Ceylan Y. The outcome of twin pregnancies complicated by single fetal death after 20 weeks of gestation. Twin Res 2004; 7: 1-4.

13. Giwnewer U, Wiznitzer A, Friedler JM, Sergienko R, Sheiner E. Intrauterine fetal death of one twin of diamnionic twins is associated with adverse perinatal outcome of the co-twin. J Matern Fetal Neonatal Med 2012; 25: 1453-5.
14. Fichera A, Zambolo C, Accorsi P, Martelli P, Ambrosi C, Frusca T. Perinatal outcome and neurological follow up of the cotwins in twin pregnancies complicated by single intrauterine death. Eur J Obstet Gynecol Reprod Biol 2009; 147: 37-40.
15. Deveer R, Engin-Ustun Y, Mert I, Sarikaya E, Bozkurt S, Deveer M, et al. Twin pregnancies with single fetal death: analysis of 38 cases. Fetal Pediatr Pathol 2013; 31: 71-5.
16. Chelli D, Methni A, Boudaya F, Marzouki Y, Zouaoui B, Jabnoun S, et al. Twin pregnancy with single fetal death: etiology, management and outcome. J Gynecol Obstet Biol Reprod (Paris) 2009; 38: 580-7.

Prognostic factors, survival outcomes, and surgical practices when dealing with uterine sarcomas: 8 years' clinical experience

Elif Meseci[1], Mehmet Murat Naki[2]

[1]Clinic of Obstetrics and Gynecology, Acıbadem Kozyatağı Hospital, İstanbul, Turkey
[2]Department of Obstetrics and Gynecology, Acıbadem University School of Medicine, İstanbul, Turkey

Abstract

Objective: To determine the clinical and pathologic characteristics, prognostic factors, surgical practice, adjuvant therapies, and survival outcomes of patients with uterine sarcoma diagnosed and treated in our institution.

Material and Methods: Patients diagnosed and treated for uterine sarcomas at our institution from 2009 to 2017 were retrospectively evaluated. All histologic slides from the specimens underwent a thorough pathologic review by a gynecologic pathologist. The following variables were assessed: age, family history of cancer, smoking status, age of menarche, parity, age at first delivery, related symptoms, clinical staging, histologic type, treatment received, disease-free period, and the time and site of recurrence, as well as treatment of the latter and overall survival.

Results: Ten patients were diagnosed as having leiomyosarcoma, a further 10 patients had malignant mixed mullerian tumors, and five had endometrial stromal sarcoma; the remaining nine patients had other tumors. At the end of our study, 12 (35.3%) patients were alive and in remission, four (11.8%) were alive with disease, 10 (29.4%) were lost to follow-up, and eight (23.5%) had died. The mean survival time was 80.92 months, and the 2-year survival rate was 75.6%. We found that survival was significantly shorter in the presence of lymph node involvement, residual tumor, and recurrence.

Conclusion: This study serves to inform physicians about the outcome of various uterine sarcomas that were diagnosed and managed at our center. We found that 35.3% of our patients were alive and in remission, 11.8% were alive with disease, 29.4% were lost to follow-up, and 23.5% of patients died. (J Turk Ger Gynecol Assoc 2019; 20: 154-64)

Keywords: Carcinosarcoma, leiomyosarcoma, prognosis, sarcoma, survival

Received: 15 April, 2019 **Accepted:** 9 July, 2019

Introduction

Uterine sarcomas are malignant tumors that originate from the mesodermal tissues (muscle and supportive tissues) of the uterus. They are usually of heterogeneous characteristics and represent a small group among the malignant neoplasms of the uterus (1,2). The prevalence of uterine sarcoma is between 1.5 and 3 cases per 100,000 for Caucasians and Afro-Americans, respectively (3).

The World Health Organization (WHO) classifies uterine sarcomas into two types: (1) malignant mesenchymal tumors, and (2) mixed epithelial and mesenchymal tumors. Pure mesenchymal tumors are further subclassified as leiomyosarcoma (LMS), low- and high-grade endometrial stromal sarcomas (LG-ESS and HG-ESS, respectively) and undifferentiated uterine sarcoma (UUS) (4). Among these, LMS is the most frequently seen type with a frequency of 60-70% among all uterine sarcomas; the remaining 3 subtypes (LG-ESS, HG-ESS and UUS) collectively comprise another 10% of uterine sarcomas (5). Mixed tumors comprise adenosarcoma (AS), rhabdomyosarcoma (RMS), and perivascular epithelioid cell

Address for Correspondence: *Elif Meseci*
e.mail: elfmsc@yahoo.com ORCID: orcid.org/0000-0002-6881-5009

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2019.0061

neoplasms (PEComa) (4,6). These are much rarer, collectively representing around 5% of all uterine sarcomas (7).

Although dependent on tumor type, uterine sarcomas are most commonly seen between the 5th and 7th decade of life. Risk factors for uterine sarcoma development have been identified as obesity, diabetes, having undergone previous pelvic irradiation therapy and/or tamoxifen treatment, and having excessively high or unopposed estrogen levels (8-12). However, data are scarce on this topic due to the rarity of uterine sarcomas; therefore, there is no universal consensus on risk factors, optimal therapeutic approaches, and the frequency of poor outcomes. Our aim in this study was to determine the clinical/pathologic characteristics, prognostic factors, surgical practices, adjuvant therapies, and survival outcomes of patients who received treatment for uterine sarcoma at our institution.

Material and Methods

Our study was a retrospective evaluation of the medical files of patients who were diagnosed as having uterine sarcomas and treated at our institution from 2009 to 2017. The study was approved by the local Ethics Committee (reference number: 2017-16/28). All histologic slides underwent a thorough pathologic review by a gynecologic pathologist. Staging was performed according to the current International Federation of Gynecology and Obstetrics (FIGO) criteria (13).

Our patient group also included those who had been diagnosed as having uterine carcinosarcomas [also called malignant mixed mullerian tumors (MMMT)] because these tumors are now classified within the uterine carcinoma group, having previously been considered as uterine sarcomas (14,15). Also of note, four patients in which endometrial sampling had not detected malignancy, but hysterectomy results were conclusive of uterine carcinoma (1 LMS, 1 MMMT, 1 LG-ESS, 1 AS), were also included in the study. Two patients who were initially diagnosed as having LG-ESS, but were found to have endometrial stromal nodule and high-grade serous carcinoma after hysterectomy, were excluded from the study. Patients with metastatic sarcoma from other gynecologic sites and those who had incomplete data for demographic analyses were excluded from the study.

All remaining patients who were confirmed to have uterine sarcomas were included in the study; however, those without sufficient data in terms of clinical findings, pathologic results, follow-up studies, and treatment approach/results were excluded from the survival analysis. The following characteristics of all patients were assessed and recorded: age, parity, age at first delivery, age at menarche, family history of cancer, smoking status, and other related symptoms. In regard to disease characteristics, the following were assessed from medical records: clinical stage, histologic type, treatment approach, disease-free period, overall survival (OS), and the time and site of recurrence.

Patients were grouped according to the following parameters: tumor size (≤5 cm, >5 cm), FIGO stage [early (I-II), advanced (III-IV)], histologic grade (low, moderate, high), myometrial invasion (absent, <50%, ≥50%). In addition, Ki-67 positivity was also evaluated on a present/absent basis with a cut-off of 14%.

The treatment plan of each patient was structured according to the most recent protocols and guidelines with regard to tumor stage/grade, age, and cell type. The use of adjuvant therapies such as chemotherapy, radiotherapy or immunotherapy were also based on the most recent guidelines. All surgical interventions were performed by our Gynecology Department and lymphadenectomies were performed according to the discretion of the primary surgeon in each operation.

Disease free survival (DFS) was defined as the period of time (in months) from diagnosis to either recurrence or last follow-up. OS was defined as the period of time (also in months) between diagnosis to either the date of death or last follow-up.

Statistical analysis

All statistical analyses were performed using the SPSS version 21 software for the Windows operating system (IBM, Armonk, NY, USA). Continuous variables are given as mean ± standard deviation, and categorical variables are presented with frequency (n) and percentage (%). The DFS and OS analyses were performed using the Kaplan-Meier method. The comparison of survival times between groups was performed using the log-rank test. Cox-regression analysis with the Backward conditional method was used to determine the effects of continuous and categorical variables on survival times. P values less than 0.05 were accepted to show statistical significance.

Results

The mean age of the 34 patients included in our study was 52.56±14.47 years. Ten patients had LMS, 10 patients had MMMT, five patients had ESS, and nine patients had other types of tumors (5 with AS, 3 with UUS, 1 with embryonal rhabdomyosarcoma). Patients with MMMT were found to have a higher mean age compared with the other groups (62.40±7.97 years vs 49.80±5.87 years in LMS, 39.60±13.22 years in ESS, and 51.89±20.74 years in other sarcomas). Age difference was only significant when the MMMT and ESS groups were compared (p=0.016). The mean follow-up duration of the patients was 31.1±31.1 months.

FIGO staging revealed that 22 patients (64.7%) were stage I, seven patients (20.6%) were stage II, one patient (2.9%) was stage III, and four patients (11.8%) were stage IV. The

majority of our patients (67.6%) were post-menopausal and had presented with bleeding (73.5%). The median primary tumor size was 6 cm (minimum-maximum: 2-15 cm). There were no significant differences between the groups in regard to tumor size (p=0.845). Nineteen patients had undergone pelvic and/or paraaortic lymph node dissection and only one patient (in the MMMT group) was found to have a positive lymph node. Nineteen (55.9%) patients received at least one kind of adjuvant therapy; six received adjuvant chemotherapy, five received radiotherapy, two received hormono therapy, and six received chemotherapy and radiotherapy in sequence. The most common chemotherapy drugs used were carboplatin + paclitaxel. Three patients were found to have residual tumor after surgery, and 14 patients had recurrence. The pelvic peritoneum was the most common site of recurrence in these patients. At the final follow-up, 12 (35.3%) patients were alive and in remission, four (11.8%) were alive with disease, 10 (29.4%) had been lost to follow-up, and 8 (23.5%) had died (Table 1).

The mean DFS was 61.21±11.11 months (Figure 1). DFS was significantly higher for patients with early FIGO stages (p=0.030). Tumors with high histologic grade had shorter DFS times compared with the low and moderate grades (p=0.005) (Figure 2). We found that DFS was significantly decreased in patients with lymphovascular involvement (p=0.015) and those with positive lymph nodes (p<0.001). We also found that those with residual tumor and positive Ki-67 indexes had shorter DFS; however, these results were not found to be significant. Receiving adjuvant therapy was found to have no significant effect on DFS (p=0.490) (Table 2).

The mean survival time was 80.92±11.46 months and the 2 year survival rate was 75.6% (Figure 3). Survival times were significantly shorter in patients who were found to have positive lymph nodes (p=0.048), those with residual tumor (p<0.001), and those with recurrence (p=0.004) (Figure 4). We also found that patients with at least one parity, early (FIGO I and II) stages, and low histologic grade had longer survival times overall, but these results were not statistically significant (Table 3).

After performing the Cox regression analysis, we found that age and parity had no significant effect on DFS times. However, those who were older at menarche had a 2.2-times higher risk for recurrence and those who were older at first delivery were found to have a 1.9-fold greater risk for recurrence. Additionally, larger tumor size also incurred a 1.5-fold higher (for each cm)

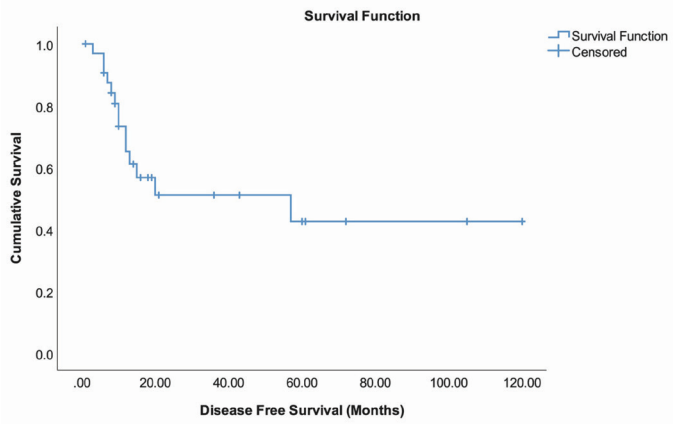


Figure 1. Disease-free survival times of patients

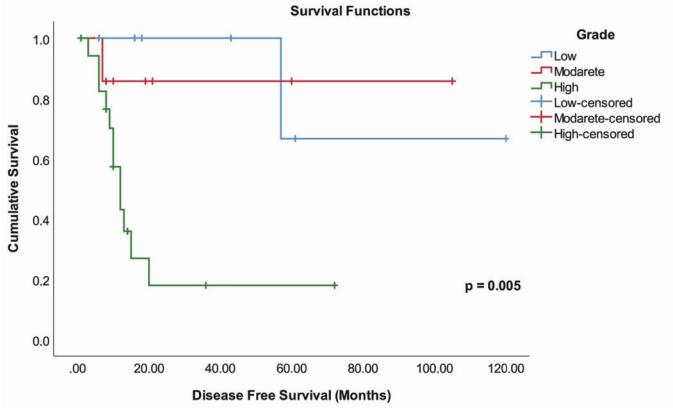


Figure 2. Disease-free survival times by tumor grade

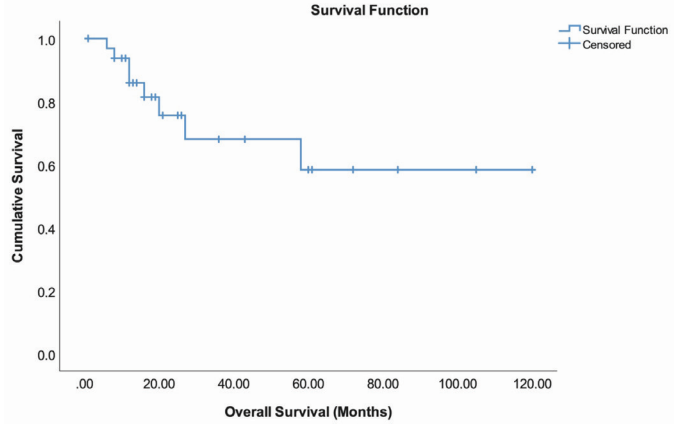


Figure 3. Overall survival times of patients

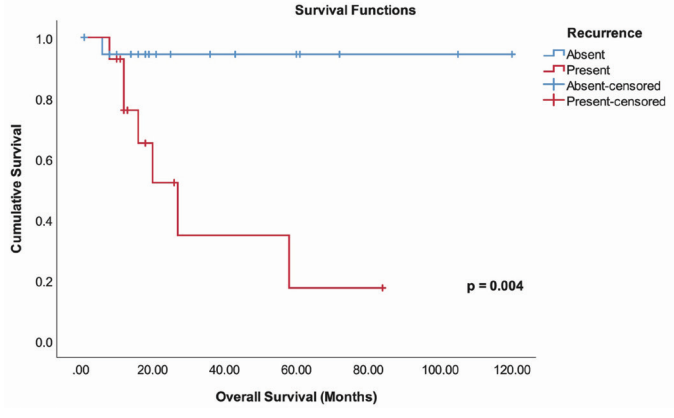


Figure 4. Overall survival times by recurrence

Table 1. Summary of our variables

	All patients (n=34)	LMS (n=10)	MMMT (n=10)	ESS (n=5)	Others (n=9)	p
Age	52.56±14.47	49.80±5.87	62.40±7.97	39.60±13.22	51.89±20.74	0.021
Family history	9 (26.5%)	4 (40.0%)	1 (10.0%)	2 (40.0%)	2 (22.2%)	0.409
Smoker	8 (23.5%)	2 (20.0%)	4 (40.0%)	1 (20.0%)	1 (11.1%)	0.497
Age at menarche	11.53±1.52	11.40±0.97	11.60±1.58	11.40±1.67	11.67±2.06	0.979
Age of menopause	49.30±2.53	48.17±1.60	49.80±2.97	49.00±1.41	49.80±2.95	0.641
Parity						
0	8 (23.5%)	2 (20.0%)	1 (10.0%)	4 (80.0%)	1 (11.1%)	0.090
1	4 (11.8%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	
2	13 (38.2%)	4 (40.0%)	6 (60.0%)	0 (0.0%)	3 (33.3%)	
≥3	9 (26.5%)	2 (20.0%)	3 (30.0%)	1 (20.0%)	3 (33.3%)	
Age at first delivery	22.19±3.16	23.00±2.62	21.89±3.37	20.00±0.00	22.0±3.78	0.795
Menopause status						
Non-menopausal	11 (32.4%)	4 (40.0%)	0 (0.0%)	3 (60.0%)	4 (44.4%)	0.060
Menopausal	23 (67.6%)	6 (60.0%)	10 (100.0%)	2 (40.0%)	5 (55.6%)	
Body mass index	26.33±4.10	25.63±3.25	28.92±4.70	24.10±3.26	25.46±3.79	0.098
Chronic disease	18 (52.9%)	5 (50.0%)	7 (70.0%)	2 (40.0%)	4 (44.4%)	0.615
Tumor size	6 (2-15)	5.75 (2-15)	6 (4-8)	5.4 (3-11)	4.7 (2-13)	0.845
Symptoms						
Bleeding	25 (73.5%)	5 (50.0%)	9 (90.0%)	3 (60.0%)	8 (88.9%)	0.082
Pain	7 (20.6%)	4 (40.0%)	1 (10.0%)	2 (40.0%)	0 (0.0%)	
Detected incidentally	2 (5.9%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	
Preop Bx						
Benign	6 (26.1%)	1 (16.7%)	2 (22.2%)	1 (50.0%)	2 (33.3%)	0.776
Malign	17 (73.9)	5 (83.3%)	7 (77.8%)	1 (50.0%)	4 (66.7%)	
Preop tumor marker						
Positive	3 (8.8%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	9 (100.0%)	0.048
Negative	31 (91.2%)	10 (100.0%)	7 (70.0%)	5 100.0%)	0 (0.0%)	
FIGO stage						
I	22 (64.7%)	8 (80.0%)	5 (50.0%)	3 (60.0%)	6 (66.7%)	0.650
II	7 (20.6%)	1 (10.0%)	3 (30.0%)	2 (40.0%)	1 (11.1%)	
III	1 (2.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	
IV	4 (11.8%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	2 (22.2%)	
Histologic grade						
Low	7 (21.2%)	1 (10.0%)	0 (0.0%)	4 (80.0%)	2 (25.0%)	0.016
Moderate	8 (24.2%)	3 (30.0%)	2 (20.0%)	0 (0.0%)	3 (37.5%)	
High	18 (54.5%)	6 (60.0%)	8 (80.0%)	1 (20.0%)	3 (37.5%)	
Myometrial invasion						
Absent	7 (24.1%)	2 (25.0%)	2 (22.2%)	2 (66.7%)	1 (11.1%)	0.202
<50%	12 (41.4%)	5 (62.5%)	2 (22.2%)	0 (0.0%)	5 (55.6%)	
≥50%	10 (34.5%)	1 (12.5%)	5 (55.6%)	1 (33.3%)	3 (33.3%)	
Mitotic index						
Positive	10 (29.4%)	9 (90.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	0.006
Negative	24 (61.6%)	1 (10.0%)	10 (100.0%)	5 (100.0%)	8 (88.9%)	

Table 1. Continued

	All patients (n=34)	LMS (n=10)	MMMT (n=10)	ESS (n=5)	Others (n=9)	p
Lymphovascular involvement	13 (41.9%)	3 (33.3%)	5 (50.0%)	2 (40.0%)	3 (42.9%)	0.908
Lymph node status						
Positive	1 (2.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0.613
Negative	18 (53.0%)	5 (50.0%)	6 (60.0%)	3 (60.0%)	4 (44.4%)	
No lymphadenectomy	15 (44.1%)	5 (50.0%)	3 (30.0%)	2 (40.0%)	5 (55.6%)	
Adnexa involvement	6 (18.8%)	1 (10.0%)	3 (30.0%)	1 (20.0%)	1 (14.3%)	0.699
Cervical involvement	7 (21.9%)	2 (20.0%)	4 (40.0%)	1 (20.0%)	0 (0.0%)	0.271
Omental involvement	2 (9.5%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0.219
Pelvic wash						
Positive	1 (2.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0.613
Negative	18 (52.9%)	4 (40.0%)	6 (60.0%)	2 (40.0%)	6 (66.7%)	
Not applied	15 (44.1%)	6 (60.0%)	3 (30.0%)	3 (60.0%)	3 (33.3%)	
Residual tumor						
Present	3 (12.5%)	1 (14.3%)	1 (12.5%)	0 (0.0%)	1 (20.0%)	0.838
Absent	21 (87.5%)	6 (85.7%)	7 (87.5%)	4 (100.0%)	4 (80.0%)	
Adjuvant therapy						
Not done	15 (44.1%)	6 (60.0%)	4 (40.0%)	1 (20.0%)	4 (44.4%)	0.246
Chemotherapy	6 (17.6%)	2 (20.0%)	2 (20.0%)	0 (0.0%)	2 (22.2%)	
Radiotherapy	5 (14.7%)	1 (10.0%)	2 (20.0%)	1 (20.0%)	1 (11.1%)	
Chemotherapy + Radiotherapy	6 (17.6%)	1 (10.0%)	2 (20.0%)	1 (20.0%)	2 (22.2%)	
Hormono therapy	2 (5.9%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	
Chemotherapy						
Not done	19 (61.3%)	5 (62.5%)	6 (60.0%)	4 (80.0%)	4 (50.0%)	0.533
Vinorelbine + Gemsitabin	1 (3.2%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Carboplatin + Paclitaxel	6 (19.4%)	0 (0.0%)	4 (40.0%)	1 (20.0%)	1 (12.5%)	
Doxorubicin	2 (6.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Dactinomycin + Vincristine	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Other multiagent regimens	2 (6.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Radiotherapy						
Not done	20 (64.5%)	6 (75.0%)	6 (60.0%)	3 (60.0%)	5 (62.5%)	0.889
Brachytherapy	3 (9.7%)	0 (0.0%)	1 (10.0%)	1 (20.0%)	1 (12.5%)	
Pelvic RT	5 (16.1%)	1 (12.5%)	2 (20.0%)	0 (0.0%)	2 (25.0%)	
Brachytherapy + Pelvic RT	3 (9.7%)	1 (12.5%)	1 (10.0%)	1 (20.0%)	0 (0.0%)	
HRT	2 (5.9%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	0.006
Recurrence	14 (41.2%)	6 (60.0%)	5 (50.0%)	1 (20.0%)	2 (22.2%)	0.257
Site of recurrence						
Pelvic periton	6 (42.9%)	2 (33.3%)	3 (60.0%)	0 (0.0%)	1 (50.0%)	0.486
Lung	3 (21.4%)	1 (16.7%)	1 (20.0%)	1 (100.0%)	0 (0.0%)	
Others	5 (35.7%)	3 (50.0%)	1 (20.0%)	0 (0.0%)	1 (50.0%)	
Ki-67						
Positive	16 (47.1%)	7 (70.0%)	3 (30.0%)	2 (40.0%)	5 (55.6%)	0.333
Negative	18 (52.9%)	3 (30.0%)	7 (70.0%)	3 (60.0%)	4 (44.4%)	

Table 1. Continued

	All patients (n=34)	LMS (n=10)	MMMT (n=10)	ESS (n=5)	Others (n=9)	p
Follow-up						
Alive, remission	12 (35.3%)	2 (20.0%)	3 (30.0%)	4 (80.0%)	3 (33.3%)	0.263
Alive with disease	4 (11.8%)	1 (10.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	
Lost to follow-up	10 (29.4%)	4 (40.0%)	2 (20.0%)	0 (0.0%)	4 (44.4%)	
Death	8 (23.5%)	3 (30.0%)	2 (20.0%)	1 (20.0%)	2 (22.2%)	

LMS: Leiomyosarcoma, MMMT: Malignant mixed mullerian tumor, ESS: Endometrial stromal sarcoma, Preop Bx: Preoperative biopsy, FIGO: International Federation of Obstetrics and Gynecology, HRT: Hormone replacement therapy, RT: Radiotherapy

Table 2. Disease-free survival times (months) with Kaplan Meier method and comparisons of groups using the Log-rank test for categorical variables

	n	Recurrence	Mean	Standard error	95% Confidence interval		p
					Lower	Upper	
Disease-free survival	34	14	61.21	11.11	39.42	82.99	N/A
Smoking status							
Smoker	8	3	41.67	12.41	17.35	65.98	0.802
Non-smoker	26	11	58.85	12.88	33.60	84.11	
Menopause status							
Non-menopausal	11	3	86.60	16.42	54.41	118.79	0.184
Menopausal	23	11	30.16	6.03	18.35	41.98	
Chronic disease							
Present	18	7	32.65	7.42	18.11	47.20	0.748
Absent	16	7	69.92	14.14	42.21	97.62	
Tumor size							
≤5 cm	12	3	85.06	16.94	51.85	118.26	0.076
>5 cm	22	11	29.67	6.11	17.67	41.63	
FIGO stage							
Early (I-II)	29	11	66.87	11.79	43.76	89.98	**0.030**
Advanced (III-IV)	5	3	9.40	1.95	5.58	13.22	
Histologic type							
Leiomyosarcoma	10	6	34.88	9.51	16.24	53.53	0.284
MMMT	10	5	22.10	8.91	4.64	39.56	
ESS	5	1	50.60	9.30	32.37	68.83	
Others	9	2	85.11	21.38	43.20	127.03	
Histologic grade							
Low	7	1	99.00	17.15	65.39	132.61	**0.005**
Moderate	8	1	91.00	12.97	65.60	116.41	
High	18	12	21.89	6.61	8.95	34.84	
Myometrial invasion							
Absent	7	4	27.86	10.18	7.91	47.80	0.186
<50%	12	6	49.16	17.33	15.19	83.13	
≥50%	10	1	93.67	10.69	72.72	114.61	
Lymphovascular involvement							
Present	13	9	26.17	12.11	2.43	49.91	**0.015**
Absent	18	5	81.92	13.82	54.83	109.00	

Table 2. Continued

	n	Recurrence	Mean	Standard error	95% Confidence interval		p
					Lower	Upper	
Lymph nodes status							
Positive	1	1	3.00	0.00	3.00	3.00	**<0.001**
Negative	18	9	50.16	11.97	26.71	73.61	
Residual tumor							
Present	3	1	9.00	0.71	7.61	10.39	**0.682**
Absent	21	9	39.01	7.78	23.75	54.26	
Adjuvant therapy							
Yes	19	9	48.77	12.69	23.90	73.63	0.490
No	15	5	71.23	16.14	39.60	102.87	
Ki-67							
Positive	16	9	31.05	7.95	15.47	46.62	**0.144**
Negative	18	5	80.67	14.32	52.61	108.72	
FIGO: International Federation of Obstetrics and Gynecology, MMMT: Malignant mixed mullerian tumor, ESS: Endometrial stromal sarcoma							

Table 3. Survival times (months) using Kaplan-Meier analysis and comparisons of groups using the Log-rank test for categorical variables

	n	Death	Mean	Standard error	95% Confidence interval		2 year survival rate (%)	p
					Lower	Upper		
Overall survival	34	8	80.92	11.46	58.47	103.38	75.6±9.0	
Smoking status								
Smoker	8	2	51.17	11.80	28.05	74.29	62.5±21.3	0.986
Non-smoker	26	6	80.85	13.33	54.74	106.97	80.7±8.9	
Menopause status								
Non-menopausal	11	2	98.00	13.99	70.57	125.43	79.5±13.1	0.371
Menopausal	23	6	52.21	9.71	33.18	71.23	74.1±11.8	
Chronic disease								
Present	18	5	51.80	10.34	31.54	72,07	73.1±14.1	0.372
Absent	16	3	97.03	11.85	73.80	120.26	78.7±11.0	
Tumor size								
≤5 cm	12	2	98.44	13.23	72.50	124.38	90.0±9.5	0.186
>5 cm	22	6	51.49	10.93	30.07	72.91	67.9±12.7	
FIGO stage								
Early (I-II)	29	6	85.06	11.88	61.77	108.34	80.0±9.3	0.089
Advanced (III-IV)	5	2	18.13	3.63	11.03	25.24	53.3±24.8	
Histologic type								
Leiomyosarcoma	10	3	55.51	12.84	30.34	80.68	75.0±15.8	0.939
MMMT	10	2	41.71	10.40	31.34	62.09	57.1±24.9	
ESS	5	1	51.20	8.77	34.02	68.38	80.0±17.9	
Others	9	2	88.96	17.91	53.87	124.06	88.9±10.5	
Histologic grade								
Low	7	1	103.71	15.08	74.16	133.27	85.7±13.2	0.114
Moderate	8	0	No statistics are computed because all cases are censored					
High	18	7	38.35	8.04	22.59	54.12	58.1±15.2	

Table 3. Continued

	n	Death	Mean	Standard error	95% Confidence interval		2 year survival rate (%)	p
					Lower	Upper		
Myometrial invasion								
Absent	7	2	44.29	9.46	25.75	62.83	62.5±21.3	0.691
<50%	12	4	65.94	18.45	29.78	102.10	77.9±14.1	
≥50%	10	1	89.50	14.15	61.77	117.23	83.3±15.2	
Lymphovascular involvement								
Present	13	5	56.97	14.86	27.84	86.10	83.6±10.8	0.062
Absent	18	3	93.57	13.28	67.55	119.60	65.8±14.1	
Lymph nodes status								
Positive	1	1	12.00	0.00	12.00	12.00	0.0±0.0	**0.048**
Negative	18	4	76.32	12.40	52.02	100.63	68.1±14.0	
Residual tumor								
Present	3	2	8.00	0.94	6.15	9.85	33.3±27.2	**<0.001**
Absent	21	4	54.4	7.53	39.65	69.15	72.7±14.1	
Adjuvant therapy								
Yes	19	5	67.97	13.13	42.25	93.69	72.2±12.2	0.553
No	15	3	85.78	16.51	53.42	118.14	79.1±13.8	
Recurrence								
Present	14	7	36.29	9.73	17.22	55.36	52.1± 16.4	**0.004**
Absent	20	1	113.67	6.16	101.60	125.73	94.4±5.4	
Site of recurrence								
Pelvic peritoneum	6	4	30.40	10.01	10.79	50.01	53.3±24.8	0.688
Lung	3	1	60.00	19.60	21.59	98.41	66.7±27.2	
Others	5	2	19.73	3.41	13.05	26.42	53.3±24.8	
Ki-67								
Positive	16	5	57.28	9.20	39.26	75.31	71.4±12.2	0.424
Negative	18	3	88.44	15.78	57.52	119.36	82.0±12.2	

FIGO: International Federation of Obstetrics and Gynecology; MMMT: Malignant mixed mullerian tumor; ESS: Endometrial stromal sarcoma

risk for recurrence (Table 4). We found no significant effect on survival rates when we took into account age, age at menarche, and age at first delivery (Table 5). Furthermore, we found that larger tumor sizes decreased survival rates but this result was deemed statistically insignificant.

Discussion

Uterine sarcoma is rare and difficult to study; therefore, it features very little in the current medical literature. This study was made up of 34 patients who were referred over an 8 year period. Histopathologic evaluations revealed that LMS and MMMT occurred in equal frequency in our group of patients (29.4%), followed by ESS (14.7%). Our data are comparable to some studies (7,16), but at the same time there are studies reporting very different histopathologic distributions in their results (17-19). It should be noted that small numbers of patients and changes in the WHO classification in each study may have caused these differences.

The mean age of our patients were 62.4 years in those with MMMT, 49.8 years in those with LMS, 39.6 years in those with ESS, and 51.8 years in other sarcomas types. Our findings are consistent with the study by Benito et al. (17) and Potikul et al. (18), with the only exception being the ESS group, which was younger in our study.

In the current study, only 7 cases of uterine sarcoma were diagnosed in patients aged under 40 years and the majority of cases were seen in postmenopausal women. Although RMS is usually associated with the pediatric age group (20), one patient was diagnosed at the age of 31 years. Another patient's

Table 4. Cox regression analysis results for disease-free survival times (months)

	Hazard ratio	95% Confidence interval		p
		Lower	Upper	
Age	0.995	0.891	1.112	0.935
Age at menarche	2.273	1.056	4.890	**0.036**
Age at first delivery	1.989	1.168	3.386	**0.011**
Parity	2.283	0.598	8.715	0.227
Tumor size	1.572	1.132	2.184	**0.007**

Table 5. Cox regression analysis results for survival times (months)

	Hazard ratio	95% Confidence interval		p
		Lower	Upper	
Age	1.103	0.966	1.260	0.146
Age at menarche	2.095	0.841	5.221	0.112
Age at first delivery	1.469	0.951	2.268	0.083
Tumor size	1.459	0.888	2.396	0.136

diagnosis was made during cesarean section by ovarian biopsy, which revealed a high-grade UUS. At the time of diagnosis, metastases had already developed in the lung, brain, and liver. One patient had a personal history of breast cancer, and four had concomitant malignancies associated with MMMT; one gastrointestinal stromal tumor, two low-grade uterine endometrioid adenocarcinomas, and one high-grade ovarian serous adenocarcinoma. Family history for cancer was positive for a total of 6 (17%) patients, with breast carcinoma being the most commonly reported type. None of the patients had a personal or family history of sarcoma, nor did they report any history of pelvic irradiation. One patient (2.9%) who had a prior history of breast carcinoma had received treatment with tamoxifen. Durnali et al. (21) reported tamoxifen treatment frequency as 1% in their study. Benito et al. (17) reported a higher incidence of a positive family history (40.4%), and prior histories of cancer were similar to those reported by Benito et al. (17) and Koivisto-Korander et al. (22) in their studies (10.1% and 11%, respectively), with breast carcinoma as the most common. Similar to our study, these studies also reported that none of their patients had a history of pelvic irradiation. Wais et al. (19) and Durnali et al. (21) reported a lower occurrence of personal cancer history among their patients (8% and 3%, respectively), and a history of pelvic irradiation was reported in only 1%.

A correct preoperative malignancy diagnosis was achieved in 17 of our patients (73.9%). Some studies have reported higher (86-88%) rates of preoperative diagnosis, whereas others reported lower rates (65%, 64%) (18,19,23). Bansal et al. (23) correctly predicted the presence of invasive tumors in 86%, while also correctly predicting the histologic subtype in 64% of their patients. Some differences in preoperative diagnostic methods may have resulted in variable results.

In this patient group, complete resection of the uterus and removal of both adnexa is the widely accepted approach to treatment of early-stage disease. It is suggested to avoid pelvic and para-aortic lymphadenectomy when unremarkable, except in patients with MMMT (5). In cases of MMMT limited to the uterus, positive lymph nodes are reported in around 30% of patients. The literature on this topic reports that OS is adversely effected by systematic lymph node involvement (5). In our study, we found that the mean number of lymph nodes that were removed was 18.9±22.4; this value was 15.1±17.4 for pelvic lymph nodes and 12.6±9.2 for paraaortic lymph nodes. According to pathology reports, one of the pelvic lymph nodes demonstrated high-grade MMMT (FIGO 3C). The OS time of this patient was 12 months. However, the literature on this topic reports higher lymph node metastasis rates. In the current study, lymph node metastases were not found in any patients with other types of sarcoma. The number of patients with positive lymph nodes was low in our study, and survival times were found to be significantly shorter for those with positive lymph nodes.

In patients with LMS limited to the uterus, the ovaries of women of childbearing age may be preserved (24,25). Additionally, preservation of the ovaries was not found to impact OS negatively in patients with LG-ESS; however, it is crucial to consider removal of ovaries on a case-by-case basis because LG-ESS is known to be an endocrine-driven tumor (26). The preservation of ovaries was performed in only five patients in the current study. One of these patients had AS and underwent TAH + BPLND, but was later (6 months) found to have adnexal metastasis. The lesion was subsequently excised and palliative chemotherapy was recommended. Eighteen months after the initial treatment she was lost to follow-up because she had settled overseas. Another patient had botryoidal-type embryonal rhabdomyosarcoma at the time of diagnosis and was pregnant. She gave birth through cesarean section at 35 weeks of gestation after confirmation of fetal lung maturation, and later underwent radical hysterectomy + BPPALND + oophoropexy with postoperative adjuvant chemotherapy (vincristine and actinomycin D). She is still alive without any evidence of disease at 105 months of follow-up. Two patients who had undergone hormone therapy were still alive at 16 and 121 months of follow-up. Brain metastasis occurred at the seventh month in a patient with LMS whilst receiving chemotherapy with the survival time being months. Due to the limited number of patients,

it is difficult to make any recommendation for ovarian preservation.

In our study, most patients were diagnosed at an early stage (85.3% were diagnosed at FIGO stages I and II). This rate is higher compared with other studies, which reported rates between 58 and 66% for early-stage disease diagnosis (17,18,21,22). In contrast to our results, MMMT was most often diagnosed during advanced stages (17,18,21). However, in our study, only 20% of MMMT cases were detected at an advanced stage. These differences may be explained by the extent of the operative procedure, the extent and type of sarcoma, and the newer FIGO staging system that we used. Given these differences, it may not be feasible to compare our study with prior studies on this field.

In patients with uterine sarcomas, the role of adjuvant therapy on survival is uncertain (7). Studies show that adjuvant chemotherapy has a positive effect on survival in MMMT and LMS (increasing OS and DFS), and receiving pelvic irradiation was associated with significantly longer OS in those with ESS and UUS (27,28). In a large study comprising 3650 patients with uterine sarcoma (MMMT, ESS, LMS and UUS), it was shown that adjuvant pelvic radiotherapy reduced local-regional failure in up to 53% of cases (29). Durnali et al. (21) showed that adjuvant radiotherapy after chemotherapy for uterine sarcomas improved DFS but had no effect on OS. In our present study, adjuvant therapy did not seem to improve OS. However, due to the low number of patients in our study, it would be unfeasible to draw conclusions in regard to the efficacy of adjuvant treatments.

Uterine sarcomas have a poor prognosis overall. Our results show the recurrence rate as 41.1% for patients with uterine sarcoma with a median follow-up time of 61.2 months. Previous reports of recurrence rates have been reported to range between 36% and 63.4% (16-18,21,30). In the current study, the following factors were found to contribute to significantly poor prognosis: later FIGO staging, higher tumor grade, lymphovascular space invasion, and lymph node involvement. We also found that the presence of residual tumor and positive Ki-67 decreased DFS; however, the decreases were not statistically significant for either comparison, presumably due to the low number of patients. However, our findings were in agreement with a few previous studies (18,30). It should also be mentioned that higher age at menarche and higher age at first birth were associated with recurrence, which are strongly considered as being risk factors for UUS (31).

The mean OS in our study was found as 80.92 months, and the 2-year survival rate was 75.6%. In previous studies, the 2-year OS has been reported within a range of 49-69%, and 5-year OS is reported as 45-59% (16,17,21,30). According to our results, survival times were significantly shorter in those with lymph node involvement, residual tumor, and tumor recurrence. We also found that patients with at least one parity, early FIGO (I & II) stages, and low histologic grade had longer survival.

There are limitations to our study. First, it is evident that our findings should be interpreted in the context of the limitations associated with retrospective studies. Secondly, the number of cases was low; however, uterine sarcomas are rare and the fact that the study was cconducted in a single center with rigorous inclusion/exclusion criteria further limited the number of patients that could be included in the study. Lastly, the number of patients lost to follow-up due to various reasons can be considered as another limitation of the study. In regard to these limitations, our results concerning the survival of these patients must be evaluated with caution.

In conclusion, at the final follow-up of the current study, 35.3% of patients were alive and in remission, 11.8% were alive with disease, 29.4% were lost to follow-up, and 23.5% had died. The mean survival time was 80.92 months and the 2-year survival rate was found as 75.6%. According to our results, survival times were significantly shorter with lymph node involvement, the presence of residual tumor, and tumor recurrence. We also found that patients with at least one parity, early FIGO stages (I & II) and low histologic grade had longer survival times. Considering the low incidence of uterine sarcomas and because of the recent changes in the classification system, it is very difficult to reach conclusions in terms of treatment strategies.

Ethics Committee Approval: *Ethics approval (reference number: 2017-16/28) was given by the Local Ethics Committee of Acıbadem Kozyatağı Hospital.*

Informed Consent: *Informed consent was not taken due to retrospective study design.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - E.M.; Design - E.M., M.M.N.; Supervision - M.M.N.; Data Collection and Processing - E.M.; Analysis and Interpretation - M.M.N.; Writer - E.M., M.M.N.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Seddon BM, Davda R. Uterine sarcomas recent progress and future challenges. Eur J Radiol 2011; 78: 30-40.

2. Ueda SM, Kapp DS, Cheung MK, Shin JY, Osann K, Husain A, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008; 198: 218. e1-6.
3. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol 2004; 93: 204-8.
4. Conklin CM, Longacre TA. Longacre, Endometrial stromal tumors: the new WHO classification. Adv Anat Pathol 2014; 21: 383-93.
5. Denschlag D, Thiel FC, Ackermann S, Harter P, Juhasz-Boess I, Mallmann P, et al. Sarcoma of the Uterus. Guideline of the DGGG (S2k-Level, AWMF Registry No. 015/074, August 2015). Geburtshilfe Frauenheilkd 2015; 75: 1028-42.
6. Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. Lancet Oncol 2009; 10: 1188-98.
7. Schnall MD, Blume J, Bluemke DA, DeAngelis GA, DeBruhl N, Harms S, et al. Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. Radiology 2006; 238: 42-53.
8. Silverberg SG, Major FJ, Blessing JA, Fetter B, Askin FB, Liao SY, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. Int J Gynecol Pathol 1990; 9: 1-19.
9. Lavie O, Barnett-Griness O, Narod SA, Rennert G. The risk of developing uterine sarcoma after tamoxifen use. Int J Gynecol Cancer 2008; 18: 352-6.
10. Schwartz SM, Weiss NS, Daling JR, Gammon MD, Liff JM, Watt J, et al. Exogenous sex hormone use, correlates of endogenous hormone levels, and the incidence of histologic types of sarcoma of the uterus. Cancer 1996; 77: 717-24.
11. Arenas M, Rovirosa A, Hernández V, Ordi J, Jorcano S, Mellado B, et al. Uterine sarcomas in breast cancer patients treated with tamoxifen. Int J Gynecol Cancer 2006; 16: 861-5.
12. Felix AS, Cook LS, Gaudet MM, Rohan TE, Schouten LJ, Setiawan VW, et al. The etiology of uterine sarcomas: a pooled analysis of the epidemiology of endometrial cancer consortium. Br J Cancer 2013; 108: 727-34.
13. Mikuta JJ. International Federation of Gynecology and Obstetrics staging of endometrial cancer 1988. Cancer 1993; 71(Suppl 4): 1460-3.
14. McCluggage W. Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas? J Clin Pathol 2002; 55: 321-5.
15. Lopez-Garcia MA, Palacios J. Pathologic and molecular features of uterine carcinosarcomas. in Seminars in diagnostic pathology. Elsevier 2010.
16. Ghaemmaghami F, Karimi-Zarchi M, Gilani MM, Mousavi A, Behtash N, Ghasemi M. Uterine sarcoma: clinicopathological characteristics, treatment and outcome in Iran. Asian Pac J Cancer Prev 2008; 9: 421-6.
17. Benito V, Lubrano A, Arencibia O, Andújar M, Alvarez E, Medina N, et al. Clinicopathologic analysis of uterine sarcomas from a single institution in the Canary Islands. Int J Gynaecol Obstet 2009; 107: 44-9.
18. Potikul C, Tangjitgamol S, Khunnarong J, Srijaipracharoen S, Thavaramara T, Pataradool K. Uterine Sarcoma: Clinical Presentation, Treatment and Survival Outcomes in Thailand. Asian Pac J Cancer Prev 2016; 17: 1759-67.
19. Wais M, Tepperman E, Bernardini MQ, Gien LT, Jimenez W, Murji A. A Multicentre Retrospective Review of Clinical Characteristics of Uterine Sarcoma. J Obstet Gynaecol Can 2017; 39: 652-8.
20. Kaseb H, Babiker HM. Cancer, Rhabdomyosarcoma, in StatPearls. 2019. StatPearls Publishing StatPearls Publishing LLC. Treasure Island (FL).
21. Durnali A, Tokluoğlu S, Özdemir N, Inanç M, Alkiş N, Zengin N, et al. Prognostic factors and treatment outcomes in 93 patients with uterine sarcoma from 4 centers in Turkey. Asian Pac J Cancer Prev 2012; 13: 1935-41.
22. Koivisto-Korander R, Scélo G, Ferro G, Mellemkjaer L, Hemminki K, Weiderpass E, et al. Second primary malignancies among women with uterine sarcoma. Gynecol Oncol 2012; 126: 30-5.
23. Bansal N, Herzog TJ, Burke W, Cohen CJ, Wright JD. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. Gynecol Oncol 2008; 110: 43-8.
24. Garg G, Shah JP, Kumar S, Bryant CS, Munkarah A, Morris RT. Ovarian and uterine carcinosarcomas: a comparative analysis of prognostic variables and survival outcomes. Int J Gynecol Cancer 2010; 20: 888-94.
25. Kapp DS, Shin JY, Chan JK. Chan, Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer 2008; 112: 820-30.
26. Amant F, De Knijf A, Van Calster B, Leunen K, Neven P, Berteloot P, et al. Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. Br J Cancer 2007; 97: 1194-9.
27. Wolfson AH, Brady MF, Rocereto T, Mannel RS, Lee YC, Futoran RJ, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol 2007; 107: 177-85.
28. Cantrell LA, Havrilesky L, Moore DT, O'Malley D, Liotta M, Secord AA, et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. Gynecol Oncol 2012; 127: 22-6.
29. Sampath S, Schultheiss TE, Ryu JK, Wong JY. The role of adjuvant radiation in uterine sarcomas. Int J Radiat Oncol Biol Phys 2010; 76: 728-34.
30. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989-2007. J Cancer Res Clin Oncol 2008; 134: 1277-87.
31. Schwartz SM, Thomas DB. A case-control study of risk factors for sarcomas of the uterus. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer 1989; 64: 2487-92.

Adnexal lesions after hysterectomy: A retrospective observational study

Ayşegül Öksüzoğlu, Şebnem Özyer, Özlem Yörük, Rıfat Taner Aksoy, Ömer Hamit Yumuşak, Özlem Evliyaoğlu

Clinic of Obstetrics and Gynecology, Gynecology and Endoscopic Surgery Unit, University of Health Sciences, Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey

Abstract

Objective: To characterize adnexal lesions detected in patients who had undergone previous hysterectomy with one or both ovaries conserved, and to define the clinical, pathologic, and surgical characteristics of the adnexal lesions in these patients.

Material and Methods: A retrospective observational study was conducted on patients who had undergone a previous abdominal hysterectomy with one or both adnexa preserved and who had subsequently presented with an adnexal lesion. Characteristics of lesions, operative, and pathologic findings in patients who required a re-operation were noted.

Results: One hundred thirty-seven patients presented with an adnexal lesion after hysterectomy. Of the 137 patients, 71 (51.8%) had undergone a re-operation (re-operated group), the rest of the patients (n=66, 48.1%) remained on follow-up (follow-up group) in whom the lesion disappeared during follow-up period. Adnexal lesions that were re-operated were significantly larger ($p<0.001$), more complicated ($p=0.04$), and had more septations ($p=0.01$) than in the follow-up group. The origin of the adnexal lesion was confirmed as the ovary in 59 (83%) patients, and as the peritoneum in 8 (11.2%) patients during surgery. All of the adnexal lesions arising after hysterectomy and required a re-operation were confirmed to be benign.

Conclusion: Almost half of the lesions detected after hysterectomy disappeared during the follow-up period. The adnexal lesions that were re-operated were more symptomatic, larger, and had more complicated lesions. All lesions that were re-operated were found to be benign, mostly originating from the ovary. (J Turk Ger Gynecol Assoc 2019; 20: 165-9)

Keywords: Adnexal lesion, adnexal preservation, hysterectomy, re-operation

Received: 17 April, 2018 **Accepted:** 20 July, 2018

Introduction

Hysterectomy is one of the most commonly performed surgical procedures among women (1), and the majority of these are performed for benign diseases of the uterus (2). There is debate about hysterectomy for benign conditions regarding the performance of concurrent prophylactic adnexal surgeries, oophorectomy or salpingectomy. The major benefits of prophylactic salpingo-oophorectomy are the prevention of subsequent ovarian and breast cancer, and the reduction in the risk of future adnexal surgery (3). However, oophorectomy is associated with a number of potential risks in the long term related with earlier surgical menopause in premenopausal women who face risks of cardiovascular disease, osteoporosis and hip fractures, neurologic and psychiatric disorders, and colorectal and lung cancers (3). The benefits must be weighed against these potential adverse effects during preoperative patient counseling and decision making. Recent studies investigating the trends of adnexal surgeries at the time of hysterectomy for benign indications suggested that the rate of ovarian preservation in women younger than 50 years of age was increasing (2,4).

Address for Correspondence: *Ayşegül Öksüzoğlu*
e.mail: oksuzoglua@yahoo.com ORCID: orcid.org/0000-0003-0042-0307

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2018.2018.0051

On the other hand, there is a risk of repeat adnexal surgery for *de novo* developed adnexal pathologies after hysterectomy when adnexa are retained. These adnexal lesions pose a challenge for gynecologists as well as the patients. The incidence of subsequent surgery after hysterectomy varies from 2.8-9.2% (5). In a cohort study of 2561 hysterectomies over 20 years, during which one or both ovaries were preserved, Dekel et al. (6) found that the most common indications for reoperation were pelvic pain (71.3%) and presence of an asymptomatic adnexal mass (24.6%).

There are a limited number of studies in the literature investigating adnexal lesions arising after hysterectomy (6-14). Within this scope, the aim of the study was to characterize adnexal lesions detected in patients who had undergone previous hysterectomy with one or both ovaries conserved, and to define the clinical, pathologic, and surgical characteristics of the adnexal lesions in these patients.

Material and Methods

A retrospective observational study was conducted at the Gynecology and Endoscopic Surgery Unit of Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital. The study was approved by the Institutional Review Board of the hospital (approval no: 2014/47). Patients who were eligible for the study were those with a previous abdominal hysterectomy for benign indications with one or both adnexa preserved during the years of 2007-2013, and had subsequently presented with an adnexal pathology. Patients who had undergone vaginal or laparoscopic hysterectomy were not included in the study. Clinical, pathologic, and surgical data related with the hysterectomy procedure and adnexal pathology were retrospectively collected from the medical records of the patients. Demographic characteristics including ages and hysterectomy details of the patients, characteristics of adnexal lesions including symptoms, interval to diagnosis, re-operation and follow-up, serum E2 and CA125 levels on detection, location, ultrasonographic features, operative and pathologic characteristics of adnexal lesions in patients who required a re-operation including type of the procedure, origin of the adnexal lesion, malignancy rate, operative complications, and length of hospital stay were noted.

Statistical analyses were performed using the SPSS statistics package (version 16.0; SPSS Inc, Chicago, IL). The Kolmogorov–Smirnov test was used for the normality testing of the data sets. The comparison of continuous variables between the groups was performed through Student's t-tests or Mann-Whitney rank sum tests, and the chi-square test was used for categorical variables. Differences with $p<0.05$ were considered to be statistically significant.

Results

Between 2007 and 2013, a total of 3566 abdominal hysterectomies were performed for benign indications in our institution. In 619 of these hysterectomies, at least one of the adnexa was saved. Among these patients who were available for follow-up in our institution, 137 (22.1%) presented with an adnexal lesion during the follow-up period. Of the 137 patients with an adnexal lesion, 71 (51.8%) had undergone a re-operation (re-operated group), and among the re-operated group, 7 (9.8%) of them had undergone a second procedure other than hysterectomy due to the adnexal pathology. The rest of the patients (n=66, 48.1%) remained on follow-up (follow-up group). The adnexal lesions detected in this group disappeared during the follow-up period. The mean age of patients at the time of hysterectomy who were later diagnosed as having adnexal lesion was 46.4±4.0 years (Table 1). The most common surgical indication for the previous hysterectomy was leiomyoma (n=94, 68.6%) (Table 1). Table 2 demonstrates the characteristics of the adnexal lesions in the re-operated and the follow-up groups. The number of symptomatic patients were statistically higher in the re-operated group ($p=0.012$). The median interval between the hysterectomy and the diagnosis of adnexal pathology was 31 (minimum 1, maximum 216) months in the re-operated group and 4 (minimum 1, maximum 56) months in the follow-up group ($p<0.001$). There were no significant differences with respect to serum E2 and CA125 levels. The mean size of the adnexal lesion was 71.3±25.2 mm in the re-operated group, whereas it was 44.0±10.9 mm in the follow-up group. Mural nodules, septations inside the adnexal lesion and abnormal Doppler findings were detected in 7 (9.9%), 48 (67.6%), 3 (4.2%) patients in the re-operation group, and 4 (6.1%), 31 (47.0%), 1 (1.5%) patients in the follow-up group, respectively. Adnexal lesions that were re-operated were significantly larger ($p<0.001$), more complicated ($p=0.04$), and had more septations ($p=0.01$) than in the follow-up group. Table 3 represents the operative and pathologic

Table 1. Age and hysterectomy details of patients

	n=137
Age at diagnosis of adnexal lesion (years, mean±SD)	46.4±4.0
Age at hysterectomy (years, mean±SD)	42.6±2.7
Indications for hysterectomy (n, %)	
Leiomyomas	94 (68.6%)
Abnormal uterine bleeding	27 (19.7%)
Pelvic pain	6 (4.4%)
Uterine polyps	3 (2.2%)
Endometrial hyperplasia	7 (5.1%)
Type of surgery (n, %)	
Hysterectomy	113 (82.5%)
Hysterectomy+unilateral salpingo-oophorectomy	24 (17.5%)

SD: Standard deviation

Table 2. Characteristics of the adnexal pathology in the re-operated and the follow-up groups

	Re-operated group (n=71)	Follow-up group (n=66)	p value
Symptomatic on admission (n, %)	58 (81.6%)	40 (60.6%)	0.012
Interval to diagnosis (months, median, minimum-maximum)	31 (1-216)	4 (1-56)	<0.001
Interval to re-operation (months, median, minimum-maximum)	36 (3-217)		
Interval to follow-up (months, median, minimum-maximum)		7 (1-42)	
Serum E_2 level on detection (pg/mL, mean±SD, minimum-maximum)	139.7±115.7 (13-450)	154.5±129.8 (19-617)	0.640
Serum CA125 level on detection (U/mL, mean±SD, minimum-maximum)	15.6±19.2 (1.9-158.2)	15.4±8.5 (3.20-39.1)	0.169
Localization of adnexal pathology (n, %)			0.038
Right	22 (30.9%)	36 (54.5%)	
Left	39 (54.9%)	26 (39.3%)	
Bilateral	10 (14.08%)	4 (6%)	
Ultrasonographic features of adnexal pathology			
Size (mm, mean±SD, minimum-maximum)	771.3±25.2 (25-160)	44.0±10.9 (25-71)	<0.001
Simple cystic (n, %)	30 (42.3%)	37 (56.1%)	0.04
Complicated cystic (n, %)	34 (47.9%)	16 (24.2%)	0.04
Cystic with mural nodules (n, %)	7 (9.9%)	4 (6.1%)	0.309
Presence of septations (n, %)	48 (67.6%)	31 (47.0%)	0.01
Abnormal Doppler findings (n, %)	3 (4.2%)	1 (1.5%)	0.338

SD: Standard deviation, Interval to diagnosis: Interval between hysterectomy and diagnosis of adnexal lesion, Interval to re-operation: Interval between diagnosis of adnexal lesion and re-operation

Table 3. Operative and pathologic characteristics of patients who were re-operated due to adnexal lesion

	n=71
Type of procedure (n, %)	
Laparoscopy	30 (42.2%)
Laparotomy	41 (57.7%)
Origin of adnexal pathology (n, %)	
Ovarian	59 (83%)
Tubal	-
Ovarian+tubal	4 (5.63%)
Other	8 (11.2%)
Pathological result (n, %)	
Benign	71 (100%)
Malignant	-
Operative complications (n, %)	
Blood transfusion	1
Urinary tract injury	2
Bowel injury	5
Length of hospital stay (days, mean±SD, minimum-maximum)	4.1±2.8 (1-18)

SD: Standard deviation

characteristics of patients who required a re-operation due to adnexal lesion. The origin of the adnexal lesion was confirmed as the ovary in 59 (83%) patients, and as the peritoneum in 8 (11.2%) patients during surgery. All of the adnexal lesions arising after hysterectomy and required a re-operation were benign; no malignancy was detected in our group of patients. Intraoperative and postoperative complications developed in 8 (11.2%) patients, including bowel injury in 5 patients, and urinary tract injury in 2 patients. Only 1 patient required a blood transfusion. The mean length of hospital stay was 4.1±2.8 (minimum 1, maximum 18) days. Table 4 presents data of 7 patients who required a second operation other than hysterectomy due to an adnexal lesion. The time interval between the diagnosis and second operation varied between 2-36 months, and all of the pathologies detected in these 7 patients were confirmed to be benign.

Discussion

The present retrospective study investigating the adnexal lesions arising after hysterectomy indicates that almost half of the pathologies (48.1%) detected after surgery disappeared during follow-up period. The adnexal lesions that were re-operated were more symptomatic, larger, and more complicated lesions with more septations, mural nodules, and abnormal Doppler findings raising doubts of malignancy. However, all lesions were found to be benign, mostly originating from the ovary.

Women and physicians are faced with the decision of whether to remove or preserve ovaries and fallopian tubes during hysterectomy for benign indications. The number of bilateral salpingo-oophorectomies performed concomitantly with hysterectomy has been declining over the last 10 years, particularly among women aged under 55 years (3). The American Congress of Obstetricians and Gynecologists, in the practice bulletin reaffirmed in 2016, states that 'strong

Table 4. Patients who were operated for the second time for adnexal lesion after hysterectomy

Patient no	1st surgery	Interval between diagnosis and re-operation	Adnexal pathology in the operation	Pathologic result	Interval between diagnosis and 2nd operation	Adnexal pathology in the operation	Pathologic result
Patient no 1	Hyst	5 months	Peritoneal	Benign	4 months	Ovarian	Benign
Patient no 2	Hyst	2 months	Ovarian	Benign	5 months	Peritoneal	Benign
Patient no 3	Hyst	9 months	Peritoneal	Benign	7 months	Ovarian	Benign
Patient no 4	Hyst	2 months	Peritoneal	Benign	7 months	Ovarian + tubal	Benign
Patient no 5	Hyst	5 months	Ovarian	Benign	2 months	Ovarian	Benign
Patient no 6	Hyst	6 months	Ovarian	Benign	6 months	Ovarian	Benign
Patient no 7	Hyst	2 months	Ovarian	Benign	36 months	Ovarian	Benign
Hyst: Hysterectomy							

consideration should be made for retaining normal ovaries' (15). However, women with ovarian preservation are at risk for future oophorectomy (16). In a recent study of Casiano et al. (12), the incidence of oophorectomy after hysterectomy was found as 9.2% (12). They postulated that disruption of ovarian blood flow after hysterectomy might alter ovarian function, which could lead to adnexal pathologies.

Our study is one of the very few that focuses on the causes of adnexal lesions after hysterectomy. The study is also distinct in terms of the inclusion of a group of patients in whom adnexal lesions disappeared during the follow-up period. In 1996, Dekel et al. (6) in their cohort study of 2561 hysterectomies (during which one or both ovaries were preserved) over a period of 20 years found that the incidence of residual ovary syndrome was 2.85%. Residual ovary syndrome was described as a persistent pelvic mass presenting with pain, tenderness or dyspareunia in patients in whom at least one of the ovaries was preserved during hysterectomy. The most common reasons for subsequent oophorectomy were pain (71.3%) and the presence of an asymptomatic adnexal mass (24.6%). Holub et al. (10) examined the re-operation rates of adnexal lesions after different approaches of hysterectomy, namely abdominal, vaginal and laparoscopic approach, and found that the highest rate of reoperation was after abdominal hysterectomy (5.67%), followed by laparoscopic (3.18%) and vaginal approaches (0.69%). They suggested that the important factors affecting the reoperation rate were age, primary histologic findings, and smaller peritoneal trauma. In the study by Baloglu et al. (9), the reoperation rate due to secondary ovarian lesions after hysterectomy was found as 4.3%-3.8% for patients without oophorectomy and 5.9% for patients with unilateral oophorectomy. They concluded that women with unilateral oophorectomy at the time of hysterectomy had more than twice the risk of secondary ovarian lesions compared with those without oophorectomy at hysterectomy.

Recently, Shiber et al. (7) investigated adnexal masses requiring reoperation in women with previous hysterectomy with or without adnexectomy. They reported that the majority of adnexal masses requiring re-operation after hysterectomy were gynecologic in origin, benign, and arose from the ovary. In accordance with this study, all lesions that were re-operated in our study were benign and mostly originating from the ovary. Apart from others, the study of Shiber et al. (7) included a group of patients returning for surgery after hysterectomy and bilateral salpingectomy, although the number of patients was small. They argued that this small number of patients requiring re-operation after hysterectomy and bilateral salpingectomy might reflect a decreased risk for future surgery or may just indicate an insufficient time interval to evaluate the development of adnexal lesion. Recent studies have challenged the traditional concept of the pathogenesis of ovarian cancer, suggesting the fallopian tubes as the originating organ for the disease. In a recent population-based study by Falconer et al. (17), it was found that salpingectomy in benign indications was associated with reduced risk of ovarian cancer. They concluded that women scheduled for hysterectomy for benign indications should be informed about the risk-reducing effect of salpingectomy on ovarian cancer, and may be offered during common procedures such as hysterectomy. Our study did not include patients who had undergone hysterectomy and bilateral salpingectomy because the procedure has gained popularity and has been truly adopted in recent years. We will be able to evaluate this group of patients when sufficient time has passed with this emerging practice.

Different from other studies, we also evaluated morbidities during these repeat surgeries. Although we did not encounter any mortality, morbidities such as need for blood transfusion, urinary tract and bowel injury were seen in 8 of the 71 patients.

There are some limitations of our study. First, we could not give the incidence of adnexal lesions emerging after hysterectomy and re-operation rate due to these lesions because we could only evaluate women with adnexal mass after hysterectomy who were available for follow-up in our instution. Secondly, we did not have a group of patients with hysterectomy and bilateral salpingectomy during the years the study was conducted. However, in our current practice, we inform patients about prophylactic and opportunistic salpingectomy, and offer it as a preventing strategy for ovarian cancer in low-risk and high-risk patients, as well as for the prevention of benign pathologies.

In conclusion, despite its limitations, our study sheds light on guidance and information on surgical decisions for women presenting with adnexal lesion after hysterectomy. In our patients, almost half of the lesions arising after hysterectomy disappeared during follow-up, and all lesions that were re-operated were benign and mostly originating from the ovary. Patient counseling and the decision to perform a repeat operation due to an adnexal lesion after hysterectomy should be made on an individual basis.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital (Approval no: 2014/47).*

Informed Consent: *Retrospective study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - A.Ö., Ş.Ö., Ö.E.; Design - A.Ö., Ö.Y., R.T.A.; Supervision - A.Ö., Ö.E.; Resource - A.Ö., Ö.H.Y., Ş.Ö.; Materials - A.Ö., Ş.Ö., Ö.E.; Data Collection or Processing - A.Ö., Ö.Y., Ö.H.Y.; Analysis or Interpretation - A.Ö., R.T.A., Ş.Ö.; Literature Search - R.T.A., Ö.H.Y., Ö.E.; Writing - A.Ö., Ö.Y., Ö.E.; Critical Reviews - Ş.Ö., Ö.E.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Michelsen TM, Dørum A, Cvancarova M, Liavaag AH, Dahl AA. Association between hysterectomy with ovarian preservation and cardiovascular disease in a Norwegian population-based sample. Gynecol Obstet Invest 2013; 75: 61-7.
2. Perera HK, Ananth CV, Richards CA, Neugut AI, Lewin SN, Lu YS, et al. Variation in ovarian conservation in women undergoing hysterectomy for benign indications. Obstet Gynecol 2013; 121: 717-26.
3. Jacoby VL. Hysterectomy controversies: ovarian and cervical preservation. Clin Obstet Gynecol 2014; 57: 95-105.
4. Mikhail E, Salemi JL, Wyman A, Salihu HM, Imudia AN, Hart S. National Trends of Bilateral Salpingectomy During Vaginal Hysterectomy With and Without Laparoscopic Assistance, United States 1998-2011. J Minim Invasive Gynecol 2015; 22: 85.
5. Karp NE, Fenner DE, Burgunder-Zdravkovski L, Morgan DM. Removal of normal ovaries in women under age 51 at the time of hysterectomy. Am J Obstet Gynecol 2015; 213: 716.
6. Dekel A, Efrat Z, Orvieto R, Levy T, Dicker D, Gal R, et al. The residual ovary syndrome: a 20-year experience. Eur J Obstet Gynecol Reprod Biol 1996; 68: 159-64.
7. Shiber LD, Gregory EJ, Gaskins JT, Biscette SM. Adnexal masses requiring reoperation in women with previous hysterectomy with or without adnexectomy. Eur J Obstet Gynecol Reprod Biol 2016; 200: 123-7.
8. Naz F, Begum A. Experience with pelvic masses following hysterectomy for benign disease. Biomedica 2004; 20: 106-9.
9. Baloglu A, Bezircioglu I, Cetinkaya B, Karci L, Bicer M. Development of secondary ovarian lesions after hysterectomy without oophorectomy versus unilateral oophorectomy for benign conditions: a retrospective analysis of patients during a nine-year period of observation. Clin Exp Obstet Gynecol 2010; 37: 299-302.
10. Holub Z, Jandourek M, Jabor A, Kliment L, Wágnerová M. Does hysterectomy without salpingo-oophorectomy influence the reoperation rate for adnexal pathology? A retrospective study. Clin Exp Obstet Gynecol 2000; 27: 109-12.
11. Plöckinger B, Kölbl H. Development of ovarian pathology after hysterectomy without oophorectomy. J Am Coll Surg 1994; 178: 581-5.
12. Casiano ER, Trabuco EC, Bharucha AE, Weaver AL, Schleck CD, Melton LJ 3rd, et al. Risk of oophorectomy after hysterectomy. Obstet Gynecol 2013; 121: 1069-74.
13. Christ JE, Lotze EC. The residual ovary syndrome. Obstet Gynecol 1975; 46: 551-6.
14. Bukovsky I, Liftshitz Y, Langer R, Weinraub Z, Sadovsky G, Caspi E. Ovarian residual syndrome. Surg Gynecol Obstet 1988; 167: 132-4.
15. ACOG. ACOG Practice Bulletin No.89. Elective and risk-reducing salpingo-oophorectomy. Obstet Gynecol 2008; 111: 231-41.
16. Berek JS, Chalas E, Edelson M, Moore DH, Burke WM, Cliby WA, et al. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer. Obstet Gynecol 2010; 116: 733-43.
17. Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst 2015: 107.

Congenital central nervous system anomalies: Ten-year single center experience on a challenging issue in perinatal medicine

Emine Aydın[1], Atakan Tanacan[2], Melek Büyükeren[3], Hasan Uçkan[2], Murat Yurdakök[3], Mehmet Sinan Beksaç[2]

[1]Clinic of Obstetrics and Gynecology, Kayseri Training and Research Hospital, Kayseri, Turkey
[2]Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine, Ankara, Turkey
[3]Department of Child Health and Diseases, Neonatology Unit, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

Objective: Our goal was to highlight the prenatal diagnosis and management of central nervous system (CNS) anomalies through sharing our clinic's experience.

Material and Methods: We evaluated prenatal findings and postnatal outcomes of neonates who had a CNS anomaly diagnosis in our clinic over a ten-year period. A total of 183 cases with various CNS anomalies were included in the study. Birth or termination preferences of mothers were recorded in all cases, and postnatal diagnosis concordance and prognosis after surgical procedures were evaluated in mothers who chose to continue the pregnancy.

Results: The mean maternal age was 28.2±5.5 years, mean gravida was 2.2±1.3, and the mean gestational age at diagnosis was 30.5±5.5 weeks. Seventy-five out of 183 (41%) patients chose to terminate their pregnancy. Twenty babies (26.6%) in the termination of pregnancy group had additional anomalies. One hundred eight patients gave birth at our institution. The mean birth weight was 3060±647.5 g, the mean gestational week at delivery was 37.9±1.7 weeks, and mean APGAR score (5th minute) was 8.8±2.3. Four neonates died on the postpartum first day. The postnatal diagnosis of 60 of the 108 (55.5%) patients who gave birth was concordant with the prenatal diagnosis, and 32 of the 108 (29.6%) babies underwent surgical interventions.

Conclusion: CNS anomalies have a broad spectrum and variable prognoses. This study highlights the limitations of prenatal diagnoses, and the need for parents to have this information in order to determine the course of their pregnancy and prepare themselves for the postnatal challenging treatment/rehabilitation process. (J Turk Ger Gynecol Assoc 2019; 20: 170-7)

Keywords: Assessment, central nervous system, congenital abnormalities, neurosurgical procedure, prenatal diagnosis

Received: 25 July, 2018 **Accepted:** 2 August, 2018

Introduction

Central nervous system (CNS) anomalies are the second most common type of congenital defects after cardiac anomalies (1). Although CNS defects vary based on society and geography, they are reported to occur in 1 to 10 of every 1000 live births (2). Currently, this congenital defect group can be screened by measuring maternal serum alpha-fetoprotein (ms-AFP) levels. Furthermore, prenatal diagnosis is possible using ultrasonography (US) and/or fetal magnetic resonance imaging (MRI) (3,4). When these pregnancies result in birth, neonates with severe CNS anomalies require long-term intensive care, surgical intervention, and a prolonged treatment and rehabilitation process, all of which place a substantial material and spiritual burden on the families (2). Besides birth, these pregnancies can be terminated. Indeed,

Address for Correspondence: *Atakan Tanacan*
e.mail: atakantanacan@yahoo.com ORCID: orcid.org/0000-0001-8209-8248

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2018.2018.0079

some parents with fetuses that exhibit anomalies during the prenatal period choose to terminate their pregnancy given the poor prognosis. On the other hand, some anomalies such as mild ventriculomegaly typically have a favorable outcome and physicians may choose conservative management options in such cases. Thus, antenatal counseling may be challenging both for families and physicians. For these reasons, CNS anomalies have attracted the attention of many researchers. Several studies have investigated the etiology of various conditions associated with such anomalies, sought to refine prenatal diagnostic methods, pursued alternatives to treatment and prevention, and have presented long-term follow-up data from infants affected by these anomalies (3,4).

In this study, we characterized the outcomes of pregnancies with fetal CNS anomalies in the prenatal period in our clinic.

Material and Methods

This study consisted of 250 prenatally diagnosed CNS abnormalities between 2006 and 2016. The Hacettepe University Perinatology database was used for data collection. We evaluated the maternal age, obstetric history, gestational age at prenatal diagnosis, US findings (CNS anomaly type), karyotyping results (if performed), presence of additional anomalies other than those of the CNS, fetal MRI (if performed), pregnancy outcomes, perinatal complications, newborn information (gestational age at delivery, neonatal birth weight, APGAR scores), postpartum examination results (for the confirmation of prenatal diagnosis), postpartum surgical intervention (if performed), results of additional examinations in the neonatal intensive care unit (cranial US, MRI), prognosis of those born in our center, and long-term follow-up of accessible cases. Sixty-seven patients were excluded from the study due to missing data. Patients who were referred from other medical institutions who had been delivered at other hospitals were excluded from the study due to a lack of sufficient data, together with some of our own patients who had missing data (n=67).

In cases where parents chose to terminate their pregnancy, we analyzed the gestational age at the time of termination, types of anomalies, and results of the autopsy of the fetuses (in cases with parental permission). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22®, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software package. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. Normally distributed data are presented as mean and standard deviations, whereas non-parametric data are presented as median (minimum-maximum values). The study protocol was approved by Hacettepe University Ethics Committee (GO 17/161). Written informed consents were obtained from all of the participants of the study.

Results

Abnormalities (n=250) were classified as follows: anencephaly (n=4), neural tube defect (NTD)/Arnold-Chiari malformation (n=58), holoprosencephaly (HPE) (n=10), disorders of the corpus callosum (CC) (n=31), Dandy-Walker malformation (DWM) (n=30), mega cisterna magna (MCM) (n=13), vermian hypoplasia (n=2), porencephalic cysts (n=6), lissencephaly (n=3), hydranencephaly (n=21), craniosynostosis (n=4), mild (10 to 12 mm) ventriculomegaly (n=49), moderate (13 to 15 mm) ventriculomegaly (n=7), and severe (≥16 mm) ventriculomegaly (n=12).

After the exclusion of patients with missing data (n=67), the remaining cases (n=183) were as follows: anencephaly (n=4), NTD/Arnold-Chiari malformation (n=44), holoprosencephaly (n=7), disorders of the CC (n=25), DWM (n=20), MCM (n=5), vermian hypoplasia (n=2), porencephalic cysts (n=5), lissencephaly (n=2), hydranencephaly (n=20), craniosynostosis (n=3), mild (10 to 12 mm) ventriculomegaly (n=32), moderate (13 to 15 mm) ventriculomegaly (n=6), and severe (≥16 mm) ventriculomegaly (n=8).

The mean maternal age was 28.2±5.5 years, mean gravida was 2.2±1.3, and the mean gestational age at diagnosis was 30.5±5.5 weeks.

A total of 75 out of 183 mothers (41%) chose pregnancy termination. The remaining 108 mothers' pregnancy follow-up and deliveries were performed at our center. The distribution of CNS anomalies in the termination group and the remaining patients are shown in Table 1.

Termination group (n=75)

In the termination group, the mean maternal age was 27.9±5.4 years, mean gravida was 2.2±1.5, and the mean gestational age during prenatal diagnosis was 21.3±4.1 weeks. The distribution of anomalies in this group is shown in Table 1. Twenty babies (20/75, 26.6%) in this group had additional anomalies other than those of the CNS (Table 2).

Fetal MRI was performed on 5 patients in this group. Preliminary prenatal diagnoses were hydranencephaly (n=3), cerebellar hypoplasia (n=1), and CC agenesis (ACC) (n=1). ACC was additionally detected using MRI in all of the 3 patients with hydranencephaly. The preliminary diagnoses of ACC and cerebellar hypoplasia were consistent with fetal MRI results.

Mothers of 11 patients (11/75, 14.6%) agreed to a karyotype analysis. Nine of these eleven patients had normal karyotype results. In the two other cases, a triploidy and 46,XY,ins(12;2) case were detected. The 46,XY,ins(12;2) case had additional anomalies as indicated in Table 2. No additional anomalies were observed in the case of the triploidy.

Patients who gave birth at our hospital (n=108)

The mean maternal age was 28.1±5.6 years, mean gravida was 2.1±1.3, and the mean gestational age at diagnosis was 29.2±5.1 weeks in this group. The distribution of anomalies in this group is shown in Table 1. Eight babies (8/108, 7.4%) in this group had additional anomalies other than those of the CNS (Table 3).

Fetal MRI was performed on 8 patients in this group. The preliminary prenatal diagnosis included mild ventriculomegaly (10-12 mm) (n=4), DWM (n=1), porencephalic cysts (n=1), ACC (n=1), and NTD/Arnold-Chiari malformation (n=1). The preliminary diagnosis of 6 cases was consistent with the fetal MRI result. The MRI diagnosis was consistent with ACC in the patient with pre-existing porencephalic cysts. Delay in brain sulcation was detected on MRI in the case of pre-diagnosis of ACC.

Mothers of 11 patients (11/75, 9.2%) agreed to a karyotype analysis. Nine of eleven patients had normal karyotype analysis results. Trisomy 18 was detected in one fetus and trisomy 13 was detected in another. These 2 fetuses' additional anomalies are defined in Table 3.

Table 1. The distribution of CNS anomalies in the termination group

	Terminated	Delivery	Total
Anencephaly	3 (4%)	1 (0.9%)	4 (2.2%)
NTD/Arnold-Chiari malformation	22 (29.3%)	22 (20.4%)	44 (24%)
HPE	4 (5.3%)	3 (2.8%)	7 (3.8%)
Disorders of the CC	7 (9.3%)	18 (16.7%)	25 (13.7%)
DWM	14 (18.7%)	6 (5.6%)	20 (10.9%)
MCM	0	5 (4.6%)	5 (2.7%)
Vermia hypoplasia	1 (1.3%)	1 (0.9%)	2 (1.1%)
Porencephalic cysts	0	5 (4.6%)	5 (2.7%)
Lissencephaly	2 (2.7%)	0	2 (1.1%)
Hydranencephaly	17 (22.7%)	3 (2.8%)	20 (10.9)
Mild ventriculomegaly (10-12 mm)	0	32 (29.6%)	32 (17.5%)
Moderate ventriculomegaly (13-15 mm)	0	6 (5.6%)	6 (3.3%)
Severe ventriculomegaly (≥16 mm)	3 (4%)	5 (4.6%)	8 (4.4%)
Craniosynostosis	2 (2.7%)	1 (0.9%)	3 (1.6%)
Total	75 (100%)	108 (100%)	183 (100%)

CC: Corpus callosum, CNS: Central nervous system, DWM: Dandy-Walker malformation, NTD: Neural tube defect, HPE: Holoprosencephaly, MCM: Mega cisterna magna

Postnatal outcomes of neonates (n=108)

The mean birth weight was 3060±647.5 g, mean gestational week at delivery was 37.9±1.7, and mean APGAR score (5th minute) was 8.8±2.3. There were seven (6.5%) in vitro fertilization (IVF) pregnancies, the others were spontaneous pregnancies (93.5%). Sixty-nine of the neonates were male (63.8%) and 39 (36.2%) were female.

Intrauterine growth restriction (IUGR) was present in 12 neonates (11.1%). The remaining 96 neonates' birth weights were compatible with the gestational week at delivery (88.9%). Patients with IUGR (n=12), had mild ventriculomegaly (n=3), severe ventriculomegaly (n=1), HPE (n=2), CC disorders (n=2), DWM (n=2), hydranencephaly (n=1), and NTD/Arnold-Chiari malformation (n=1).

Four neonates died in the neonatal intensive care unit on the postpartum first day. Three of these four babies had IUGR (1 DWM, 1 CC disorders, and 1 HPE). These three babies were born at term (39th, 40th, and 37th gestational week, respectively). The remaining one neonate, with anencephaly, was born at the 33rd gestational week and without IUGR. This fetus was referred to our center from another health care center with preterm prelabor rupture of the membranes. The remaining 104 neonates all underwent postnatal testing and treatment (if any) in the neonatology department.

Neonates whose prenatal diagnosis was consistent with postnatal definitive diagnosis (n=60, 55.6%)

Postnatal examinations and imaging (US and/or MRI) were used for the definitive diagnosis of the CNS anomalies of the 108 neonates who were born at our center. Patients with a postnatal final diagnosis of anencephaly (n=1), NTD/Arnold-Chiari malformation (n=22), holoprosencephaly (n=3), DWM (n=6), vermian hypoplasia (n=1), hydranencephaly (n=3), craniosynostosis (n=1), and severe (≥16 mm) ventriculomegaly (n=5), were consistent with their prenatal diagnosis. Furthermore, diagnoses were consistent with the prenatal diagnosis of porencephalic cyst in one case, men who have sex with men (MSM) in one case, and CC disorders in 16 cases.

Neonates whose prenatal diagnosis was discordant with postnatal definitive diagnosis (n=48, 45.4%)

In the porencephalic cyst group (n=4), ACC was detected in 3, and resorbed hematoma was detected in 1 neonate. In the MCM group (n=5), 4 were normal at the neonatal period. In the CC disorders group, 2 were normal at the neonatal period. In the moderate (13 to 15 mm) ventriculomegaly group (n=6), five fetuses were normal and one fetus had mild ventriculomegaly at the neonatal period. All patients in the mild (10 to 12 mm) ventriculomegaly group (n=32) had normal postnatal

diagnostic results. In the postnatal period evaluation, 44 babies were totally normal.

Surgical intervention outcomes

Operated group: Neurosurgical procedures (n=28, 26%) included the repair of myelomeningocele and ventriculo-peritoneal (VP) shunt insertions. These 28 neonates had NTD/Arnold-Chiari malformation (n=20), and patients with CC disorders (n=4), severe ventriculomegaly (n=1), hydranencephaly (n=1), cerebellar hypoplasia (n=1), and DWM (n=1) had undergone VP shunt operation due to hydrocephalus. One of these patients died at the postoperative 6th month, the others survived.

Table 2. Additional anomalies in the termination group other than CNS

Case no	Gestational age at diagnosis	CNS anomaly	Additional anomalies other than CNS	Karyotyping results (if performed)
1	23.40	NTD, Arnold-Chiari malformation	VSD, TGA	-
2	23.30	DWM	VSD	-
3	24.40	CC disorders	Shortness in all long bones, flexion contracture in hands	-
4	24.20	Lissencephaly	Single umbilical artery, short femur	-
5	18.20	Hydranencephaly	HLHS	-
6	24.10	HPE	PS, bilateral rocker bottom foot	-
7	27.30	DWM	VSD, TGA	Normal
8	29.40	DWM	TOF	
9	26.20	DWM	Nasal bone hypoplasia	46,XY,ins(12:2)
10	18.00	Hydranencephaly	flexion contracture in all extremities	-
11	18.50	CC disorders	Bilateral dysplastic kidney, flexion contracture in hands, bilateral club foot	-
12	19.00	NTD, Arnold-Chiari malformation	dextrocardia	-
13	21.50	Severe ventriculomegaly (>16 mm)	Bilateral dysplastic kidney	-
14	17.40	Craniosynostosis	Sandal gap sign at right foot, hypertelorism	-
15	25.30	NTD, Arnold-Chiari malformation	Bilateral club foot	-
16	19.10	NTD, Arnold-Chiari malformation	Bilateral club foot	-
17	29.30	DWM	Bilateral pleural effusion	-
18	19.20	Severe ventriculomegaly (>16 mm)	Abdominal lymphangioma	Normal
19	22.40	DWM	Bilateral multicystic dysplastic kidney,	-
20	26.40	Craniosynostosis	Micromelia in all extremities	-

CC: Corpus callosum, CNS: Central nervous system, DWM: Dandy-Walker malformation, HLHS: Hypoplastic left heart syndrome, HPE: Holoprosencephaly, NTD: Neural tube defect, PS: Pulmonary valve stenosis, TGA: Transposition of the great arteries, TOF: Tetralogy of fallot, VSD: Ventricular septal defect

Table 3. Additional anomalies in the delivery group other than CNS

Case no	Gestational age at diagnosis	CNS anomaly	Additional anomalies other than CNS	Karyotyping results (if performed)
1	25.0	DWM	Cleft palate and lip, VSD	Trisomy 13
2	24.1	Mild ventriculomegaly (10-12 mm)	Single umbilical artery	Normal
3	33.2	NTD, Arnold-Chiari malformation	Rocker bottom foot	-
4	33.5	Mild ventriculomegaly (10-12 mm)	Hydroureteronephrosis (right sided)	-
5	30.6	HPE	HLHS	-
6	26.40	DWM	Single umbilical artery	-
7	28.00	CC disorders	Single umbilical artery, VSD	-
8	31.00	Hydranencephaly	Bilateral club foot, VSD, Single umbilical artery	Trisomy 18

CC: Corpus callosum, CNS: Central nervous system, DWM: Dandy-Walker malformation, HLHS: Hypoplastic left heart syndrome, HPE: Holoprosencephaly, NTD: Neural tube defect, VSD: Ventricular septal defect

Eleven neonates from this operated group received long-term follow-ups at our centers in the Children's Hospital (Hacettepe Children's Hospital). All 11 children had severe motor mental retardation (MMR). In two patients, neurogenic bladder was diagnosed. It was learned that the families of the other two NTD/Arnold-Chiari malformation patients, who could not be operated on, refused treatment and left the hospital with the neonates.

Non-operated group: There were 76 neonates (70%) that did not undergo surgery in our center. It was learned that 12 of the remaining 76 neonates who did not undergo surgery had died. The distribution of these 12 fetuses was as follows: anencephaly (n=1), mild ventriculomegaly (death due to kidney failure in the postnatal period) (n=1), moderate ventriculomegaly (postnatal diagnosis of Walker-Warburg syndrome) (n=1), HPE (n=2), ACC (n=1), DWM (n=2; one fetus had trisomy 18 and one fetus had trisomy 13), MSM (due to heart failure at the postnatal period) (n=1), porencephalic cyst (n=1), and hydranencephaly (n=1). One child who had a porencephalic cyst diagnosis prenatally and periventricular hemorrhage diagnosis in the postnatal period died at the age of six years.

A total of 31 of the remaining 64 un-operated patients continued their long-term follow-ups at our hospital. We could not track the information of the remaining 33 patients because they completed long-term follow-ups at other centers. Twenty-two of these 31 patients were found to be neurologically normal; these included cases of CC disorder (n=3) for which the postnatal diagnoses was CC hypoplasia, MSM (n=1), moderate ventriculomegaly (n=2), and mild ventriculomegaly (n=16).

The remaining nine children had the following postnatal diagnoses: epilepsy [n=4; prenatal diagnoses were mild ventriculomegaly (n=1), severe ventriculomegaly (n=1), and ACC (n=2)], metabolic disorder (n=1; methylmalonic acidemia, prenatal diagnosis was moderate ventriculomegaly), lalopathy (n=1; prenatal diagnosis was severe ventriculomegaly), and MMR [n=3; prenatal diagnoses were porencephalic cyst (n=1), CC disorders (n=1), and severe ventriculomegaly (n=1)]. One of the patients with MMR (the patient with CC disorder) had the diagnosis of trisomy 9 and monosomy 21 by postnatal genetic counseling. This child's family had not accepted a karyotype analysis in the prenatal period.

Discussion

CNS malformations are the second most common cause of congenital anomalies, after congenital heart disease (5,6). Management and correct diagnosis remain a challenge for physicians. Many studies have been conducted to identify and classify major CNS anomalies. CNS malformations can be briefly classified as follows: NTD/Arnold-Chiari malformations (exencephaly, anencephaly, cephalocele, iniencephaly, spinal dysraphism/spina bifida, Arnold-Chiari type ll malformation), ventriculomegalies (mild, moderate, or severe), and those other than neural tube defects and ventriculomegaly [holoprosencephaly, CC disorders, cavum septi pellucidi, cavum vergae and cavum veli interpositi anomalies, posterior fossa abnormalities (DWM, MSM, Blake's pouch cyst, vermian hypoplasia), arachnoid cysts, aneurysm of the vein of Galen, schizencephaly, porencephalic cysts, hydranencephaly, lissencephaly, pachygyria, microgyria, heterotopias, and tumors] (1).

The screening and diagnostic process of these conditions started with ms-AFP screening, continued with USG, and now extends to fetal MRI. A thorough understanding of the normal sonographic appearance of the CNS across gestation is crucial for an accurate diagnosis because the presence or absence of a structure may be normal or abnormal depending on the age of the fetus. Poor timing of the examination, rather than poor sensitivity, can be an important factor in failing to detect a CNS abnormality (7). For example, a sonogram of the fetal brain at 14 weeks of gestation cannot detect ACC because the CC does not become sonographically apparent until 18 to 20 weeks of gestation and does not reach its final form until 28 to 30 weeks. Ideally, pregnancies at increased risk of fetal CNS anomalies and those with suspicious findings on a basic examination should undergo fetal neurosonography performed by physicians with expertise in this area. Our mean gestational age at diagnosis was 29.18±5.05 weeks. Late-diagnosed cases arise because patients live beyond reach of a healthcare center providing routine second-trimester screening.

MRI is an option for further evaluation in cases of diagnostic uncertainty when additional information will influence subsequent management of the pregnancy (7). The absence of shadowing artifacts and the better contrast resolution provided by fetal MRI compared with ultrasound makes it particularly suited for detailed imaging of the fetal brain (8,9). Fetal MRI is a relatively new method in our center, and our radiology team is more experienced at CNS malformations from congenital anomalies. There were 13 fetal MRIs in our series. Their US diagnosis, MRI diagnosis, and additional MRI findings are shown in Table 4. US diagnoses were correct in these patients and the MRIs gave additional findings in five patients.

Different anomalies and chromosomal and non-chromosomal syndromes can be accompanied by CNS anomaly subgroups (10-12). Their frequency and prognostic effects differ according to the anomalies (13). We identified 28 fetuses with extra structural abnormalities outside the CNS in our series (out of the total number of patients, including those in both termination and delivery groups). There were four cases of chromosomal abnormalities; trisomy 13, trisomy 18,46,XY,ins(12:2), and trisomy 9+monosomy 21 (postnatal diagnosis; prenatal

Table 4. Additional findings in MRI

Case no	US diagnosis	MRI diagnosis	Additional findings at MRI
1	Hydranencephaly	Hydranencephaly	CC agenesis
2	Hydranencephaly	Hydranencephaly	CC agenesis
3	Hydranencephaly	Hydranencephaly	CC agenesis
4	Hypoplasia of cerebellum	Hypoplasia of cerebellum	-
5	CC agenesis	CC agenesis	-
6	Mild ventriculomegaly (10-12 mm)	Mild ventriculomegaly (10-12 mm)	-
7	Mild ventriculomegaly (10-12 mm)	Mild ventriculomegaly (10-12 mm)	-
8	Mild ventriculomegaly (10-12 mm)	Mild ventriculomegaly (10-12 mm)	-
9	Mild ventriculomegaly (10-12 mm)	Mild ventriculomegaly (10-12 mm)	-
10	DWM	DWM	-
11	Porencephalic cyst	Porencephalic cyst	CC agenesis
12	CC agenesis	CC agenesis	Delay in brain sulcation
13	NTD, Arnold-Chiari malformation	NTD, Arnold-Chiari malformation	-

CNS: Central nervous system, NTD: Neural tube defect, CC: Corpus callosum, DWM: Dandy-Walker malformation, VSD: Ventricular septal defect, MRI: Magnetic resonance imaging

diagnosis was unavailable because of lack of family consent). We also had two cases of Walker-Warburg syndrome and methylmalonic acidemia in the postnatal period.

When we evaluated perinatal, obstetric, and neonatal outcomes, we did not detect a greater frequency of IUGR, preterm delivery, or IVF pregnancies, contrary to previous work (14). Indeed, there is no clear evidence in literature for these associations with CNS anomalies.

Prenatal diagnosis is very important for parents deciding whether to continue or terminate their pregnancy, and to prepare themselves for the results. A recent review reported that the prenatal diagnosis of CNS anomalies and autopsy outcomes were 79.4% compatible (15). Also, it was reported that the prenatal diagnosis of CNS anomalies is the most consistent anomaly group in autopsy (15). In our series, prenatal and postnatal diagnoses were consistent in 55.6% of the diagnoses. On the other hand, the discordant group consisted of cases with prenatal diagnosis of porencephalic cyst, MCM, CC and moderate/mild ventriculomegaly. Porencephalic cysts are observed as a fluid-filled cavity in the cerebral hemisphere and they can involve the infratentorial or supratentorial space or both. The differential diagnosis can be challenging as tumoral lesions, arachnoid cysts and intracranial hemorrhagic changes may mimic the US findings according to a recent study in France (16). ACC was detected in 3, and resorbed hematoma was detected in 1 neonate whose prenatal diagnosis was porencephalic cyst in our study. MCM refers to enlargement of the cicterna magna to >10 mm on an oblique transverse plane with normal cerebellar hemispheres and vermis. In a systemic review of isolated prenatal posterior fossa malformations, the rates of additional CNS and other system anomalies were found as 12.6% and 16.6%, respectively (17). Furthermore, isolated MCM has a favorable outcome (18). The differential diagnosis of posterior fossa enlargement is another challenging subject in prenatal diagnosis and MCM, Blake's pouch cyst and vermian hypoplasia may all cause similar US findings (19). MCM may resolve after delivery or it may be variant of normal anatomy (19). Four out of five neonates in this group had normal findings in the postnatal period.

Prenatal diagnosis for the disorders of the CC may be difficult for physicians. Developmental abnormalities of the CC include complete agenesis, partial agenesis, hypoplasia or hyperplasia. In a retrospective study that included 1722 prenatal US examinations, a positive predictive value of 47% (95% CI: 38-56) and a negative predictive value of 97% (95% CI: 96-98) were found for detecting agenesis of CC (20). In the CC disorders group, 2 were normal at the neonatal period in our study. Fetuses with isolated mild ventriculomegaly had a normal postnatal evaluation in more than 90% of cases and isolated moderate ventriculomegaly was associated with normal neonatal outcomes in 75% to 93% of cases, according to a recent review (21). In the moderate (13 to 15 mm) ventriculomegaly group (n=6), five fetuses were normal and one fetus had mild ventriculomegaly in the neonatal period. Additionally, all patients in the mild (10 to 12 mm) ventriculomegaly group (n=32) had normal postnatal diagnostic results in our study. Thus, our results were consistent with the literature and most of the discussed US findings in the discordant prenatal diagnosis group were probably variants of normal anatomy. On the other hand, a vast majority of the congenital CNS anomalies that were associated with adverse neonatal outcomes were detected prenatally in our institution.

The greatest problem with these pregnancies is the care of children after birth, and the spiritual and monetary burden on the family as well as the State. We were able to reach long-term follow-ups of 42 children in our series (operated and un-operated). Many of these children had mild and moderate ventriculomegaly (n=18). It is well known that an isolated, mild-to-moderate ventriculomegaly is linked to an abnormal outcome in 10%-20% of children (14), whereas ventriculomegaly with associated anomalies, or as part of a more complex syndrome, is characterized by abnormal outcomes in up to 40%-50% of children (22). In our study, all of the cases that resulted normally in follow-up were isolated. We could not determine the postnatal diagnosis of infants who died in the postnatal period who received a diagnosis of mild ventriculomegaly in the prenatal period because of families' refusal of additional tests or autopsy. However, it is suspected that these deaths were related to the syndrome. Another patient with a prenatal diagnosis of mild ventriculomegaly was diagnosed as having epilepsy in the postnatal period.

Severe ventriculomegaly has often shown to be associated with poor neurologic outcomes in continued pregnancies (23). Long-term follow-ups of the three patients with severe ventriculomegaly in our series were as follows: one had severe MMR, one was epileptic, and one had lalopathy. Patients with NTD/Arnold-Chiari malformation who continued with post-operative follow-ups had severe MMR (n=11). Approximately 75% of patients who undergo myelomeningocele repair in infancy survive into early adulthood (24,25). Long-term prognosis is dependent upon the following factors: myelomeningocele level (thoracic and high lumbar defects are associated with greater disability and a higher risk of mortality compared with sacral and lower lumbar defects), the severity of the Chiari II malformation (a greater degree of hindbrain herniation is associated with a worse prognosis), and presence or absence of hydrocephalus (hydrocephalus is associated with greater disability and a higher risk of mortality). In addition, many of the complications (e.g., shunt malfunction, tethered cord, scoliosis, hydromyelia, and seizures) may negatively impact long-term prognosis. All of these details that predicted the prognosis were not completely clear in our data. However, it has previously been reported that 73% of these patients were neurologically symptomatic at any level (26). From this point of view, the current results support these data. For example, 6 patients with CC disorders whose follow-ups are ongoing at our center, support the findings of variable outcomes of CC disorders (27). It was seen that three of these patients were neurologically normal, two were epileptic, and one had severe MMR (the patient with trisomy 9+monosomy 21).

In the long-term follow-up of a patient who was diagnosed as having a porencephalic cyst in the prenatal period, hydrocephalus developed during the postnatal period, and the child now has severe MMR. The last patient under long-term follow-up is the child with MCM. It has been previously reported that, when isolated, MCM has a favorable outcome in 92% to 100% of cases (28).

The main strengths of our study were the relatively high sample size, which reflected over ten years' data and the presence of long-term neonatal outcomes in most cases. However, its retrospective design and single-center experience are the main limitations of our study.

In conclusion, CNS anomalies have a broad spectrum and, even within disorders, their prognosis varies greatly. Diagnosis in the prenatal period is important for families so they can prepare themselves for the postnatal challenging treatment/rehabilitation process and determine the course of the pregnancy. Finally, these type of case series are becoming more and more important in preparing defensive reports to medic-legal issues.

Ethics Committee Approval: *The study protocol was approved by Hacettepe University Ethics Committee (GO 17/161).*

Informed Consent: *Written informed consents were obtained from all of the participants of the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Design - E.A., M.S.B.; Critical Review - M.Y., M.S.B.; Data Collection and/or Processing - M.S.B.; Analysis and/or Interpretation - E.A., A.T., M.S.B.; Writer - E.A., A.T., M.B., H.U., M.Y., M.S.B.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Icenogle DA, Kaplan AM. A review of congenital neurologic malformations. Clin Pediatr (Phila) 1981; 20: 565-76.
2. De Noronha L, Medeiros F, Martins VD, Sampaio GA, Serapiao MJ, Kastin G, et al. Malformations of the central nervous system: analysis of 157 pediatric autopsies. Arq Neuropsiquiatr 2000; 58: 890-6.
3. Kehl S, Schelkle A, Thomas A, Puhl A, Meqdad K, Tuschy B, et al. Single deepest vertical pocket or amniotic fluid index as evaluation test for predicting adverse pregnancy outcome (SAFE trial): a multicenter, open-label, randomized controlled trial. Ultrasound Obstet Gynecol 2016; 47: 674-9.
4. Rossi AC, Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system

anomalies: a systematic review of the literature. Ultrasound Obstet Gynecol 2014; 44: 388-93.
5. Spirt BA, Oliphant M, Gordon LP. Fetal central nervous system abnormalities. Radiol Clin North Am 1990; 28: 59-73.
6. Bayar Ü, Başaran M, Usal D, Özcan O, Kalaycı M. Prenatal diagnosis and management of congenital abnormalities of central nervous system. Gynecology Obstetrics & Reproductive Medicine 2006; 12: 202-8.
7. Rossi C, Brisou G, Baseggio L, Roch J, Safar V, Karlin L, et al. Central nervous system involvement in chronic lymphocytic leukemia: uncommon manifestation with undefined therapeutic management. Leuk Lymphoma 2014; 55: 1939-41.
8. Pugash D, Brugger PC, Bettelheim D, Prayer D. Prenatal ultrasound and fetal MRI: the comparative value of each modality in prenatal diagnosis. Eur J Radiol 2008; 68: 214-26.
9. Weston MJ. Magnetic resonance imaging in fetal medicine: a pictorial review of current and developing indications. Postgrad Med J 2010; 86: 42-51.
10. Wallis D, Muenke M. Mutations in holoprosencephaly. Hum Mutat 2000; 16: 99-108.
11. Timor-Tritsch IE, Monteagudo A, Cohen HL. Ultrasonography of the prenatal and neonatal brain: McGraw-Hill, Medical Publishing Division; 2001.
12. Balci S, Aypar E, Altinok G, Boduroglu K, Beksac MS. Prenatal diagnosis in three cases of iniencephaly with unusual postmortem findings. Prenat Diagn 2001; 21: 558-62.
13. Paladini D, Volpe P. Ultrasound of Congenital Fetal Anomalies: Differential Diagnosis and Prognostic Indicators: Taylor & Francis; 2007.
14. Levi Setti PE, Moioli M, Smeraldi A, Cesaratto E, Menduni F, Livio S, et al. Obstetric outcome and incidence of congenital anomalies in 2351 IVF/ICSI babies. J Assist Reprod Genet 2016; 33: 711-7.
15. Rossi AC, Prefumo F. Correlation between fetal autopsy and prenatal diagnosis by ultrasound: A systematic review. Eur J Obstet Gynecol Reprod Biol 2017; 210: 201-6.
16. Abergel A, Lacalm A, Massoud M, Massardier J, des Portes V, Guibaud L. Expanding porencephalic cysts: prenatal imaging and differential diagnosis. Fetal Diagn Ther 2017; 41: 226-33.
17. D'Antonio F, Khalil A, Garel C, Pilu G, Rizzo G, Lerman-Sagie T, et al. Systematic review and meta-analysis of isolated posterior fossa malformations on prenatal ultrasound imaging (part 1): nomenclature, diagnostic accuracy and associated anomalies. Ultrasound Obstet Gynecol 2016; 47: 690-7.
18. Liu Z, Han J, Fu F, Liu J, Li R, Yang X, et al. Outcome of isolated enlarged cisterna magna identified in utero: experience at a single medical center in mainland China. Prenat Diagn 2017; 37: 575-82.
19. Wüest A, Surbek D, Wiest R, Weisstanner C, Bonel H, Steinlin M, et al. Enlarged posterior fossa on prenatal imaging: differential diagnosis, associated anomalies and postnatal outcome. Acta Obstet Gynecol Scand 2017; 96: 837-43.
20. Craven I, Bradburn MJ, Griffiths PD. Antenatal diagnosis of agenesis of the corpus callosum. Clin Radiol 2015; 70: 248-53.
21. Society for Maternal-Fetal Medicine (SMFM); Electronic address: pubs@smfm.org, Fox NS, Monteagudo A, Kuller JA, Craigo S, Norton ME. Mild fetal ventriculomegaly: diagnosis, evaluation, and management. Am J Obstet Gynecol 2018; 219: 2-9.
22. Bulas D. Fetal magnetic resonance imaging as a complement to fetal ultrasonography. Ultrasound Q 2007; 23: 3-22.
23. Breeze AC, Alexander PM, Murdoch EM, Missfelder-Lobos HH, Hackett GA, Lees CC. Obstetric and neonatal outcomes in severe fetal ventriculomegaly. Prenat Diagn 2007; 27: 124-9.
24. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA. Spina bifida outcome: a 25-year prospective. Pediatr Neurosurg 2001; 34: 114-20.
25. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. Lancet 2010; 375: 649-56.
26. Amer N, Amer M, Kolkailah M, Al-Dumairy M. Foetal central nervous system anomalies: frequency and foeto-maternal outcome. J Pak Med Assoc 2014; 64: 1282-6.
27. Vasudevan C, McKechnie L, Levene M. Long-term outcome of antenatally diagnosed agenesis of corpus callosum and cerebellar malformations. Semin Fetal Neonatal Med 2012; 17: 295-300.
28. Garel C, Moutard ML. Main congenital cerebral anomalies: how prenatal imaging aids counseling. Fetal Diagn Ther 2014; 35: 229-39.

Evaluation and comparison of the effects of various cognitive-behavioral therapy methods on climacteric symptoms: A systematic review study

Leila Mollaahmadi[1], Afsaneh Keramat[2], Nasrin Changizi[3], Mansoureh Yazdkhasti[4], Bahare Afshar[5]

[1]Student Research Committee, School of Nursing and Midwifery, Shahroud University of Medical Sciences, Shahroud, Iran
[2]Reproductive Studies and Women's Health Research Center, Shahroud University of Medical Sciences, Shahroud, Iran
[3]Ministry of Health and Medical Education, Tehran, Iran
[4]Department of Midwifery, School of Medicine, Social Determinants of Health Research Center, Alborz University of Medical Sciences, Karaj, Iran
[5]Student Research Committee, School of Nursing and Midwifery, Iran University of Medical Sciences, Tehran, Iran

Abstract

Objective: Climacteric syndrome, which is related to many symptoms, often causes discomfort in women. Non-pharmacologic treatment is one of the treatment options for affected individuals, and this syndrome can be cured with psychological treatments such as cognitive behavioral therapy (CBT). The present study aimed to compare the efficacy of various CBT methods on the improvement of climacteric symptoms.

Material and Methods: PubMed, Scopus, Cochrane, Medline, PsycINFO, and Google Scholar were searched for relevant articles published between January 1990 and August 2018. Data extraction and quality assessment were conducted by two authors.

Results: A total of 15 articles including 910 women were entered. We divided the CBT methods into two categories, face-to-face (individual and group CBT) and indirect (self-help CBT) methods. Among the three CBT approaches, three articles covered individual CBT, nine articles carried out group CBT, and in five articles, the self-help approach was used. The climacteric symptoms that improved with CBT were categorized into three groups as vasomotor symptoms, psychological symptoms, and organic disorders. Generally, the face-to-face method played a key positive effect on symptom improvement, and the group CBT approach was more effective on psychological symptoms.

Conclusion: Although the indirect method is more cost-effective, it has less impact than the face-to-face method; it is better to use face-to-face approaches to achieve better results, if possible. Further studies are required in this regard, particularly in the individual and self-help CBT approaches, to measure the impact of these approaches on more varied symptoms of menopause. (J Turk Ger Gynecol Assoc 2019; 20: 178-95)

Keywords: Climacteric, cognitive behavioral therapy, menopause, symptoms

Received: 29 December, 2018 **Accepted:** 5 February, 2019

Introduction

Climacteric and menopause are closely related concepts; however, they do not denote to exactly the same thing. Climacteric is the process of aging in women, including three periods. The first stage is peri-menopause, occurring within one and eight years before the beginning of menopause. A series of gradual changes occur during this period. The second period is menopause, which is confirmed by having experienced a year of amenorrhea, and the postmenopausal stage, which is the third phase, begins when menopause is confirmed and lasts until old age (1). From a practical point of view, the term *menopause* globally refers to the aging process of the ovary and includes any period of peri-menopausal and postmenopausal in women (2).

The climacteric period can be associated with symptoms in four different classifications: 1- vasomotor vegetative symptoms (e.g. hot flashes, night sweats, palpitations); 2- psychological symptoms (e.g. anxiety, depression, nervousness, insomnia, decreased libido, memory loss, melancholy, fatigue); 3- organic disorders (e.g. osteoporosis, cutaneous atrophy, urogenital atrophy, arthralgia, myalgia); and 4- metabolic disorders (e.g. obesity, arterial hypertension) (Table 1). The pathogenesis is related to a decline in sex hormone concentration, particularly the decrease in estrogens (3,4). Moreover, some factors such as genetic and lifestyle factors, psychological disposition and personal attitudes as well as educational background (5), have a key impact in experiencing menopause in the climacteric period in women (6). The average age of menopause is 51 years (7), and the age of menopause remains constant in spite of the increased life expectancy in women, Therefore, with an increase in life expectancy, women spend about one-third of their lives after menopause and have problems caused by menopausal symptoms (8). As expressed by women, they consider menopause "the beginning of new phase of life", "dissatisfaction with sexual acts" and "change in physical and mental health" (9). Thus, performing therapeutic interventions is essential to reduce the negative effect of climacteric syndrome on lifestyle.

Hormone replacement therapy (HRT) is the most extensively used treatment for the main symptoms of menopause, causing a 70-90% reduction of the symptoms (10). Although HRT has been the treatment of choice for climacteric syndrome for many years, uncertainty about its benefits and costs has emerged since the publication of the Women's Health Initiative's results (11). Many women prefer non-medical treatments for menopausal symptoms (12) and they are always concerned about the adverse effects and possible long-term health risks of HRT (13). Strong and convincing evidence exists indicating that the long-term risk of using estrogen and progestin to avoid postmenopausal diseases is much greater than its benefits (11). These results have challenged health providers to find alternative treatments for menopausal women (14). The evidence base for non-medical treatments is being increasingly examined with mixed results (4,13-22.) In addition, there has been considerable interest in developing effective nonmedical interventions to help women manage menopausal symptoms (4,17,19,23).

Considering the physical and psychological problems that occur in this period, it seems that non-medical therapies that help women to deal with their problems, particularly psychological therapies will be useful. Cognitive behavioral therapy (CBT) is one of the effective methods (24,25). Nowadays, CBT is used in the management of many conditions such as anxiety, depression, phobia, and stress (26). CBT-based psychological treatments were developed as treatments for menopausal disorders (21). This therapy helps people to think differently and due to this new thinking, they can confront undesirable events with more acceptable behaviors (27,28). In recent studies, it was shown that cognitive behavioral treatment, including psychoeducation, paced breathing/relaxation, and CBT could help women to manage symptoms such as HF/NS, which was acceptable to women, showed promise in exploratory trials of individual and group CBT, and reduced the symptoms (14,17,29).

Various CBT methods (group, individual and self-help CBT) were implemented in the climacteric period in several trials on the health of women.

The present systematic review aimed to compare the efficacy of various methods of CBT on the improvement of the climacteric symptoms.

Material and Methods

Search strategy

The current systematic literature review was performed using electronic databases such as PubMed, Scopus, Cochrane, Medline, PsycINFO, and Google Scholar. The search was performed from January 1990 to August 2018 by using the following related keywords in titles and abstracts (women OR female) AND (menopause* OR peri-menopause OR "post menopause") AND (climacteric treatment OR therapy OR "cognitive behavioral therapy" OR CBT OR "psychological treatment symptom") AND ("hot flashes" OR sweat OR anxiety OR depression OR insomnia OR "menopausal symptoms" OR "climacteric syndrome").

Moreover, the reference section of relevant trials, systematic reviews and meta-analyses were manually checked to recognize the related trials missed by electronic database searches.

Two authors independently conducted the search and screened studies against the inclusion criteria; first, the authors independently extracted data and then checked the extracted data. Any discrepancies were resolved via discussion and consensus.

The following data were extracted with the use of PICOS criteria: population (e.g. sample size, women with natural menopause), intervention (e.g. various CBT methods: group, individual and self-help CBT, duration, length of program), comparison (e.g. non-CBT therapy group or no treatment control), outcomes (e.g. reported in the form of the improvement scores of climacteric symptoms), study design (e.g. RCT, clinical trial, quasi-experimental). Thus, the data were extracted and classified under the following headings in systematic tables (Table 1-4): author, country, year (to establish a historical timeline), study design, sample size, specifications of population, comparison condition, scale, intervention, and the main findings of the studies, which can be reported in the form of scores and changes.

Address for Correspondence: *Afsaneh Keramat*
e.mail: keafsaneh@gmail.com ORCID: orcid.org/0000-0002-8728-7790

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2018.0170

Inclusion and exclusion criteria

The inclusion criteria for entering evidence in the current systematic review included original and quantitative interventional studies in English or at least with an English abstract, which could offer adequate information regarding the impact of any kind of CBT methods on the improvement of menopausal symptoms, which were published in peer-reviewed journals. Studies with randomized-control trial, clinical trial, experimental, semi-experimental, and pilot designs were entered and the subjects of the studies were healthy women in the climacteric period with normal menopause (not because of surgery) and receiving CBT for the treatment of the symptoms.

The exclusion criteria included the qualitative and quantitative interventional studies without numerical outcome data, and observational, cohort, case-control, cross-sectional, retrospective, and prospective studies were also excluded.

Screening

A total number of 1628 articles were identified and imported to Endnote X8, and after removal of duplicates (n=415), we screened titles and abstracts of the remaining articles (n=1213). After evaluating the inclusion criteria in remaining papers, the texts of 59 potentially relevant articles were fully assessed for more screening. These articles were evaluated for eligibility, and finally, 15 studies were entered in the current systematic review.

Based on the type of CBT interventions, the entered studies were classified into two groups based on the type of CBT interventions; the first classification was face-to-face CBT, including individual and group CBT, and the second was indirect CBT, containing self-help CBT. In the indirect method, the support is provided by a professional therapist by telephone, email, or any other communication tools.

Quality assessment

The quality of the studies was evaluated using the Cochrane Collaboration's tool to assess the risk of bias in randomized trials by two authors independently (27). In addition, the tool has six criteria assessed in the entered studies, which are random sequence generation, allocation concealment, description of drop-outs, blinding of participants and personnel, power analysis, and intention-to-treat analysis or no drop-outs. One point was given for each criterion observed in each study. Based on this assessment tool, the quality of a study was evaluated as "high" when five or six criteria were observed, "moderate" when three or four criteria were observed, and "low" when fewer than three criteria were observed. Any disagreements between the two authors were discussed until consensus was reached and if any variation remained, it was settled through discussions with a third researcher.

Results

From all the related papers, based on the title and abstract screening, we can observe the inclusion criteria in 15 studies. Figure 1 represents a flow diagram of PRISMA.

Characteristics of the included studies

A total of 15 articles were published between 1996 and 2018. Among all the final articles, the designs of most studies (n=8) were randomized controlled trials (RCTs) (17,19-21,31-35), three were pilot studies (4,14,34), one of the remaining articles had a randomized clinical trial design (36), and two studies were clinical trials (33,35), we also have a quasi-experimental design in all the articles (23). Among the articles, two articles of Hassan (31) and Khoshbooii (32) were obtained from the findings of one study and had similar results.

Demographic characteristics of subjects

According to the total number of subjects in all entered studies, 910 women were entered in the current systematic review. The sample size of the study population per study varied from 8 to 140 women, and the age range of the participants in the articles was assessed from 35 to 71 years.

The women involved in these studies were fairly healthy, mostly married or cohabiting, and had at least one child. Educational level was divided between those educated up to lower than primary school education, and the majority had at least elementary education and housekeeping (4,17,19,21,34,35,37). All of the participants were employed in one study (36). In two studies, the demographic variables were not described completely (14,33).

Methods of recruitment

Six studies recruited participants from health centers (17,21,31-33,35), three through Women's Health Clinics (4,23,34), and five studies through general practices, breast screening clinics, menopause websites, and local newspaper advertisements (14,19,20,37,38), and finally, one study recruited participants from public and private sectors (36).

The following scales were used in the entered studies to assess the symptoms changes: Insomnia Severity index, BDI-II Questionnaire, Women's Health Questionnaire, the Depression, Anxiety, and Stress Scale-21, Blatt's Kupperman Menopausal index, Hospital Anxiety and Depression scale, HF/NS problem-rating, Center for Epidemiologic Studies Depression scale, the Greene Climacteric scale, the Montgomery-Asberg Depression Rating scale, the Hamilton Anxiety scale, Menopause Rating scale, and the Hot Flashes Related Daily Interference scale.

The number of studies based on their countries included five studies from the United Kingdom, four from the United States, three from Iran, two from Spain, and one study from Switzerland.

Quality assessment

In total, the six quality criteria were assessed for 15 studies. The lowest score was 1 (four studies), and the highest score was 5 (three studies). The overall study quality was low, one study (6%) was rated with a high quality, six (40%) with a moderate quality, and eight (54%) with a low quality. The descriptions of the method were as follows: generation of the allocation sequence (sequence generation) was reported in zero studies; concealment of the allocation sequence (allocation concealment) was reported in 10 studies; blinding of the main outcome assessment was described in only five studies; in 10 studies, description of drop-outs was observed; a power-analysis was conducted in nine studies, and four studies had no drop-outs.

Features of CBT sessions

Generally, in these articles, the CBT sessions were held to improve the following climacteric symptoms, which from the highest to the lowest level, were as follows: hot flashes and night sweats (HF/NS), depression, anxiety, insomnia, nervousness, melancholy, myalgia, vertigo, fatigue, irritability, headaches, palpitations, paresthesia, dysesthesia, sleeping problems, cardiac symptoms, sexual problems, urinary symptoms, vaginal dryness, and joint and muscle pain. Table 1 presents the classification of these symptoms.

As mentioned earlier, in general, we divided the studies into two general classifications in terms of the CBT method used (face-to-face and indirect), where the face-to-face method includes individual CBT and group CBT. Based on the studies reporting the individual CBT, this approach was conducted in the form of 4-6 sessions of one hour per 6-8 weeks. In general, group CBT sessions consisted of 4 to 16 sessions of 60 to 160 minutes, usually held weekly, and women were in groups of 4 to 12 people. All studies considering the self-help CBT as a subset of indirect CBT used a booklet and participants had to complete this protocol during a 4-week period, and two studies, in addition to the booklet, had 2-week telephone guide sessions.

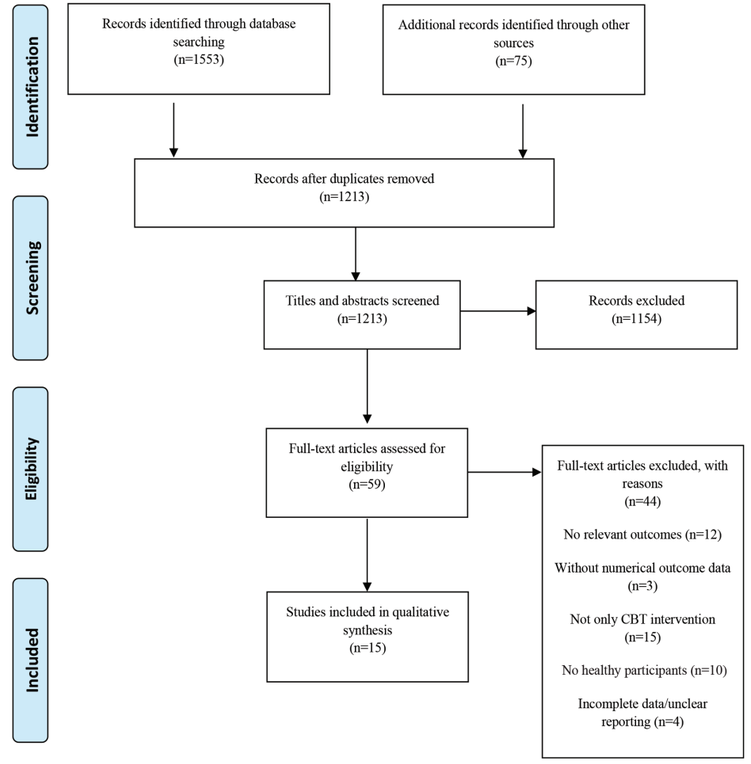


Figure 1. PRISMA flow diagram

Table 1. The classification of the climacteric symptoms improved by CBT

Vasomotor symptoms	Psychological symptoms	Organic disorder
Hot flash	Depression	Myalgia
Night sweat	Anxiety	Urinary complaints
Vertigo	Insomnia (sleeping problems)	Vaginal dryness
Headache	Nervous	Joint and muscle pain
Palpitation	Melancholy	
Paresthesia	Fatigue	
Cardiac complaints	Irritability	
	Sexual problems	

Statistical analysis

To assess the effect of CBT methods on climacteric symptoms and to assess clinically meaningful individual change in symptoms, symptom changes scores were calculated as follows (mean difference):

MD= Pre-treatment symptom score – Last post treatment symptom score

For better a comparison between all the main results, and so as to not equalize the score before the treatment in the studies, we converted the MD score to a percentage.

Accordingly, the number in the table in percentage form represents the decrease or increase in the severity of the symptoms after the treatment (compared with the initial score).

$$Percentage = \frac{MD}{Pre\text{-}treatment\ symptom\ score}$$

The Effect of CBT Methods on Climacteric Symptoms

a. The effect of evaluating each CBT approach on symptoms reviewed in studies (Table 2-4)

HF/NS frequency

According to the findings;

Individual CBT was able to decrease the pre-test score of HF/NS frequency up to 59% (Table 2).

Group CBT was successful in decreasing the initial score of HF/NS frequency by 3.9-40% (Table 3).

Self-help CBT made a decline in the baseline score of HF/NS frequency by 3.9-48% (Table 4).

HF/NS problem rating

Individual CBT caused a 33% reduction from the baseline score of HF/NS problem rating (Table 2).

Group CBT was able to make a 22-52% reduction in the pre-test score of HF/NS problem rating (Table 3).

Self-help CBT was successful in decreasing the initial score of HF/NS problem-rating by 20-52% (Table 4).

Hot flashes

Group CBT reduced baseline score of hot flashes by 11-57%.

Night sweats

Group CBT was not able to significantly reduce night sweats. In the study by Kefeer and Blanchard (14), group CBT reduced night sweats up to 41% in the immediate group, but the score was nearly doubled in the delay group (Table 3).

Depression

Individual CBT was able to make a 50-63% reduction in the pre-test score of depression (Table 2).

Group CBT was successful in decreasing the initial score of depression by 27-72% (Table 3).

Anxiety

Group CBT was able to reduce baseline scores of anxiety by 18-71% (Table 3).

Insomnia

Individual CBT caused a 73% reduction from the baseline score of insomnia (Table 2).

Group CBT could not only make a considerable failure in the baseline score of insomnia, but also caused a 19% increase in the pre-test score (Table 3).

Self-help CBT was successful in decreasing the initial score of insomnia by 71% (Table 4).

Nervousness

Group CBT was able to make an approximately 18% reduction in the pre-test score of nervousness in women (Table 3).

Melancholy

Group CBT was successful in decreasing the initial score of melancholy up to 41%.

Cardiac symptoms

Group CBT could cause a 42% reduction from the baseline score of cardiac symptoms.

Sexual problems

Group CBT was able to make a 29% reduction in the pre-test score of sexual problems.

Vaginal dryness

Group CBT was able to reduce the pre-test score of vaginal dryness up to 29%.

Urinary symptoms

Group CBT was not successful in decreasing the initial score of urinary symptoms and the score in the follow-up period had a 10% increase of baseline (Table 3).

Joint and muscle pain

Group CBT was successful in decreasing the initial score of joint and muscle pain up to 16%.

Myalgia, vertigo, fatigue, irritability, headaches, palpitations, paresthesia, and dysesthesia

Group CBT was unable to create a considerable decline in the follow-up score of each of them, separately (Table 3).

b. The effectiveness of the face-to-face CBT method

To evaluate this method, first of all, we will determine the impact of individual and group CBT approach according to Table 2 and Table 3 and our main findings mentioned above.

Individual CBT

Only three studies referred to this method, and if we determine which symptoms can be improved by this approach, HF/NS, the frequency in the vasomotor cluster can be indicated. Individual CBT can have excellent effects on insomnia, which is classified in the category of psychological symptoms. The overall findings of this approach cannot be regarded because few studies have evaluated the effects of individual CBT (Table 2).

Group CBT

Since only group therapy was conducted on each of the vasomotor symptoms separately, we can conclude that group CBT could not be successful in treating most of the vasomotor symptoms, and it just improved hot flashes and cardiac symptoms among the seven symptoms of this classification. However, it can make the HF/NS rate better than with the other approaches.

Most of the psychological symptoms (except insomnia) had a greater improvement in the group CBT approach, and only vaginal dryness in the organic disorder category could be under the effect of group CBT, and most of them did not have significantly positive changes. Generally, group CBT was more effective on psychological symptoms (Table 3).

c. The efficiency of indirect CBT method

In this part, we examine the self-help CBT approach.

Self-help CBT

Self-help CBT approach has improved symptoms such as HF/NS frequency and problem rating, but the individual approach is more effective. Also this approach had the same positive effect as individual therapy on insomnia (Table 4).

Discussion

Considering the many studies conducted to improve the menopause symptoms using group CBT, we can show that in general, the treatment group has more favorable effects on psychological symptoms. However, considering the fact that apart from group therapy, other approaches have not been applied to psychological symptoms and owing to the good effect of individual and self-help CBT in depression and insomnia, group CBT cannot be absolutely chosen as the best approach (31,32). Moreover, limited studies were conducted on individual and self-help CBT and most of them focused on HF/NS frequency and problem rating in each approach. Among these, individual CBT played a further role on HF/NS frequency, which due to the limited number of studies conducted using this approach, this part of our findings obtained from the results of one study cannot be generalized (17). Obviously, it is worth mentioning that group and self-help CBT also played a positive and similar role on HF/NS frequency, which resulted from more studies (33-38).

According to three articles comparing the different approaches (19,20,32), two studies compared the effects of group and self-help CBT on HF/NS frequency and problem rating. The group CBT treatment consists of psycho-education, stress management, paced breathing, and self-help CBT includes a self-help book that is learned during a four-week course and two phone calls made by a psychologist. Both of them, as already mentioned, indicated an almost equal effect of the two approaches; however, group CBT was somewhat more successful than self-help CBT (19,20), consistent with our findings.

In the study of Khoshbooii (32), the impacts of individual and group CBT on depression were compared with each other. The individual sessions are tailored to the needs of women and are flexible, but the general format of CBT sessions covered the main components such as psycho-education, cognitive interventions, behavioral interventions, assigning homework, and relapse prevention. According to their findings, both approaches had the same effect on depression, and the effect of individual CBT was negligibly greater than group CBT (32). In addition, as mentioned earlier, both group and individual CBT had a positive and significant impact on depression but the findings from group therapy were more widespread (32,34,35), which could be a result of the alterations in the conditions of the samples, the number of treatment sessions, the content or the kind of follow-up in studies; therefore, group CBT cannot be considered a guaranteed approach, but if properly implemented, it can reduce up to 72% of the initial depression score; otherwise, it can only be up to 27% effective. Thus, the preliminary treatment approach for depression can be group CBT sessions held in good conditions.

Based on the findings of the present study, it can be concluded that if an individual has an insomnia problem, group CBT cannot produce a good result, but individual and self-help

Face-to-Face CBT methods

Table 2. The efficiency of individual CBT on Climacteric symptoms

Author/year/ country	Study design	Sample size	Specifications of population	Comparison condition	Scale	Intervention	Main findings						
Nowakowski et al. (33)	Clinical trial	n total: 40	Mean age= 55±6.2 Reported ≥ 1 nocturnal hot flash	MEC Pre and post treatment	1. ISI 2.CES-D	MEC and CBTMI 4 sessions 50 minute over 8 weeks (Psycho-education cognitive interventions)	**SX***		**Pre-treatment**	**Post-treatment**	**MD (%)**		**p value**
							Insomnia severity	**CBTMI**	15±3.5	4±3.7	-11 (73%↓)		=0.003
								MEC	16±4.2	10±5.0	-6 (37%↓)		
							Depression	**CBTMI**	16±9.0	8±7.4	-6 (37%↓)		=0.019
								MEC	15±11.1	13±9.2	-2 (13%↓)		
Khoshbooii (32)	RCT	n total: 42 n intervention: 20 n control: 22	Age range: 41-55 With a depression score between 21- 56	Control group Follow up periods	BDI-II Questionnaire	(I-CBT) 8 sessions 60 minute over 8 weeks Skills group information based on cognitive behavioral assumptions	**SX***		**Pre- test**	**Post test**	**4 weeks**	**MD (%)**	**p value**
							Depression	**I**	32.30±8.73	10.85±6.17	11.75±6.59	-20.55 (63%↓)	=0.001
								C	34.09±8.34	32.77±6.92	33.77±7.17	-0.32 (0.9%↓)	
Hunter et al. (29)	RCT	n total: 61 n CBT: 27 n HRT: 19 n control: 15	Age range 45-71 Women who reported hot flashes (or night sweats) once a week or more frequently	CBT compare with HRT and no treatment control group (NT) Follow up periods	1.Women's Health Questionnaire 2. A checklist for assessment of hot flashes	4 sessions 60 minute over 6-8 weeks Relaxation, rhythmic breathing Cognitive-behavioural to cope with hot flushes	**SX**		**Baseline**	**Monitor**	**Post-treatment**	**Follow-up**	**MD (%)**	**p value**
							HF/NS frequency	**CBT**	28.08±21.06	28.87±25.41	14.37±16.47	11.41±17.52	-16.67 (59%↓)	<0.01
								HRT	42.92±33.46	37.25±35.43	11.75±14.63	9.50±14.06	-33.42 (77%↓)	<0.01
								Control	24.19±19.65	22.19±18.14	23.19±16.26	20.07±17.87	-4.12 (17%↓)	>0.05
							HF/NS problem	**CBT**	5.49±2.58	5.28±2.37	3.13±1.77	3.65±2.39	-1.84 (33%↓)	<0.01
								HRT	5.36±1.98	5.33±2.47	5.13±1.39	5.23±2.04	-0.13 (2.4%↓)	>0.05
								Control	4.21±1.83	3.32±1.63	3.82±1.71	3.82±2.23	-0.39 (9.2%↓)	>0.05

*SX: The abbreviation of symptoms, MEC: Menopause education control, ISI: Insomnia Severity index, CES-D: Center for epidemiologic studies depression scale, CBTMI: Cognitive behavioral therapy for menopausal insomnia, RCT: Randomized controlled trial, BDI: Beck's depression inventory, I-CBT: Internet-based cognitive behavioral therapy, CBT: Cognitive-behavioral therapy, HRT: Hormone therapy

Table 3. The efficiency of group CBT on menopausal symptoms

Author/year/ country	Study design	Sample size	Specifications of population	Comparison condition	Scale	Intervention	Main findings
Soori et al. (21)	RCT	n total: 76 n intervention: 38 n control: 38	Rage age: 47-57 Rage of time passed from menopause: 1 to 4 years	Control group Pre and post treatment	DASS-21	6 sessions 60 to 90 minutes Groups of 11 to 12 women Relaxation, respiration, familiar with negative thoughts. To talk about the stress and discussing about them	**SX*** / **Pre-treatment** / **Post-treatment** / **1 month later** / **MD (%)** / **p value** **Depression** **I**: 9.63±3.72 / 2.63±1.97 / 2.35±1.66 / -7.01 (72%↓) / <0.001 **C**: 8.50±3.42 / 7.81±3.97 / 7.44±2.66 / -1.06 (12%↓) / >0.05
Larroy et al. (23)	Quasi-experimental	n total: 53 n intervention: 28 n control: 25	Age range: 42 to 55	Control group Follow up periods	1. BKMI 2. HADS	8 sessions 120 minutes weekly Groups of 8 -10 women Psycho education, relaxation, exercise and nutrition, Kegel exercises. Sexual re-education, problem-solving	**SX*** / **Pre- test** / **Post test** / **MD (%)** / **p value** **Hot flashes** **I**: 8.29±3.91 / 4.29±3.76 / -4 (48%↓) / <0.001 **C**: 10.4±2.58 / 10.8±2.86 / 0.40 (3.8%↑) / >0.05 **Nervous** **I**: 4.46±1.64 / 3.64±2.04 / -0.82 (18%↓) / <0.05 **C**: 3.40±1.91 / 3.60±2.00 / 0.20 (5.8%↑) / >0.05 **Melancholia** **I**: 2.14±0.93 / 1.25±0.84 / -0.89 (41%↓) / <0.001 **C**: 1.68±1.18 / 1.60±1.19 / 0.80 (47%↑) / >0.05 **Anxiety** **I**: 11.79±3.05 / 8.14±3.19 / -3.58 (30%↓) / <0.001 **C**: 10.60±1.98 / 10.28±1.43 / -0.32 (3%↓) / >0.05 **Depression** **I**: 6.71±3.71 / 4.79±2.63 / -1.92 (28%↓) / <0.001 **C**: 4.65±3.69 / 4.88±3.39 / 0.23 (4.9%↑) / >0.05 **Intensity of symptom** **I**: 28.75±5.75 / 19.36±8.62 / -9.39 (32%↓) / <0.001 **C**: 28.88±6.63 / 28.48±5.97 / -0.40 (1.3%↓) / >0.05
Norton et al. (20)	RCT	n total: 93 n intervention: 48 n control: 45	Mean age: 53.09±5.4 18 years or older Having problematic HFNS	Control group Follow up periods	HFNS problem rating (HFRS)	4 session Weekly 160 minutes Groups of 6-8 women Received a relaxation/ paced breathing CD	**SX** / **Baseline** / **6 weeks** / **26 weeks** / **MD (%)** / **p value** **HF/NS problem rating** **I**: 5.87±2.28 / 3.75±0.76 / 4.54±0.8 / -1.33 (22%↓) / =0.001 **C**: 5.87±2.28 / Not significant difference / Not significant difference **HF/NS frequency** **I**: 63.15±49.24 / 60.67±1.61 Small significant reduction / -2.48 (3.9%↓) / <0.05 **C**: 63.15±49.24 / Not significant difference / Not significant difference
Green et al. (34)	A pilot study	n total: 8	Age range: 40-60	Pre and post treatment	1. HFRDIS 2. GCS 3. MADRS 4. The Hamilton Anxiety Scale	10 session Weekly 160 minutes Groups of 4 women Psychoeducation, cognitive, restructuring, relaxation, Behavioral modification for urogenital complaints	**SX** / **Pre-treatment** / **Post-treatment** / **MD (%)** / **p value** **Hot flash daily interference** 39.8±12.4 / 16.9±9.5 / -22.90 (57%↓) / =0.01 **Anxiety** 19.8±6.0 / 12.8±6.7 / -7 (35%↓) / =0.00 **Depression** 6.9±3.6 / 4.6±4.1 / -2.3 (33%↓) / =0.04 **Variety of menopausal symptoms** 23.1±10.7 / 19.0±13.7 / -4.1 (17%↓) / =0.19
Ayers et al. (19)	RCT	n total: 93 n intervention: 48 n control: 45	Average age: 53.09 years Women having 10 or more problematic hot flaflashshes and night sweats (HF/NS) a week for at least a month	Control group Follow up period	Subscale of the HFRS	4 session Weekly 160 minutes Groups of 4 women Using PowerPoint presentations, a relaxation/paced breathing CD, and handouts	**SX** / **Baseline** / **6 weeks** / **26 weeks** / **MD (%)** / **p value** **HF/NS problem rating** **I**: 6.00±2.15 / 3.01±2.11 / 2.86±2.11 / -3.14 (52%↓) / =0.001 **C**: 5.79±2.76 / 4.97±2.44 / 4.18±2.45 / -1.61 (27%↓) **HF/NS frequency** **I**: 61.83±38.17 / 43.85±42.16 / 36.77±50.71 / -25.06 (40%↓) / =0.004 **C**: 56.69±50.43 / 49.67±48.55 / 44.05±45.18 / -12.64 (22%↓)

Table 3. Continued

Author/year/ country	Study design	Sample size	Specifications of population	Comparison condition	Scale	Intervention	Main findings					
Khoshbooii (32)	RCT	n total: 44 n intervention: 22 n control: 22	Aged range: 41- 55 With a depression score between 21 and 56	Control group Pre and post treatment + follow up	BDI-II Questionnaire	16 sessions twice weekly 160 minutes Psycho-education Cognitive Interventions Behavioral Intervention	**SX**		**Pre-test**	**Post test**	**4 weeks**	**MD (%)**	**p value**
							Depression	**I**	33.95±9.64	12.04±5.89	12.63±6.41	-21.32 (62%↓)	=0.001
								C	34.09±8.34	32.77±6.92	33.77±7.17	-1.13 (3.3%↓)	
Larroy García and Gómez-Calcerrada (4)	A pilot study	n total: 49 n intervention: 21 n control: 28	Range age: 43-56	Control group Pre and post treatment	1. HADS 2.Kupperman and Blatt Menopausal Index	8 sessions weekly 160 minutes Psycho education, relaxation, Kegel exercises, and problem-solving techniques	**SX**		**Pre-treatment**	**Post-treatment**	**MD (%)**	**p value**	
							Anxiety	**I**	6.43±4.3	5.24±3.40	-1.19 (18%↓)	<0.010	
								C	10.60±1.98	10.28±1.43	-0.32 (3%↓)	>0.05	
							Depression	**I**	4.05±3.19	2.76±2.98	-1.29 (31%↓)	<0.025	
								C	4.72±3.69	4.88±3.39	0.16 (3.3%↑)	>0.05	
							Intensity of symptoms	**I**	14.14±7.03	11.24±6.47	-2.9 (20%↓)	<0.030	
								C	28.88±6.66	28.48±5.97	-0.40 (1.3%↓)	>0.05	
							Hot flashes	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Paresthesia	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Insomnia	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Nervousness	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Melancholy	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Vertigo	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Fatigue	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Myalgia	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Headaches	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Palpitations	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	
							Dysaesthesia	**I**	Not significant difference			>0.05	
								C	Not significant difference			>0.05	

Table 3. Continued

Author/year/ country	Study design	Sample size	Specifications of population	Comparison condition	Scale
Alder 2006 Switzerland (35)	Clinical trial	n total: 30	Ages ranged: 42-65 Twelve (40%) were on HRT during the study period	Follow up periods	1. MRS 2.HADS (German version)
Keefer 2005 New York (14)	Pilot study	n total: 19 n immediate: 11 n delayed: 8	Mean age: 51.0±4.7	Follow up periods	1.The Women's Health Questionnaire 2. Daily vasomotor symptom diary

GCS: The Greene Climacteric Scale, MADRS: Montgomery–Asberg Depression Rating Scale, HADS: Hospital Anxiety and Depression Scale, BKMI: Blat's Kupperman Menopausal Index, HFNS: Hot flashes and night sweats, HFRDIS: The Hot Flash related Daily Interference Scale

Intervention	Main findings					
7 sessions weekly 90 minutes Groups of 4-8 women Relaxation techniques, breathing, Exercise for coping with sexual problem one follow-up group session 3 months after the intervention	**SX**		**T1 10 weeks before**	**T2 before beginning**	**T3 after last session**	**MD (%)**	**p value**
	Hot flashes		4.3±2.2	3.4±2.0	2.6±1.7	-1.7 (39%↓)	<0.01
	Cardiac complaints		1.4±1.7	1.7±2.1	0.8±0.6	-0.6 (42%↓)	<0.01
	Sleeping problems		3.1±2.5	3.3±1.9	3.7±4.8	0.6 (19%↑)	N.S**
	Depressive mood		3.6±2.5	3.8±2.8	2.6±2.2	-1 (27%↓)	<0.02
	Irritability		3.4±2.2	4.1±2.5	3.2±2.4	-0.2 (5.8%↓)	N.S
	Reduced effectiveness		3.8±2.3	4.2±2.7	3.2±2.3	-0.6 (15%↓)	<0.04
	Sexual problems		4.8±3.1	4.3±3.2	3.4±2.7	-1.4 (29%↓)	0.06
	Urinary complaints		1.0±1.3	1.4±1.4	1.1±1.2	0.1 (10%↑)	N.S
	Vaginal dryness		4.1±3.5	4.0±3.0	2.9±2.5	-1.2 (29%↓)	<0.03
	Joint and muscle pain		3.1±2.6	2.7±2.1	2.6±2.0	-0.5 (16%↓)	N.S
	Anxiety		7.7±4.5	8.2±4.8	6.2±4.2	-1.5 (19%↓)	<0.01
	Depression		5.8±4.4	6.7±5.4	4.7±3.9	-1.1 (18%↓)	<0.02
Participants were randomized into either immediate treatment or delayed treatment Immediate group treatment 8 sessions weekly 90 minutes Groups of 4-6 women. Psychoeducation, cognitive restructuring and paced respiration education	**SX**			**Pre-treatment**	**Post-treatment**	**MD (%)**	**p value**
	Hot flashes	**Immediate**		65.63±71.06	37.81±58.44	-27.82 (42%↓)	=0.21
		Delayed		66.54±60.63	58.75±95.13	-7.79 (11%↓)	
	Night sweats	**Immediate**		11.73±8.76	6.91±8.25	-4.82 (41%↓)	=0.09
		Delayed		32.89±23.47	68.00±88.12	35.11 (>100%↑)	
	Distress rating	**Immediate**		3.78±2.22	2.59±2.71	-1.19 (31%↓)	=0.06
		Delayed		4.86±1.48	5.15±1.60	0.29 (6.3%↑)	
	Problem rating	**Immediate**		4.42±1.97	2.72±2.79	-1.7 (38%↓)	=0.18
		Delayed		9.17±12.97	3.83±1.78	-5.34 (58%↓)	
	Total vasomotor	**Immediate**		78.27±44.73	44.73±62.43	-33.54 (42%↓)	=0.01
		Delayed		98.50±64.98	126.75±121.85	28.25 (28%↑)	

MRS: Menopause Rating Scale, *SX: The abbreviation of symptoms, **N.S: Not significant, DASS-21: The Depression Anxiety and Stress Scale,

Indirect CBT methods

Table 4. The efficiency of self-help CBT on menopausal symptoms

Author/year/country	Study design	Sample size	Specifications of population	Comparison condition	Scale
Hardy et al. (36)	Multicenter randomized controlled trial	n total: 124 n intervention: 60 n control: 64	Range age: 45-60 Working women Having problematic HF/NS for at least 2 months	Control group Follow-up period	Hot flash rating scale as used in the MENOS2 trial
McCurry et al. (37)	A single-site, randomized clinical trial	n total: 106 n CBT: 53 n MEC: 53	Range age: 40-65 With moderate insomnia symptoms [(ISI) score, ≥12] and 2 or more daily hot flashes	MEC Follow-up periods	ISI score
Stefanopoulou and Hunter (38)	RCT	n total: 92 n intervention: 47 n control: 45	Range age: 44-77 age from 18 years or older With problematic hot flashes and night sweats (HF/NS score >2) for at least 1 month and minimum frequency of 10 flashes per week	Control group Follow-up periods	HFRS
Norton et al. (20)	RCT	n total: 92 n intervention: 47 n control: 45	Mean age: 53.09±5.4 18 years or older Having problematic HFNS (score >2)	Control group Follow-up periods	HFNS problem rating (HFRS)
Ayers et al. (19)	RCT	n total: 92 n intervention: 47 n control: 45	Average age: 53.09 years Women having 10 or more problematic hot flashes and night sweats a week for at least a month	Control group Follow-up periods	Subscale of the HFRS

GCS: The Greene Climacteric Scale, MADRS: Montgomery–Asberg Depression Rating Scale, HADS: Hospital Anxiety and Depression Scale, BKMI: Blat's Kupperman Menopausal Index, HFNS: Hot flashes and night sweats, HFRDIS: The Hot Flash related Daily Interference Scale

Intervention	Improvement score						
Self-help cognitive behavior therapy The final SH-CBT intervention was an A5 sized, color booklet with instructions and four chapters (with information, exercises and homework tasks) to be completed over 4 weeks	**SX***		**Baseline**	**6 weeks**	**20 weeks**	**MD (%)**	**p value**
	HF/NS problem rating	**I**	6.25±1.97	4.38±2.21	4.36±2.29	-1.89 (30%↓)	6w: p<0.001 20w: p=0.01
		C	6.80±1.90	6.16±2.31	5.80±2.30	-1 (14%↓)	
	HF/NS frequency	**I**	53.13±34.34	40.59±26.03	34.28±27.62	18.85 (35%↓)	6w: p=0.01 20w: p=0.05
		C	54.28±38.11	54.02±43.00	46.03±37.92	-8.25 (15%↓)	
Telephone-based cognitive behavioral therapy Six CBT-I or MEC telephone sessions in 8 weeks Behavioral sleep plan Stimulus control instructions, behavioral sleep plan	**SX**		**Baseline**	**8 weeks**	**24 weeks**	**MD (%)**	**p value**
	Insomnia	**CBT-I**	15.6±0.8	5.7±1.3	4.9±1.2	-10.7 (71%↓)	<0.001
		MEC	16.8±1	12.1±1.4	9.4±1.7	-7.4 (46%↓)	<0.001
	Hot flashes	**CBT-I**	-	Baseline -15.7±4.7	Baseline -22.8±5.9	-22.8	=0.03
		MEC	-	Baseline -7.1±7.5	Baseline -11.6±7.8	-11.6	=0.003
Telephone-guided self-help cognitive behavioral therapy Women completed a Self-Help CBT intervention (booklet and relaxation/paced breathing CD) during a 4-week period. women also received one 'guiding' telephone call from a clinical psychologist two weeks into treatment	**SX**		**Baseline**	**6 weeks**	**3 month**	**MD (%)**	**p value**
	HF/NS frequency	**I**	55.52±38.34	37.85±30.33	28.54±27.55	-26.98 (48%↓)	=0.001
		C	56.69±50.43	49.67±48.55	44.05±45.18	-12.64 (22%↓)	
	HF/NS problem rating	**I**	6.23±2.16	3.74±1.87	2.98±1.36	-3.25 (52%↓)	<0.0001
		C	5.79±2.76	4.97±2.44	4.18±2.45	-1.54 (26%↓)	
Self-help cognitive behavior therapy The material in booklet form; and received a relaxation/paced breathing CD during a 4-week period	**SX**		**Baseline**	**6 weeks**	**26 weeks**	**MD (%)**	**p value**
	HF/NS problem rating	**I**	5.87±2.28	3.79±0.58	4.68±0.83	-1.19 (20%↓)	6w: p<0.001 26w: p=0.001
		C	5.87±2.28	-	-		
	HF/NS frequency	**I**	63.15±49.24	60.67± 0.21 Small significant reduction		-2.48 (3.9%↓)	Small significant
		C	63.15±49.24	-	-		
Self-help cognitive behavior therapy Self-help CBT includes a self-help book completed during a 4-week period and two contacts with a clinical psychologist (one introductory session and a guiding telephone call 2 week into treatment)	**SX**		**Baseline**	**6 weeks**	**26 weeks**	**MD (%)**	**p value**
	HF/NS problem rating	**I**	5.84±1.93	2.96±1.76	3.07±1.93	-2.77 (47%↓)	6w: p<0.001 26w: p=0.005
		C	5.79±2.76	4.97±2.44	4.18±2.45	-1.61 (27%↓)	
	HF/NS frequency	**I**	70.68±57.49	49.20±39.24	44.94±42.70	-25.74 (36%↓)	6w: p=0.668 26w: p<0.05
		C	56.69±50.43	49.67±48.55	44.05±45.18	-12.64 (22%↓)	

MRS: Menopause Rating Scale, *SX: The abbreviation of symptoms, **N.S: Not significant, DASS-21: The Depression Anxiety and Stress Scale,

approaches can reduce over 70% of the initial insomnia score. Furthermore, in a study by Keefer and Blanchard (14) the intervention group was classified into two immediate and delayed treatment groups in the case of assessing night sweats, depression, and total vasomotor symptoms. Treatment sessions were designed weekly and consist of education, relaxation training, and cognitive restructuring. In this regard, they reported a positive effect in the group with immediate treatment, but in the group whose treatment was delayed, the result was the opposite, and all of these three scores were increased. For example, the score for night sweats was more than twice the initial score. According to this finding, the start time of group therapy is noticeable, and if the treatment begins at a later stage, the result can be obtained in the opposite way (14).

Although in the study of Larroy García and Gómez-Calcerrada (4), the symptoms measured by the Kupperman and Blatt Menopausal index questionnaire separately did not have a significant alteration after group CBT, the total score represents a 20% decrease from the initial score, indicating the effectiveness of the group approach.

Study limitation

We were not able to perform a meta-analysis in the present study due to the alteration in the questionnaires used to measure the symptoms, and the difference in the implementation method, including the number of treatment sessions or the number of participants in the group meetings. Moreover, as a result of the low and moderate quality of most studies involved in this systematic review, more studies with high quality should be conducted in individual and self-help CBT approaches to measure the impact of these approaches on more varied symptoms of menopause.

It can be concluded that although the indirect method is more cost-effective, it has less impact than the face-to-face method, and if there are possibilities, it is better to use face-to-face approaches to achieve a better result. However, in countries with less facilities, self-help CBT (indirect methods) can be beneficial.

Peer-review: *Externally peer-reviewed.*

Conflict of Interest: *No conflict of interest was declared by the authors.*

Financial Disclosure: *The present study was supported by Shahroud University of medical sciences as a PhD Thesis. We hereby acknowledge the research deputy for grant No 9659. Also, we hereby acknowledge from student research committee of Shahroud University of Medical Sciences.*

References

1. Marín RM. Atención integral a la mujer de mediana edad. En: Sánchez-Cánovas J, coordinador. Menopausia y salud. Barcelona: Ariel, 1996; 87-128.
2. Malacara JM. Prólogo. Revista de Endocrinología y Nutrición 2006; 14: 131-2.
3. Mast MS, Hornung R, Gutzwiller F, Buddeberg C. Sexualität in der zweiten Lebenshälfte. Gynäkologisch-geburtshilfliche Rundschau 2000; 40: 13-9.
4. Larroy García C, Gómez-Calcerrada SG. Cognitive-behavioral intervention among women with slight menopausal symptoms: a pilot study. Span J Psychol 2011; 14: 344-55.
5. Caltabiano ML, Holzheimer M. Dispositional factors, coping and adaptation during menopause. Climacteric 1999; 2: 21-8.
6. Gannon L, Hansel S, Goodwin J. Correlates of menopausal hot flashes. J Behav Med 1987; 10: 277-85.
7. Burkman RT. Berek & Novak's gynecology. JAMA 2012; 308: 516-7.
8. Nourolahi T, Ghaemi Z, Goodarzi HM, Naeneeni O, Jafari S, Ghaderi S, et al. 1390 national census of population and housing. Statistical Center of Iran. 2011.
9. Manesh MJ, Moghadam Z. The experiences of menopause through the lens of Iranian women: Content analysis study. Aust J Basic Appl Sci 2011; 5: 1543-8.
10. MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2001; CD002978.
11. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321-33.
12. Karimian Z, Keramat A. Hot Flashes of Menopause and Herbal Medicine in Iran: A Systematic Review. J of Iranian Obstetrics, Gynecology and Infertility 2014; 17: 1-11.
13. Ussher JM (edt). Body Talk: The Material and Discursive Regulation of Sexuality, Madness and Reproduction. Routledge; 1997.
14. Keefer L, Blanchard EB. A behavioral group treatment program for menopausal hot flashes: results of a pilot study. Appl Psychophysiol Biofeedback 2005; 30: 21-30.
15. Blake F. Cognitive therapy for premenstrual syndrome. Cogn Behav Pract 1995; 2: 167-85.
16. Blake F, Salkovskis P, Gath D, Day A, Garrod A. Cognitive therapy for premenstrual syndrome: a controlled trial. J Psychosom Res 1998; 45: 307-18.
17. Hunter MS, Liao KLM. Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes. Br J Health Psychol 1996; 1: 113-25.
18. Hunter MS, Ussher JM, Browne SJ, Cariss M, Jelley R, Katz M. A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder. J Psychosom Obstet Gynaecol 2002; 23: 193-9.
19. Ayers B, Smith M, Hellier J, Mann E, Hunter MS. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. Menopause 2012; 19: 749-59.
20. Norton S, Chilcot J, Hunter MS. Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects. Menopause 2014; 21: 574-8.
21. Soori M, Kolivand M, Momtaz Ya, Salari N. The Effect of Group Cognitive-Behavioral Therapy on Depression in Menopausal Women: A Randomized Clinical Trial. International J Life Science and Pharma Research 2018; 8: 12-9.
22. Yazdkhasti M, Simbar M, Abdi F. Empowerment and coping strategies in menopause women: a review. Iran Red Crescent Med J 2015; 17: e18944.
23. Larroy C, Marín C, Gutiérrez S. The effects of cognitive-behavioral techniques on hot flushes, depression and anxiety related to menopause in Spanish women. Wulfenia Journal 2015; 22.
24. Hunter M. Cognitive behavioural interventions for premenstrual and menopausal symptoms. Journal of Reprod and Infant Psychology 2003; 21: 183-93.
25. Tremblay A, Sheeran L, Aranda SK. Psychoeducational interventions to alleviate hot flashes: a systematic review. Menopause 2008; 15: 193-202.
26. Stanley MA, Wilson NL, Novy DM, Rhoades HM, Wagener PD, Greisinger AJ, et al. Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care: a randomized clinical trial. JAMA 2009; 301: 1460-7.
27. Abdollahpour S, Keramat A, Mousavi SA, Khosravi A. The effect of debriefing and brief cognitive-behavioral therapy on postpartum depression in traumatic childbirth: a randomized clinical trial. Journal of Midwifery and Reproductive Health 2018; 6: 1122-31.
28. Yoo MS, Lee H, Yoon JA. Effects of a cognitive-behavioral nursing intervention on anxiety and depression in women with breast cancer undergoing radiotherapy. J Korean Acad Nurs 2009; 39: 157-65.
29. Hunter MS, Coventry S, Hamed H, Fentiman I, Grunfeld EA. Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment. Psychooncology 2009; 18: 560-3.
30. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
31. Hassan SA. Effectiveness of group cognitive behavioral therapy on depression among Iranian women around menopause. Australian Journal of Basic and Applied Sciences 2011; 5: 991-5.
32. Khoshbooii R. Comparison group and individual cognitive behavioral therapy in treatment of depression among Iranian women around menopause. Int J Psychol Stud 2012; 4: 174.
33. Nowakowski S, Thurston R, Meers JM, Stout-Aguilar J, Sadruddin S, Hayman J, et al., editors. Cognitive Behavioral Therapy for Menopausal Insomnia in Midlife Women with Insomnia and Nocturnal Hot Flashes. Menopauçse-The Journal of The North American Menopause Society; 2017: LippincottWillams & Wilkins Two Commerce SQ, 2001 Market ST, Philadelphia, 19103 USA.
34. Green SM, Haber E, McCabe RE, Soares CN. Cognitive-behavioral group treatment for menopausal symptoms: a pilot study. Arch Womens Ment Health 2013; 16: 325-32.
35. Alder J, Eymann Besken K, Armbruster U, Decio R, Gairing A, Kang A, et al. Cognitive-behavioural group intervention for climacteric syndrome. Psychother Psychosom 2006; 75: 298-303.
36. Hardy C, Griffiths A, Norton S, Hunter MS. Self-help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@Work): a multicenter randomized controlled trial. Menopause 2018; 25: 508-19.
37. McCurry SM, Guthrie KA, Morin CM, Woods NF, Landis CA, Ensrud KE, et al. Telephone-Based Cognitive Behavioral Therapy for Insomnia in Perimenopausal and Postmenopausal Women With Vasomotor Symptoms: A MsFLASH Randomized Clinical Trial. JAMA Intern Med 2016; 176: 913-20.
38. Stefanopoulou E, Hunter MS. Telephone-guided Self-Help Cognitive Behavioural Therapy for menopausal symptoms. Maturitas 2014; 77: 73-7.

Fertility preservation in Turkey: a global look for nationwide strategy development

Şafak Hatırnaz[1], Kadir Bakay[2], Ebru Hatırnaz[1], Davut Güven[2], Alper Başbuğ[3], Önder Çelik[4], Gazi Yıldırım[5], Cihat Ünlü[6]

[1]In Vitro Fertilization-IVM Center, Medicana Samsun International Hospital, Samsun, Turkey
[2]Department of Obstetrics and Gynecology, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[3]Department of Obstetrics and Gynecology, Düzce University School of Medicine, Düzce, Turkey
[4]Private Office, Uşak, Turkey
[5]Department of Obstetrics and Gynecology, Yeditepe University Faculty of Medicine, İstanbul, Turkey
[6]Department of Obstetrics and Gynecology, Acıbadem University Faculty of Medicine, İstanbul, Turkey

Abstract

As the reproductive technology advanced along with the improved outcome in cancer treatment demands implementing new fertility preservation, developing algorithms on fertility preservation requires tailoring for each society. Here, the authors attempt to modify the current medical literature on fertility preservation for the Turkish population. A PubMed search was conducted using the search term *fertility preservation*. Initially, 280 items of literature were accessed. In the second evaluation, 126 articles were examined and 154 items were discarded due to the low quality of the literature. In the final round, only 68 publications that were the most relevant were found eligible for inclusion in this review article. In order to develop a more systematic national guideline, forming a multidisciplinary approach to create a web-based network would be the first step. Both physicians and patients will have open access to the information. This database should be linked to an international consortium to stay integrated and open for updating. The aim of this review was to evaluate the relationship between the current situation in our country and the developments in the world in light of the literature, and to establish infrastructure for the development of future approaches in our country. (J Turk Ger Gynecol Assoc 2019; 20: 196-207)

Keywords: Fertility preservation, oncofertility, oocyte-embryo freezing, treatment modalities, national program

Received: 31 August, 2018 **Accepted:** 9 February, 2019

Introduction

We, as doctors, must always keep in our minds the basic message from the Hippocratic Oath ***'primum non nocere'***. However, every medical or surgical treatment carries certain degrees of side effects or complications, which may cause the deterioration of some functions while improving the others. Tremendous advances in medical diagnosis and therapy have increased the survival rates in children and young age women with malignancies. Thus, *fertility preservation* has become a must in the routine practice of oncology (1). This necessitates consultations with reproductive endocrinologists before and after the oncologic treatment (2). Developed countries started to arrange guidelines and established organizations and societies related to oncofertility and fertility preservation because the demand of consultation for fertility preservation became a serious matter. The Oncofertility Consortium (OC), supported by National Institutes of Health, was founded in 2007, and evolved as the largest organization for the improvement of fertility expectations of patients with cancer and medical professionals dealing with oncofertility

Address for Correspondence: *Şafak Hatırnaz*
e.mail: safakhatirnaz@gmail.com ORCID: orcid.org/0000-0001-8859-0639

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2018.0116

worldwide (3). Nineteen countries are involved in the OC but only 6 organizations actively contribute to the OC, the others remain inactive. FertiPROTEKT, a strong organization for fertility preservation in Europe, expanded the indications and added severe rheumatic diseases and social indications, and also developed strategies and guidelines and recommendations for those diseases (4). Indications for fertility preservation apart from oncofertility include premature ovarian failure due to genetic reasons and autoimmune disorders such as diabetes mellitus, thyroid dysfunction, Addison syndrome, myasthenia gravis, Crohn's disease, lupus, and rheumatoid arthritis (5).

Oncofertility can be defined as a new discipline hosting many medical and social disciplines, which aims to give cancer survivors an opportunity to preserve their potential to have baby. Fertility preservation comprises the efforts made to preserve the potential to obtain oocytes or embryos for future use by either surgical or medical methods in patients with cancer (6).

The current situation in Turkey is confusing. Turkey seems to be a member of the OC but it is not actively involved in OC activities. Oncofertility is an issue seems to have a place in gynecologic oncology and infertility congresses, but not more than that. There exists no official organization or society that deals specifically with fertility preservation. There appears to be no web-based program that to inform patients and medical professionals who deal with fertility preservation.

This review article aims to refresh the current knowledge on fertility preservation methods and to recommend what can be done in order to have a nationwide fertility preservation program in Turkey.

A PubMed search was conducted using the search term fertility preservation. About 280 items of literature were accessed and 126 of these literature items were subjected to a second evaluation. Sixty-eight publications were included in this review study.

Discussion

Oncofertility is a multidisciplinary approach, and if it can be implemented in the same institution, it could be of great benefit. However, this is not a convenience that can always be present in all institutions at all times. Disorganization as well as detachment between the disciplines seems to be one of the fundamental problems related to the preservation of fertility. Another significant point is concerned with the evaluation of how much sensitivity physicians working in the field of oncology have. For this purpose, a pilot study conducted in the United States of America (USA) in 2009 revealed striking results. Sixty-one percent of the oncologists who participated in the survey stated that they always or most of the time explained the effects of oncologic treatments on fertility to their patients but 45% indicated that they did not refer their patients to an infertility specialist. The sensitivity of physicians who have previously attended a seminar on the subject matter of fertility preservation is higher than those who have never participated in such seminars (45% and 33%, respectively). Fifty-five percent of the physicians who participated in a seminar recommended the administration of a less aggressive chemotherapy, whereas this rate was determined as 29% for those who had not taken part in seminars. Patient attitudes, bad prognosis, and the immediacy required for the initiation of treatment seem to be the leading reasons why physicians are insensitive towards this issue. It is possible to consolidate the bridge between oncologists and infertility specialists further through increasing the number of training sessions as well as approaches that are geared towards enhancing sensitivity. Thus, fertility can be preserved in young patients with cancer whose survival rate has increased (7). A survey study conducted among hematologists in Turkey inquired about their attitudes and behaviors toward the preservation of fertility. Twenty-five physicians were contacted, and it was observed that all hematologists showed sensitivity towards fertility preservation; however, 8% of the participants stated that they were not aware of fertility preservation at all; 76% pointed out that they did not have sufficient knowledge of the subject matter; 88% of the physicians who responded to the survey stated that they wanted to be informed more about fertility preservation; and 23% suggested that a written brochure or written resource would be required on this subject matter. All the participating hematologists agreed upon the recommendation that Turkish Hematology Association should prepare a guideline on the subject and a sessions on fertility preservation should be held at congresses on a regular basis (8).

The differences in the physicians' attitudes and behaviors pose an obstacle to the options for fertility preservation in cases where hematopoietic stem cell transplantation has been implemented. Accordingly, an invitation was sent to 1035 physicians in the USA, and only 185 of the physicians responded to the 29-question survey. It was revealed that the responding physicians had awareness as to the preservation of fertility, and having discussions over fertility preservation made them feel better. Yet, it was found out that only 55% of them referred their patients to an infertility specialist. Sixty-three percent of the participating physicians pointed out that their patients were so ill that they were not in the position of being able to postpone the transplantation. It was also maintained that the patients had natural barriers such as already being infertile during the onset of the treatment (92%). The study revealed that the demographic attributes of the physicians, and their knowledge and perception on the subject matter had predictive significance with regard to referring patients for the preservation of fertility (9).

Following a pilot study, Forman et al. (10) conducted a survey across the USA in 2010. They sent a questionnaire to oncology physicians three times in one year over the web- based SurveyMonkey system, requesting online responses from the participants of the survey. They received responses from 249 physicians out of 1701 questionnaires sent. Ninety-five percent of the physicians said that they discussed fertility preservation with their patients. Even though 82% of the physicians stated that they referred patients to an infertility specialist, only half of those patients attended such a consultation. Thirty percent of the physicians stated that they acted in an indifferent way regarding fertility while planning the treatment. It was observed that gynecologic oncologists attached much more importance to fertility compared with medical oncologists. In a similar vein, gynecologic oncologists considered preserving fertility by planning less aggressive treatments. The rates of oncologists who refer patients in academic hospitals are much fewer when compared with gynecologic oncologists. According to oncologists, patients can take the chance of having a 5% reduction in their survival rates for the preservation of their fertility (10).

New diagnoses and treatments emerge as a result of increasing genetic and epigenetic studies, as well as the revealing of the human genome (11). It is known that male infertility increases the risk of developing cancer in the future. The same applies for female infertility as well. Besides this, it is also thought that the medications used for female infertility may increase cancer risk. It is believed that infertility and cancer have common predispositions in terms of genetic and epigenetic aspects. Apart from these, common environmental factors also play a role in exacerbating these problems. Hanson et al. (12) studied that male infertility carries the risk of developing testicular cancer, bladder cancer, and thyroid cancer, as well as lymphoma and leukemia. The authors also observed that such a risk would also apply for their close relatives, concluding that a genetic common predisposing element triggered in germline cells could exist (12). Nagirnaja et al. (13) studied the genetic links between cancer and infertility, examining the known oncogenes and important genes in spermatogenesis. They inquired as to whether there was a link between these, having concluded that extensive genomic studies should be performed, and susceptible locations should be identified related to both infertility and cancer through germline scanning (13). James and Jenkins (14) determined that epigenetic changes in male infertility and cancer increase susceptibility for these two pictures. They also drew a conclusion through the two-hit hypothesis, that one epimutation causes infertility, while the other one leads to cancer.

A significant increase in the life expectancies of patients with cancer at young age has been observed owing to the novelties in treatments. The most frequently seen cancer types among young individuals aged 15-24 years in Europe are Hodgkin's lymphoma, testicular cancer, and malignant melanoma (15). The 5-year survival among young patients is over 90%. The most commonly observed forms of cancer seen among adults aged 25-49 are breast cancer, colorectal carcinoma, cervical cancer, and malignant melanoma (16). The most frequently encountered malignancy among those aged below 35 years in the United Kingdom is breast cancer. Mortality rates in patients with breast cancer aged under 50 years have decreased significantly through the polychemotherapy approach. Nonetheless, aggressive chemotherapy and radiation therapy administrations are lamentably required for many frequently encountered cancer types, which may cause permanent damage of reproductive functions (17). This situation accompanies many others that have to do with quality of life, apart from the loss of fertility, including osteoporosis, depression, cognitive disorders, cardiovascular diseases, and sexual dysfunction. There is an increasing amount of interest in fertility preservation both among oncologists and also among reproductive endocrinologists and infertility specialists, which have brought about the production of many new treatment strategies. The preservation of fertility as a multidisciplinary approach was put on the agenda at the 2009 Evian Annual Reproduction Meeting (18).

No evidence exists as to the direct impact of cancer on the reproductive system, yet treatments thereof may bring about adverse effects in several locations. For instance, in cases where the entire body is exposed to radiation therapy during childhood with doses of 14-30 Gy, it is known that uterine growth and development slows down (19). Administration of uterine radiation therapy during childhood and the young youth period causes an increase in the frequency of miscarriage and intrauterine growth restriction in the future (20). The risks of acute ovarian insufficiency, premature ovarian insufficiency, premature menopause, low ovarian volume, and being of low weight in newborn babies were observed to be increased among patients with cancer who were exposed to radiation therapy and/or chemotherapy administered with alkylating agents (21). As for chemotherapy and radiation therapy, the target cells in the ovary are follicular, and this causes a huge amount of reduction in the follicles. In adddition, based on this situation, endocrine and reproductive functions deteriorate. The decreased primordial follicular pool raises the probability of ovarian insufficiency and premature menopause probability (17). The lethal dose for primordial follicles is 2 Gy (22). The gonadotoxic medication impact in the ovary causes a vicious cycle and follicle-stimulating hormone (FSH) release increases because the breakdown of primordial follicles reduces the secretion of estradiol and inhibin, which in turn leads to more

follicles entering the cohort, causing much more follicular damage as a consequence (23). This point reveals that more sensitivity is required to be shown in the approach towards women with regard to the preservation of fertility. Premature ovarian insufficiency emerges at later ages and persistent amenorrhea is accepted as a marker of ovarian insufficiency (24). Checking the number of antral follicles (AFC) and antimullerian hormone (AMH) concentration before the initiation of the treatment and conducting follow-ups in the post-treatment period can be used as a marker for the detection of the harm of gonadotoxic treatment (25).

Radiation therapy and chemotherapy administered to the pelvic or spinal location is gonadotoxic and toxicity is concerned with either the mode of treatment or the relevant dose of the treatment (26). Chemotherapeutic agents are generally used in combination so as to benefit from their synergic effects and to achieve a more effective result on the tumor. The agents known to be the most gonadotoxic are those with an alkylating agent, which increase the cyclophosphamide toxicities in taxanes used in adjuvant treatments (27). Radiation therapy-induced damage is based on the dose, area of treatment, and frequency of its administration (20 Wallace 2005).

The highest gonadotoxicity is seen in cases when intensive combined chemotherapy and entire body radiation therapy are applied prior to bone marrow transplantation, in cases of metastatic Ewing sarcoma and soft tissue sarcoma, as well as in Hodgkin lymphoma in which alkylating agents are used (28).

Preservation of fertility should be recommended to young patients with cancer as early as possible; however, cancer treatment may take precedence over fertility preservation most of the time (29). It is recommended that patients should be consulted by an infertility specialist who should inform the patient accordingly so as to clarify the issue of fertility preservation (30). If there is the possibility and ample time for medical treatment, it could be tried out. If no such opportunity is present, then fertility-preserving cancer treatments should be considered. Fertility remains intact if medical treatment is administered in endometrial cancer or conservative modes such as radical trachelectomy are administered in the early phase of cervical cancer. Despite this, protection of the gonads from pelvic radiation and storage of the gametes and embryos should also be considered as alternative options (29,31).

The new oncology treatments provide the chance of leading a normal life to an increasing number of patients with cancer, particularly young patients. Such treatments also confer the opportunity of having children. Correspondingly, increasing achievements in assisted reproductive techniques (ART) have also boosted hopes, and the belief that cancer-induced and cancer treatment-induced infertility can be solved through medical approaches has been conceived. A significant proportion of young patients with cancer state that they cannot find the opportunity to discuss fertility sufficiently; some attribute this to cancer, whereas others attribute this situation to the scarcity of time (29,32). Most of the time, it is too late. Moreover, recommendations related to fertility preservation are often offered in an inappropriate manner and this overlaps with the period when the patients are overly confused with regard to their cancer treatments. This destabilizes the patients as a consequence. In some cases, a number of choices such as removing the ovarian tissue, breaking it up and implanting it under the skin have been developed; however, it has been observed that the right differentiation has not been made in terms of the presentation of these options. What is more, such works have been popularized dramatically by the media before the scientific findings have been revealed (33).

Freezing the ovarian tissue, urgent *in vitro* fertilization (IVF), *in vitro* maturation (IVM) and ovarian suppression by gonadotropin-releasing hormone (GnRH) analogues, and random start ovarian stimulations can be used as several methods for the preservation of fertility (34,35). An important issue worth taking into consideration at this point is the necessity of having an immediate discussion about two matters, which are cancer and the preservation of fecundity. It is for this reason that cancer and fertility-preservation matters need to be managed by adopting a multidisciplinary perception, putting forth all the possible choices and then determining the most appropriate approach. What is desired indeed is to form a "task force" in local medical committees that are competent in cancer and fecundity. For such local committees to be formed, it is necessary that organizations that are capable of administering all the aforementioned fertility-preserving approaches exist. There are insufficient numbers of centers on IVM and this situation seems to be a deficit. One of the important functions of task forces is that they closely follow studies on fertility preservation.

It is required to set the priorities and decide on whether to have a narrow or broad dimension for the formation of a committed "task force". A task force with an inadequate dimension would fail to satisfy offering services, and a broad task force would experience difficulties in offering treatment options with a required level of sensitivity due to their increasing work burden. A sample study for such a task force was put into practice in Switzerland, in a French-speaking region of the country. An area with 1.5 million residents was chosen to be the pilot region (36). The number of patients with breast cancer (the most frequently encountered type of cancer that develops in one year and is seen among young women) was calculated. The results showed that 115 new patients among the age group below 45 years in such a population density emerged every year. Assuming that discussions about fertility preservation are

made with the 50-70% of the young patients with cancer, it has been foreseen that the task force could only have contact with 60-85 of the patients. With the premise that patients with breast cancer account for 40% of young patients with cancer, it can be predicted that the total number of patients that the task force can see per year would be between 15 and 210 patients (when 1.5 million people are taken as the basis). Based on such data, it was concluded that such numbers could be at the threshold of low numbers for IVF centers, and the ideal target population density should be between 2-7 million in this regard (33).

At this point, this question may be addressed: do such patients become completely infertile or could they have a chance of spontaneous pregnancy?

The possibilities of natural conception through fertility-preservation approaches should be discussed with all patients with cancer. It is also important to act in line with the cancer type. As a general principle, it is known that primordial follicles are more resistant to chemotherapy compared with developing follicles. This situation also provides an explanation for the fact that patients menstruate 6-9 months after chemotherapy treatment. This period overlaps with the new development phase of primordial follicles from the primordial follicle pool.

Hematologic malignancies and particularly Hodgkin lymphoma come to mind when young age cancers are at stake; however, breast cancer appears to be the mostly encountered cancer during the reproductive period (at 13% during the reproductive period of a person) due to its prevalence (37). It is possible to observe spontaneous pregnancies following breast cancer treatment owing to the nature of the chemotherapies used in breast cancer. For this reason, it is of importance to bear in mind the high probabilities of conception in patients with breast cancer prior to identifying the fertility-preserving approaches. In addition to this, the fact that there will be a difference between menstruating and fertility periods should not be disregarded. Thus, checking AFC and AMH before cancer treatment and performing a reevaluation after the treatment can ensure the revealing of the dimension of ovarian reserve loss (38).

Despite having such possibilities, it is quite difficult to know who would be able to become pregnant and who would not be able to do so. However, ensuring fecundity is possible only through conception. Furthermore, chemotherapy agents that are used could have long-term effects and they may lead to infertility or menopause (39).

Ovarian functions and fecundity ameliorate following chemotherapy in breast cancer cases. It is generally seen in women in their 30s and there is a 3-6 week period between surgery and chemotherapy. For these reasons, the possibility of performing urgent IVF in the intermittent period emerges. Thus, it is important to avoid oophorectomy and the grafting of ovarian tissue as far as possible for patients in this age group, particularly in cases of breast cancer. Unilateral oophorectomy may cause FSH increase and premature menopause in patients in their 30s (40). Instead, administration of an urgent IVF and embryo freezing procedure could be opted for. In this period of 3-6 weeks, using aromatase inhibitors in ovarian stimulation also increases the probability of retrieving eggs and reduces exposure to estrogen (41). Another point to be paid attention to is that such an administration can be performed only on cases in which the patient first underwent surgery, and afterwards received chemotherapy. For patients with administration of neoadjuvant chemotherapy and subsequent surgery, such a treatment would not be preferred.

Current strategies for fertility preservation in females

According to the data of the American Cancer Society, it is predicted that new cancer diagnoses were made for 790,000 women in 2012 (42). Eighty-three percent of the women aged below 45 years who were diagnosed as having cancer between 2002-2012 maintained their lives (43). The treatment of many types of cancer in the reproductive period of an individual involves either the removal of reproductive organs through surgery or the use of cytotoxic medications that partially or entirely affect the reproductive functions. Ovaries act as the target organs for cytotoxic treatments, and primordial follicles are affected directly by these treatments (44). The primary reasons why ovarian insufficiency develops after cancer treatments are dependent on the ovary reserve of the patient prior to the onset of the treatment, the dose of the treatment agent used, and its duration (45). Entire ovarian tissue freezing, ovarian cortical tissue freezing, ovarian transplantation, oocyte and embryo freezing, as well as using GnRH analogues happen to be several treatments planned. However, the treatment approach recommended by the American Society for Reproductive Medicine is the cryopreservation of the oocytes or embryos that are obtained by IVF (46,47). Other approaches are still regarded as experimental treatments. Controlled ovarian stimulation (COS/COH) is an approach of treatment that is preferred owing to its high success and efficacy rates (48). Many patients start their treatment without receiving any consultation about fertility preservation despite the time elapsed. Afterwards, cancer survivors have expectations about fertility. In the above parts of this review, the treatment choices for patients who are consulted and have contact with reproductive endocrinology and infertility specialists have been presented. Another point in question is how can patients who have expectations about fertility be treated after their targeted cancer treatments have proved to be successful? Cases of targeted cancer therapy enable the maintaining of cancer treatments while being able to sustain fertility-preserving approaches.

Freezing oocytes or embryos could be used for postpubertal patients and patients who are married. The possibility of performing this procedure is dependent on the following factors: the existence of an IVF center, having the competency of performing ovarian stimulation to patients with cancer, and being experienced in good embryo development and cryopreservation. This approach is no longer considered to be experimental (46). Data related to the egg freezing of patients with cancer and their pregnancies after treatment are highly limited. In recent years, randomized controlled studies in which pregnancies achieved through oocyte vitrification were compared with fresh oocyte embryo transfers reported that similar results were obtained in terms of implantation and pregnancy rates (48-50). For the time being, ovarian stimulation for the embryo or mature oocyte freezing is considered to be the most appropriate strategy for attaining pregnancy. This can be attempted if the following conditions are present: the patient does not have a situation that would prevent the collection of oocytes, there is available time for ovarian stimulation, the patient has a medical condition that is fit for this procedure and it is safe to perform ovarian stimulation. The most important problem at stake is that the patient is not on her menstrual period and the possibility that the treatment may cause delay. The AFC, AMH, and FSH levels have importance in determining the gonadotropin dose to be used (51). Short-term gonadotropin antagonist treatments could be preferred. However, in a situation where menstruation does not start, a mode of treatment independent of the menstrual cycle and that is even on luteal phase can be planned through random start protocols in order to avoid time loss (52,53). By taking into consideration the fact that the patients have the possibility of receiving treatment for themselves only, the most suitable treatment choice should be administered. On the other hand, it is important to avoid OHSS. The use of agonist triggers in antagonist cycles could be of benefit to serve this purpose (54).

Medical or surgical treatments can be performed conservatively, particularly for early phase tumors and borderline tumors in women; thus, fertility is preserved in this way.

For patients to whom local pelvic radiation therapy will be administered, as a result of ovarian transposition operation, the ovary can be detracted from the area where radiation therapy will have impact. In this way, it could be possible to preserve fertility. If it is planned to collect eggs following such an operation, transabdominal collection would be more apt.

All the treatments conducted for the purpose of fertility preservation other than those already specified are considered to be experimental treatments, this is particularly the case in the USA. Treatments that fall into experimental categories are stated below:

a. Ovarian tissue freezing

b. In vitro oocyte maturation (IVM)

c. Ovarian suppression by GnRH analogues

In some specific cases, there may exist an available time interval following the surgery of the patients, this time frame extends up until postoperative chemotherapy. For example, in patients with breast cancer who have undergone lumpectomy or mastectomy, there is a long period of time for chemotherapy following the surgery. The major concern here is the hypoestrogenic effect that will be induced by ovarian stimulation and also the emergence of adverse effects in the course of the disease due to ovarian stimulation. It is for this reason that gonadotropins can be used along with an aromatase inhibitor on such patients rather than being used alone (55). Similarly, the administration of bilateral prophylactic salpingo-oophorectomy (BSO) could be recommended for patients who are BRCA mutation carriers (56). Ideally, BSO should be performed after fertility comes to an end; however, there are alternative options for such patients such as the intermittent collection of oocytes and freezing the embryo or oocytes. In addition, PGD could be administered on these patients in the future, and through embryo transfer with the BRCA mutation discarded, it would be possible to prevent passing on the mutation to subsequent generations. Ovarian tissue transplantation is not recommended to BRCA mutation carriers.

Hematologic malignancies pose a serious problem to fertility preservation considering the thought that the course of the disease is severe and even a minor surgical intervention could cause a serious deterioration in the blood picture. Furthermore, even if the ovarian tissue is removed and can be transplanted subsequently, it is important not to overlook the probability that leukemia might be implanted once again through this tissue (57,58). Even though patients with lymphoma are more appropriate for fertility preservation, consultation is not recommended that much at the beginning because the treatments administered have minor gonadotoxic effects. For this reason, referral of patients in hematologic malignancies is done in cases of recurrence, or after chemotherapy or induction treatment, or prior to stem cell transplantation. Thus, patients have already started gonadotoxic treatment in hematologic malignancies (59).

The most sensitive patient groups in fertility preservation are children and adolescents. The determination of the appropriate strategy for these patients should be considered very carefully. It is harder to talk about this issue with patients and their families than one might anticipate. Besides this, fertility-preserving infrastructure does not exist or fails to be sufficient in children's hospitals. It is possible to perform oocyte collection in postpubertal girls aged below 18 years. This option

is also possible for peripubertal adolescents. IVM can also be recommended to such population.

Other indications for fertility preservation

Fertility preservation is not only restricted to patients with cancer but can also be used in some other medical conditions (60). The indications of fertility preservation other than cancer are listed below:

a. Premature ovarian failure (POF),

b. Chromosomal and genetic abnormalities (Turner syndrome, 47, XXX, Fragile X GALT enzyme or FSH receptor mutation),

c. Autoimmune diseases (thyroid, polyglandular, multiple endocrine),

d. Environmental factors (malaria, varicella, Shigella may cause POF),

e. Surgical menopause (benign ovarian disease, prophylactic oophorectomy),

f. Cytotoxic agents for hematologic and autoimmune diseases,

g. Postponing fertility/social indications.

Fertility preservation strategies in males

When compared with female cases, fertility preservation in males is slightly easier. Sperm freezing does not require any treatment beforehand, it does not cause time loss for the patient, and it is a simple procedure of giving a sample, which is also repeatable. Sperm cryopreservation is a male fertility-preservation method that is recommended on standard basis. It is important that semen samples have already been retrieved prior to chemotherapy and radiation therapy. At least 3 samples of semen are to be taken ideally and the storage should be performed by using many vials for the cryopreservation procedure. It could be hard to provide samples in young adults so it is important that they give the sample in an environment that is peaceful and comfortable. There are other challenges regarding the provision of sample, which are anxiety, fatigue, pain, additional morbidities, neurologic problems, diabetes mellitus, and hypogonadism. In such cases, the following approaches are recommended to be used to obtain samples:

a. Phosphodiesterase type 5, which is generally used in erectile dysfunction, but it is preferred in situations where giving sample is challenging (61),

b. Penile vibratory stimulation,

c. Electroejaculation,

d. Retrograde sperm collection and cryopreservation,

e. Cryopreservation of sperms obtained by surgery.

GnRH analogue treatment and the storage of testicular tissue from the prepubertal period for male fertility preservation are still considered to be experimental (62,63).

When the effects of cancer on male fertility are analyzed, 30% of patients with testicular cancer demonstrate semen anomalies at the onset. Interestingly enough, semen problems at such a scale are also seen in patients who encounter other types of cancer at a young age. In a study conducted on 158 patients (aged 16-52 years) with Hodgkin lymphoma, it was revealed that 111 (70%) patients had degeneration in their semen parameters (64). Germinal epithelium is a highly sensitive tissue, and it is chemo-radiosensitive (65). Major subfertility is observed in cases where alkylating agents and radiation therapy are used. In radiation therapy administered with a dose that exceeds 4Gy, permanent fertility loss, namely sterility, is observed (20). Moreover, sperm tests, which show a downward trend within a period of 3-6 months after chemotherapy and radiation therapy, may start to get better slowly. When 2 years elapse following the treatment, spermatogenesis relapses in several phases with a probability of 97% and 94% after chemotherapy and radiation therapy, respectively (66). Azoospermia develops with a rate 59% in patients who are treated due to lymphoma, and its relapse duration is much longer (45 months) (67). Testicular somatic cells, namely Sertoli and Leydig cells, are more resistant than germ cells. However, alkylating agents or agents similar to those may affect sperm production by damaging these cells (Figure 1, 2) (68).

Setting up a nationwide fertility preservation/ oncofertility program in Turkey: Recommendations

The following recommendations have been put forth for preserving fertility and the efficacy of the oncofertility system concerning adolescents and young patients with cancer:

a. Dissemination of information, knowledge, training and available data,

b. Developing relations with the external centers, and being in contact with all the oncology units, family physicians, and nurses in places where multidisciplinary approach does not exist,

c. Establishing male-female fertility-preservation consultations and psychosocial support mechanisms through an internal referral system,

d. Generating referral forms, enabling the admission of patients from internal referral systems in other places,

e. Internal and external referral systems should keep in contact with one another periodically, hold meetings, and also perform professional updates,

f. Have robust database software,

g. Determining multimodal approaches that would offer maximum benefit, and physicians having discussions about these matters with their patients,

It is also very important to develop a record system related to fertility-preservation approaches administered to patients with cancer. It is recommended that such records be registered together with general records where ART data are collected across the country. The treatment approach administered on cancer type, rates of taking a baby home, and spontaneous pregnancy rates in similar cases are suggested to be noted in such records. Local fertility foundations should be involved in lobbying activities along with medical associations and Ministry of Health.

h. There should be liaison/contact points that serve the communication needs of the patients so that they can achieve results in a timely manner by accessing the points easily and also establishing prompt contact with the relevant physicians. Local task forces are also recommended to be established for this purpose.

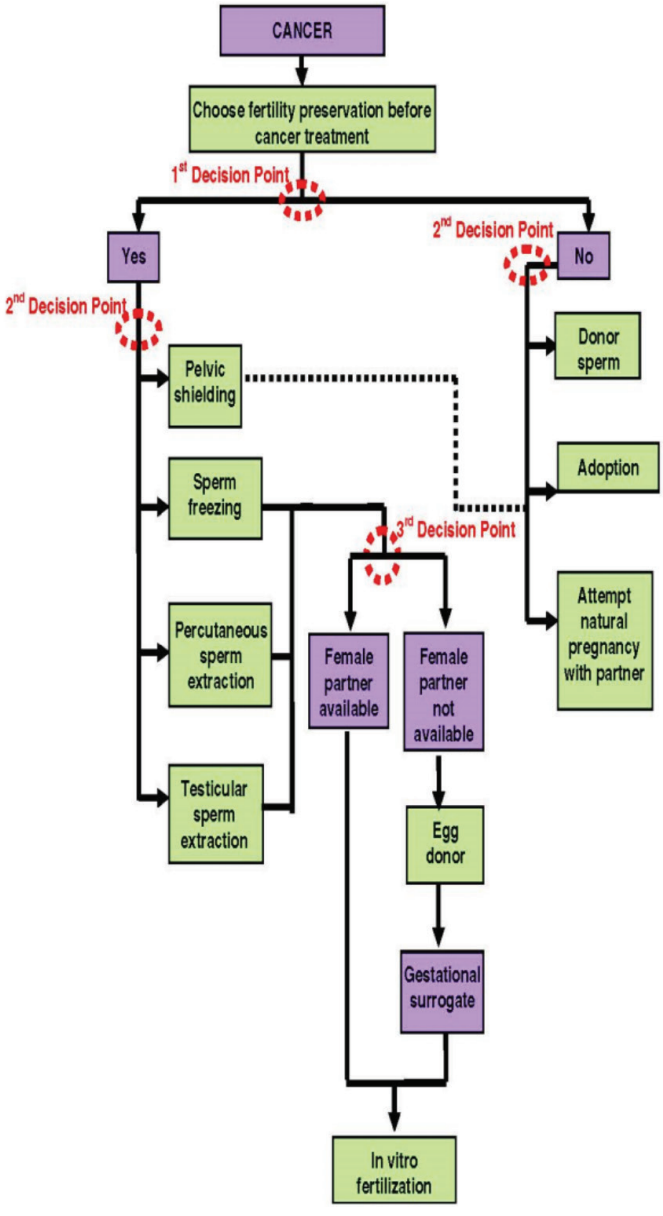


Figure 1. Decision tree for male oncofertility patient (with the permission of Theressa K. Woodruff)

i. Oncologists, reproductive endocrinologists, urologists, and surgeons competent in gonadectomy are required to act as part of an interdisciplinary medical team.

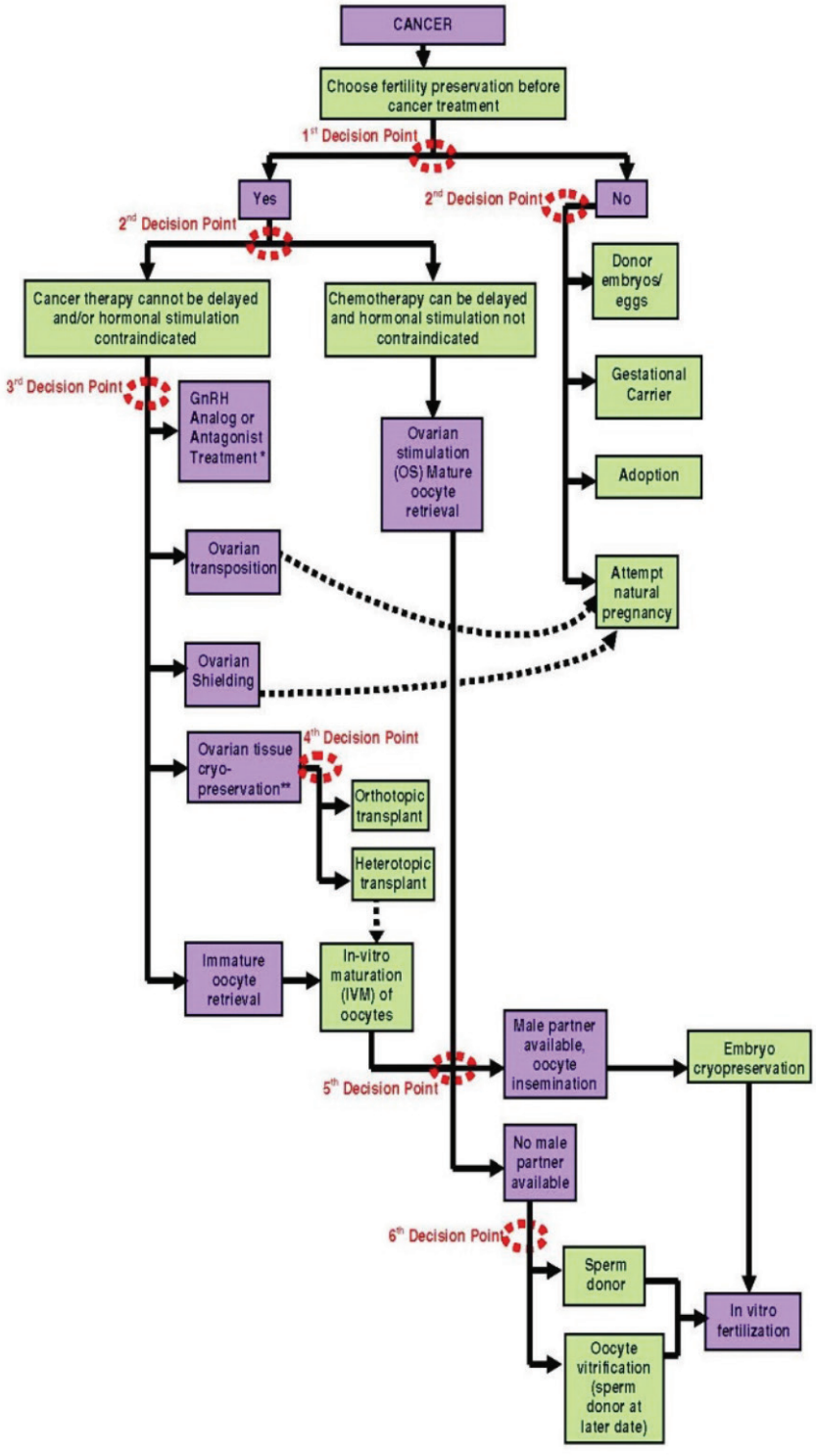
j. As the most important arm of this matter, centers of assisted reproductive techniques (IVF centers) that are competent and experienced in the area should exist. Such centers are expected to be qualified in fertility-preservation methods, stimulation protocols, oocyte freezing, embryo freezing, and IVM. Further competence is also required in regard to the freezing of both sperm and testicular tissue. There are directives in our country regarding sperm, egg, and embryo freezing. Ideally, these centers would be able to perform ovarian and testicular tissue freezing procedures even in prepubertal patients whose informed consent have been obtained. Such procedures are still accepted as experimental, however.

k. The support of mental health professionals should be taken in order to overcome the difficulty experienced by young adults, children or premenopausal patients when they are to make a decision. By performing genetic consultations, patients should be informed about passing the current disease on to the next generation genetically. One of the most crucial issues is making the financial situation clear and obtaining financial consultancy for this process, for which the government does not grant aid. In this way, approaches that will help to curtail costs could be identified.

l. Interdisciplinary collaboration is of crucial importance in fertility preservation. Patients should be referred to a competent reproductive endocrinologist or urologist after having a thorough discussion on the situation of the patient. If possible, all patients, including those at premenopausal age and adolescence, should undergo such a mechanism of referral. This is highly important so as to identify the optimal treatment and arrange the timing for fertility preservation. It is also important to eliminate legal and ethical problems along with professional arrangements.

m. When patients are referred to a reproductive endocrinologist, it is important to discuss at length all the medical and surgical options available for the preservation of fertility. It is also vital to talk about the existence of alternative treatment approaches such as donation and adoption, which are not legal in our country. The current situation of the patient should definitely be taken into consideration as to the decision. It may not be deemed appropriate to present matters related to fertility preservation to an individual who is too ill to be treated. The potential safety of future pregnancy after cancer treatment should be explained to the patient. Patients whose gametes

and embryos are planned to be frozen should definitely be advised to go through scans for infectious diseases. Concerning patients who make the decision of freezing gametes, embryo, and tissue, what might lie ahead in the event of the death of the patient should also be discussed. This discussion should also be documented and recorded. If there is available time, patients are recommended to meet physicians, nurses, and mental counsellors.



*Conflicting evidence to support its use in females: current data does not support GnRH antagonists in men
**Currently characterized as experimental techniques

Figure 2. Decision tree for female oncofertility patient (with the permission of Theressa K. Woodruff)

Further recommendations for a nationwide fertility preservation program

1. This organization must be controlled with a registration system by the Ministry of Health of Turkey.
2. It is recommended to be a part of the OC in a country-based program.
3. A web-based program should be implemented with the aid of the OC.
4. Societies related to oncofertility may be recommended to organize annual meetings to upgrade the knowledge concerning oncofertility and fertility preservation.
5. A nurse training program may be initiated by the Ministry of Health.
6. IVF centers experienced in IVM and ovarian tissue freezing need to be recognized and regionally selected centers and their staff must be trained for IVM and ovarian tissue freezing in order to establish regional centers for tissue and gamete freezing.
7. A multidisciplinary approach including oncologists, reproductive endocrinologists, embryologists, genetic specialists, radiologists and specialized nurses and social workers should be arranged for proper fertility preservation counselling.
8. Internationally accepted ovarian stimulation regimens should be implemented for IVF protocols.
9. Periodical multidisciplinary team counselling linked with task forces or satellite hospitals to manage the oncofertility patients in an appropriate manner.
10. Annual reports of the whole country together with registration of every single patient from the centers to the health ministry registration system.
11. Standardization of documents derived from the sources of OC should be carried out.

Concluding remarks

Although there are centers dealing with oncofertility and fertility preservation individually, there is a strong necessity to have a nationwide registry that gathers all information from selected and accredited centers disseminated across all major regions in Turkey. For this, a colaborative study should be started with oncology societies, gynecology, and infertility societies, and of course the Society of Clinical Embryology, which may then be connected to the global Oncofertility Consortium to develop new strategies together with already experienced world centers that have been dealing with fertility preservation voluntariliy for many years.

Acknowledgement: *Authors of this review would like thank by heart to Teresa K. Woodruff M.D, Professor, PhD, Dean, The Graduate School and Associate Provost for Graduate Education Northwestern University, Chicago, Illinois, USA and The Watkins Professor of Obstetrics and Gynecology, Feinberg School of Medicine, Chicago, Illinois, USA and Lauren Ataman M.D, Professor Administrative Director, Oncofertility Consortium Research Project Manager OB/GYN, Feinberg School of Medicine Northwestern University, Chicago, Illinois, USA for their great support for the make-up of this study and kind acceptance of the figures to be used in this review.*

Peer-review: *Externally peer-reviewed.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. Fertil Steril 2012; 97: 134-40.e1.
2. West ER, Zelinski MB, Kondapalli LA, Gracia C, Chang J, Coutifaris C, et al. Preserving female fertility following cancer treatment: current options and future possibilities. Pediatr Blood Cancer 2009; 53: 289-95.
3. Ataman LM, Rodrigues JK, Marinho RM, Caetano JP, Chehin MB, Alves da Motta EL, et al. Creating a Global Community of Practice for Oncofertility. J Glob Oncol 2016; 2: 83-96.
4. von Wolff M, Germeyer A, Liebenthron J, Korell M, Nawroth F. Practical recommendations for fertility preservation in women by the FertiPROTEKT network. Part II: fertility preservation techniques. Arch Gynecol Obstet 2018; 297: 257-67.
5. González C, Boada M, Devesa M, Veiga A. Concise review: fertility preservation: an update. Stem Cells Transl Med 2012; 1: 668-72.
6. Gardino SL, Jeruss JS, Woodruff TK. Using decision trees to enhance interdisciplinary team work: the case of oncofertility. J Assist Reprod Genet 2010; 27: 227-31.
7. Forman EJ, Anders CK, Behera MA. Pilot survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. J Reprod Med 2009; 54: 203-7.
8. Küçük M, Yavaşoğlu I, Bolaman AZ, Kadıköylü G. Knowledge, attitudes, and practices of hematologists regarding fertility preservation in Turkey. Turk J Haematol 2013; 30: 269-74.
9. Loren AW, Brazauskas R, Chow EJ, Gilleece M, Halter J, Jacobsohn DA, et al. Physician perceptions and practice patterns regarding fertility preservation in hematopoietic cell transplant recipients. Bone Marrow Transplant 2013; 48: 1091-7.
10. Forman EJ, Anders CK, Behera MA. A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. Fertil Steril 2010; 94: 1652-6.
11. Hotaling JM, Laufer N, Rosenwaks Z. Introduction: Cancer biomarkers and fertility. Fertil Steril 2018; 109: 4-5.
12. Hanson BM, Eisenberg ML, Hotaling JM. Male infertility: a biomarker of individual and familial cancer risk. Fertil Steril 2018; 109: 6-19.
13. Nagirnaja L, Aston KI, Conrad DF. Genetic intersection of male infertility and cancer. Fertil Steril 2018; 109: 20-6.
14. James E, Jenkins TG. Epigenetics, infertility, and cancer: future directions. Fertil Steril 2018; 109: 27-32.

15. Cancer Stats Incidence 2008-UK. Cancer Research UK 2011 Registered charity in England and Wales (1089464) and Scotland (SC041666).
16. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009; 45: 992-1005.
17. Donnez J, Martinez-Madrid B, Jadoul P, Van Langendonckt A, Demylle D, Dolmans MM. Ovarian tissue cryopreservation and transplantation: a review. Hum Reprod Update 2006; 12: 519-35.
18. Diedrich K, Fauser BC, Devroey P; Evian Annual Reproduction (EVAR) Workshop Group 2009. Cancer and fertility: strategies to preserve fertility. Reprod Biomed Online 2011; 22: 232-48.
19. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. J Natl Cancer Inst Monogr 2005; 64-8.
20. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005; 62: 738-44.
21. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 2002; 187: 1070-80.
22. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod 2003; 18: 117-21.
23. Blumenfeld Z, von Wolff M. GnRH-analogues and oral contraceptives for fertility preservation in women during chemotherapy. Hum Reprod Update 2008; 14: 543-52.
24. Petrek JA, Naughton MJ, Case LD, Paskett ED, Naftalis EZ, Singletary SE, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. J Clin Oncol 2006; 24: 1045-51.
25. Broekmans FJ, Visser JA, Laven JS, Broer SL, Themmen AP, Fauser BC. Anti-Müllerian hormone and ovarian dysfunction. Trends Endocrinol Metab 2008; 19: 340-7.
26. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001; 7: 535-43.
27. Anderson RA, Themmen AP, Al-Qahtani A, Groome NP, Cameron DA. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. Hum Reprod 2006; 21: 2583-92.
28. Donnez J, Dolmans MM, Martinez-Madrid B, Demylle D, Van Langendonckt A. The role of cryopreservation for women prior to treatment of malignancy. Curr Opin Obstet Gynecol 2005; 17: 333-8.
29. Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004; 22: 4174-83.
30. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005; 83: 1622-8.
31. Eskander RN, Randall LM, Berman ML, Tewari KS, Disaia PJ, Bristow RE. Fertility preserving options in patients with gynecologic malignancies. Am J Obstet Gynecol 2011; 205: 103-10.
32. Partridge AH, Gelber S, Peppercorn J, Ginsburg E, Sampson E, Rosenberg R, et al. Fertility and menopausal outcomes in young breast cancer survivors. Clin Breast Cancer 2008; 8: 65-9.
33. de Ziegler D, Streuli I, Vasilopoulos I, Decanter C, This P, Chapron C. Cancer and fecundity issues mandate a multidisciplinary approach. Fertil Steril 2010; 93: 691-6.
34. Hatırnaz Ş, Ata B, Hatırnaz ES, Dahan MH, Tannus S, Tan J, et al. Oocyte in vitro maturation: A sytematic review. Turk J Obstet Gynecol 2018; 15: 112-25.
35. Hatirnaz S, Basbug A, Akarsu S, Hatirnaz E, Demirci H, Dahan MH. Outcomes of random start versus clomiphene citrate and gonadotropin cycles in occult premature ovarian insufficiency patients, refusing oocyte donation: a retrospective cohort study. Gynecol Endocrinol 2018; 34: 949-54.
36. Zaman K, Ambrosetti A, Perey L, Jeanneret-Sozzi W, Delaloye JF, De Ziegler D. Breast cancer in young women: adjuvant therapy and fertility. Rev Med Suisse 2007; 3: 1298-1300, 1302, 1304.
37. Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. N Engl J Med 2000; 342: 564-71.
38. Decanter C, Morschhauser F, Pigny P, Lefebvre C, Gallo C, Dewailly D. Anti-Müllerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results. Reprod Biomed Online 2010; 20: 280-5.
39. De Bruin ML, Huisbrink J, Hauptmann M, Kuenen MA, Ouwens GM, van't Veer MB, et al. Treatment-related risk factors for premature menopause following Hodgkin lymphoma. Blood 2008; 111: 101-8.
40. Cramer DW, Xu H, Harlow BL. Does "incessant" ovulation increase risk for early menopause? Am J Obstet Gynecol 1995; 172: 568-73.
41. Azim AA, Costantini-Ferrando M, Lostritto K, Oktay K. Relative potencies of anastrozole and letrozole to suppress estradiol in breast cancer patients undergoing ovarian stimulation before in vitro fertilization. J Clin Endocrinol Metab 2007; 92: 2197-200.
42. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Data-base: North American Association of Central Cancer Registries (NAACCR) Incidence-ChiNA Analytic File, 1995-2008, for Expanded Races, custom file with county, ACS Facts & Figures projection project, North American Association of Central Can-cer Registries. Bethesda: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch; 2011.
43. Howlader N, Noone AM, Yu M, Cronin KA. Use of imputed population-based cancer registry data as a method of accounting for missing information: application to estrogen receptor status for breast cancer. Am J Epidemiol 2012; 176: 347-56.
44. Rodriguez-Wallberg KA, Oktay K. Recent advances in oocyte and ovarian tissue cryopreservation and transplantation. Best Pract Res Clin Obstet Gynaecol 2012; 26: 391-405.
45. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 2001; 7: 535-43.
46. Meirow D, Nugent D. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Hum Reprod Update 2001; 7: 535-43.
47. Cakmak H, Rosen MP. Ovarian stimulation in cancer patients. Fertil Steril 2013; 99: 1476-84.
48. Cobo A, Bellver J, Domingo J, Pérez S, Crespo J, Pellicer A, et al. New options in assisted reproduction technology: the Cryotop method of oocyte vitrification. Reprod Biomed Online 2008; 17: 68-72.
49. Rienzi L, Romano S, Albricci L, Maggiulli R, Capalbo A, Baroni E, et al. Embryo development of fresh 'versus' vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study. Hum Reprod 2010; 25: 66-73.
50. Parmegiani L, Cognigni GE, Bernardi S, Cuomo S, Ciampaglia W, Infante FE, et al. Efficiency of aseptic open vitrification and hermetical cryostorage of human oocytes. Reprod Biomed Online 2011; 23: 505-12.
51. Anderson RA, Anckaert E, Bosch E, Dewailly D, Dunlop CE, Fehr D, et al. Prospective study into the value of the automated Elecsys antimüllerian hormone assay for the assessment of the ovarian growing follicle pool. Fertil Steril 2015; 103: 1074-1080.e4.
52. Ozkaya E, San Roman G, Oktay K. Luteal phase GnRHa trigger in random start fertility preservation cycles. J Assist Reprod Genet 2012; 29: 503-5.

53. Sönmezer M, Türkçüoğlu I, Coşkun U, Oktay K. Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles. Fertil Steril 2011; 95: 2125.e9-11.
54. von Wolff M, Thaler CJ, Frambach T, Zeeb C, Lawrenz B, Popovici RM, et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril 2009; 92: 1360-5.
55. Madrigrano A, Westphal L, Wapnir I. Egg retrieval with cryopreservation does not delay breast cancer treatment. Am J Surg 2007; 194: 477-81.
56. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol 2008; 26: 1331-7.
57. Dolmans MM, Marinescu C, Saussoy P, Van Langendonckt A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood 2010; 116: 2908-14.
58. Meirow D, Hardan I, Dor J, Fridman E, Elizur S, Ra'anani H, et al. Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. Hum Reprod 2008; 23: 1007-13.
59. Maltaris T, Seufert R, Fischl F, Schaffrath M, Pollow K, Koelbl H, et al. The effect of cancer treatment on female fertility and strategies for preserving fertility. Eur J Obstet Gynecol Reprod Biol 2007; 130: 148-55.
60. Gidoni Y, Holzer H, Tulandi T, Tan SL. Fertility preservation in patients with non-oncological conditions. Reprod Biomed Online 2008; 16: 792-800.
61. Tur-Kaspa I, Segal S, Moffa F, Massobrio M, Meltzer S. Viagra for temporary erectile dysfunction during treatments with assisted reproductive technologies. Hum Reprod 1999; 14: 1783-4.
62. Meistrich ML, Shetty G. Hormonal suppression for fertility preservation in males and females. Reproduction 2008; 136: 691-701.
63. Brook PF, Radford JA, Shalet SM, Joyce AD, Gosden RG. Isolation of germ cells from human testicular tissue for low temperature storage and autotransplantation. Fertil Steril 2001; 75: 269-74.
64. Rueffer U, Breuer K, Josting A, Lathan B, Sieber M, Manzke O, et al. Male gonadal dysfunction in patients with Hodgkin's disease prior to treatment. Ann Oncol 2001; 12: 1307-11.
65. Orwig KE, Schlatt S. Cryopreservation and transplantation of spermatogonia and testicular tissue for preservation of male fertility. J Natl Cancer Inst Monogr 2005; 51-6.
66. Cardis E, Krewski D, Boniol M, Drozdovitch V, Darby SC, Gilbert ES, et al. Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. Int J Cancer 2006; 119: 1224-35.
67. Bahadur G, Ozturk O, Muneer A, Wafa R, Ashraf A, Jaman N, et al. Semen quality before and after gonadotoxic treatment. Hum Reprod 2005; 20: 774-81.
68. Pastink A, Schalet AP, Vreeken C, Parádi E, Eeken JC. The nature of radiation-induced mutations at the white locus of Drosophila melanogaster. Mutat Res 1987; 177: 101-15.

What is your diagnosis?

An adolescent girl aged 16 years presented to the emergency department with features of shock. She had severe pallor with feeble pulse of 120/min, blood pressure: 80/40 mm Hg, respiratory rate: 22/min, peripheral capillary oxygen saturation (SpO_2): 98%, and urine output was almost nil. Initial resuscitation was performed. The history could not be elicited from the patient herself. Her relatives revealed that she had a 4-month history of amenorrhea along with pain in the abdomen and bleeding per vaginum for the last one day. A urine pregnancy test was positive. The parents denied any history of pill intake or surgical procedures for termination of pregnancy.

The abdominal examination was within normal limits. There was no guarding, rigidity, tenderness or any palpable mass felt. Bleeding was present on local examination. A gentle vaginal examination revealed a 6x6 cm smooth, tender, round mass in the vagina, the cervical rim and uterus could not be felt. The patient did not allow a proper examination because it was very painful. An urgent blood investigation was suggestive of hemoglobin of 6.9 gm%, total leucocyte count: 28,000/cumm with normal coagulation profile. The patient was planned for examination under anesthesia (EUA).

Received: 4 February, 2019 **Accepted:** 15 April, 2019

Answer

The patient was taken to the operation room for EUA in view of the uncertainty of diagnosis and hemodynamic instability. Informed and written consent was obtained for EUA along with emergency laparotomy if required. The remote possibility of hysterectomy was also explained. EUA was suggestive of second-degree uterine inversion, tissues were edematous and bleeding was present (Figure 1), the fundus of the uterus was not palpable on manual palpation. An intra-operative trans-abdominal scan (Figure 2) also gave rise to the suspicion of inverted uterus. Manual repositioning as well as the hydrostatic technique did not work. Laparotomy and repair of uterine inversion using the Haultain technique was performed. Intra-operatively, a cervical constriction ring with a depression was observed in place of the uterus and bilateral round ligaments, the fallopian tubes and ovaries were seen dragged into the depression along with the upper half of the uterine body (Figure 3). A vertical incision was made over the posterior aspect of the constricted cervical ring. The inversion was then corrected by following the principle 'the part which goes first should be repositioned first'. The uterus was well retracted after correction. The incision site was repaired with delayed absorbable suture in two layers. A total of 4 units of packed red blood cells and 4 units of fresh frozen plasma was transfused to the patient. Her postoperative recovery was uneventful.

Puerperal uterine inversion is a life-threatening emergency condition that occurs after vaginal or cesarean delivery,

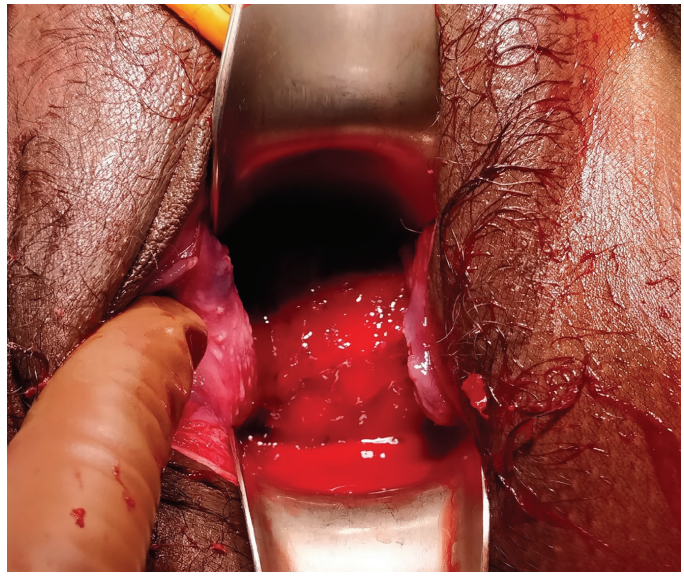


Figure 1. Speculum examination shows a rounded smooth mass in vagina, bleeding^{++}

Address for Correspondence: *Kavita Khoiwal*
e.mail: kavita.kh27@gmail.com - kavita.kh27@yahoo.com ORCID: orcid.org/0000-0002-3156-7486

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2019.0024

even with hysterotomy. It has been classified on the basis of the time of occurrence from delivery (acute <24 hours, subacute 24 hours to 4 weeks, and chronic ≥4 weeks) (1). Most cases present within 24 hours of delivery (2) with severe postpartum hemorrhage followed by hypovolemic shock. In addition, neurogenic shock due to stretching of the pelvic parasympathetic nerves worsens the condition. The incidence varies in different populations, ranging from 1 in 3500 to 20,000 deliveries (3,4). There are only few case reports of uterine inversion after mid trimester abortion (5,6). Though it is a rare event, healthcare workers should be aware and vigilant about this condition because if not timely diagnosed and managed, it can lead to shock and even death.

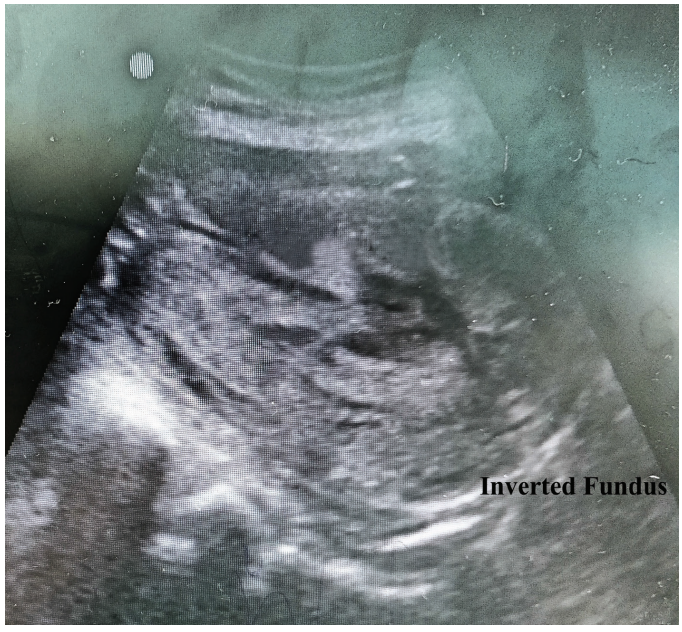


Figure 2. Transabdominal scan suggestive of inverted uterus

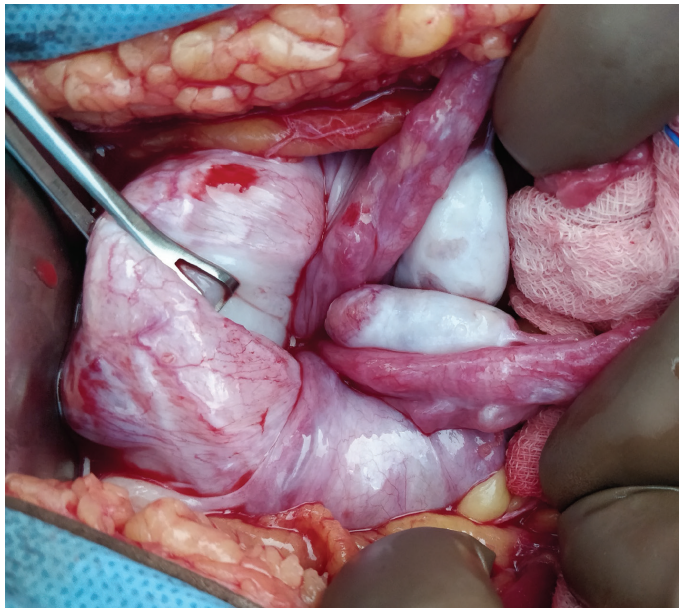


Figure 3. Bilateral round ligaments, fallopian tubes and ovaries seen dragged into the depression along with the upper half of the uterine body. Cervical constriction ring is seen being held with Babcock's forceps

The incidence of non-puerperal uterine inversion is further less than puerperal uterine inversion. In a systemic review of the literature (7), a total of 170 case reports of non-puerperal uterine inversion were found. The reason behind its occurrence is an polypoid tumor of uterus mostly submucosal fibroid (57.2%) followed by sarcoma (13.5%). Most of these patients (86.8%) underwent hysterectomy.

Uterine inversion is typically diagnosed through clinical findings including vaginal bleeding, lower abdomen pain, features of shock may or may not be present, inability to palpate the uterus on abdominal examination, and presence of a round smooth mass protruding from the cervix or vagina. Imaging studies are not recommended but they have a role in a few cases with uncertain diagnosis, provided that the patient is hemodynamically stable (8).

The objectives of management are to stabilize the patient by managing postpartum hemorrhage and shock, if present, and repositioning of the uterus. Prompt recognition and timely intervention is the key of management. After initial resuscitation, manual replacement of the inverted uterus should be attempted. Do not remove the placenta, if attached. If the immediate replacement maneuvers do not work, surgical methods for replacement should be considered. Surgical procedures include the Huntington procedure (giving upward traction on the inverted uterus with a clamp) or the Haultain procedure, which involves making an incision on the cervical constriction ring posteriorly to increase its size, followed by repositioning of the inverted uterus, followed by repair of the incision.

Hydrostatic reduction is an option if all other interventions have failed and surgical intervention is not possible (9).

The reported incidence of complications associated with puerperal uterine inversion are postpartum hemorrhage (38%), need of blood products (22%), laparotomy (6%), hysterectomy (3%), hypotension (2%), and shock (1.3%) (4). There are insufficient data to report the rate of recurrence in subsequent pregnancies. No recurrence was noticed in a case series (n=40) by Baskett (10).

The mode of is based upon the management option used; if the woman underwent surgical replacement with an incision over the uterus, cesarean section is a better option (11).

Puerperal uterine inversion is a rare but life-threatening condition, it may present in any woman of reproductive age. Healthcare workers should be aware and vigilant about this condition and keep it in mind whenever a woman presents

with pain in the abdomen and bleeding per vaginum leading to shock in the post-partum or post-abortion period. Early diagnosis and immediate management is the key of successful outcome.

Kavita Khoiwal, Anshu Gupta, K. Rupendra, Jaya Chaturvedi, Amrita Gaurav

All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

References

1. Livingston SL, Booker C, Kramer P, Dodson WC. Chronic uterine inversion at 14 weeks postpartum. Obstet Gynecol 2007; 109: 555-7.
2. Dali SM, Rajbhandari S, Shrestha S. Puerperal inversion of the uterus in Nepal: case reports and review of literature. J Obstet Gynaecol Res 1997; 23: 319-25.
3. Witteveen T, van Stralen G, Zwart J, van Roosmalen J. Puerperal uterine inversion in the Netherlands: a nationwide cohort study. Acta Obstet Gynecol Scand 2013; 92: 334-7.
4. Coad SL, Dahlgren LS, Hutcheon JA. Risks and consequences of puerperal uterine inversion in the United States, 2004 through 2013. Am J Obstet Gynecol 2017; 217: 377.
5. Begam N, Ganguly S, Anwer BR, Islam F. Inversion of Uterus-Presenting as a Complication of Abortion. Bangladesh of J Obstet Gynaecol 2014; 29: 54-5.
6. Mishra S. Chronic Uterine Inversion Following Mid-Trimester Abortion. J Obstet Gynaecol India 2018; 68: 320-2.
7. Rosa SB, de Oliveira MF, Uggioni ML, Grande AJ, Chiaramonte SN, Colonetti T, et al. Non-Puerperal Uterine Inversion: A Systematic Review. Gynecol Obstet Invest 2018; 83: 428-36.
8. Hsieh TT, Lee JD. Sonographic findings in acute puerperal uterine inversion. J Clin Ultrasound 1991; 19: 306-9.
9. Tan KH, Luddin NS. Hydrostatic reduction of acute uterine inversion. Int J Gynaecol Obstet 2005; 91: 63-4.
10. Baskett TF. Acute uterine inversion: a review of 40 cases. J Obstet Gynaecol Can 2002; 24: 953.
11. Wendel MP, Shnaekel KL, Magann EF. Uterine Inversion: A Review of a Life-Threatening Obstetrical Emergency. Obstet Gynecol Surv 2018; 73: 411-7.

Laparoscopic assisted robotic myomectomy of a huge myoma; Does robotic surgery change the borders in minimally invasive gynecology?

Özgüç Takmaz[1], Savaş Gündoğan[1], Esra Özbaşlı[1], Emine Karabük[2], Murat Naki[1], Faruk Köse[1], Mete Güngör[1]

[1]Clinic of Obstetrics and Gynecology, Acıbadem Mehmet Ali Aydınlar University, Maslak Hospital, İstanbul, Turkey
[2]Clinic of Obstetrics and Gynecology, Acıbadem Mehmet Ali Aydınlar University, Atakent Hospital, İstanbul, Turkey

Abstract

Today, the adoption of minimal invasive gynecologic procedures is expanding their routine use in clinical practice. Until recently, a diameter of 8 cm was the recommended maximal size for laparoscopic removal of fibroids. However, robot-assisted laparoscopy improved the capacity and the feasibility of the many gynecologic procedures. Here, we report a video of robotic myomectomy of a huge myoma. (J Turk Ger Gynecol Assoc 2019; 20: 211-2)

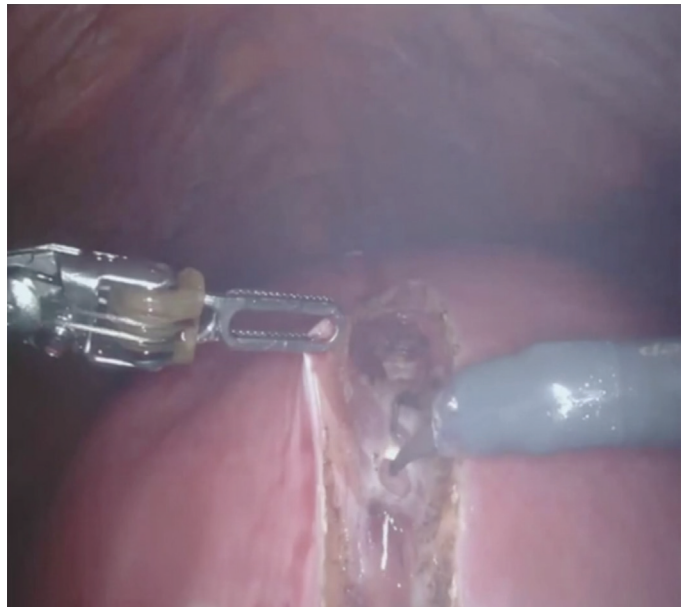
Keywords: Robotic myomectomy, huge myoma, fibroid

Received: 17 February, 2019 **Accepted:** 8 May, 2019

Introduction

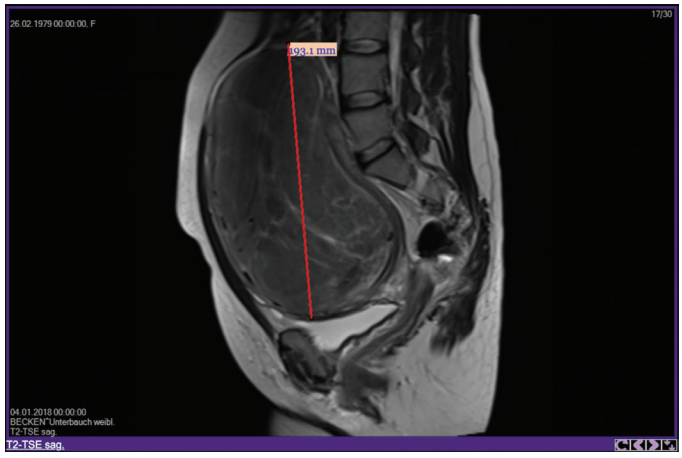
To demonstrate the feasibility of robotic myomectomy of a huge fibroid, we recorded a robotic myomectomy operation video of a 19 cm diameter (FIGO type 3-4) myoma (Canadian Task Force Classification III) at a university-affiliated private hospital.

A 38-year-old, gravida 2 (vaginal birth) patient with a 19 cm intramural fibroid was admitted to our clinic with a request of endoscopic removal of the fibroid. The patient was given detailed information about risk of the surgery, defining the risk of disseminating malignant cells through the abdominal cavity. It was then decided to perform a myomectomy operation using a robotic platform. The operation was performed using a Da Vinci Xi platform (Intuitive Surgical, Inc., Sunnyvale, Ca); the patient card was docked centrally, and three robotic arms and an assistant port with a smoke evacuator (AirsealR SurgiQuest, Inc., CT, USA) were used.



Address for Correspondence: *Özgüç Takmaz*
e.mail: ozguctakmaz@hotmail.com ORCID: orcid.org/0000-0002-3397-7980

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2019.0029



The surgical time (skin to skin) was 205 min, and the docking time was 6 min. A 2.0 barbed suture was used for uterine closure. The estimated blood loss (calculated with the difference between irrigation and suction) was 350 cc, and two erythrocyte suspension transfusions were given after the operation. The first gas discharge was 13 hours after the surgery, the length of hospital stay was 2 days. No complications occurred peri-operatively.

Huge fibroids can be removed using robot-assisted laparoscopy.

Video 1. DOI: 10.4274/jtgga.galenos.2019.2019.0029.video.1

Conflict of Interest: *No conflict of interest was declared by the authors.*

Financial Disclosure: *The authors declared that this study has received no financial support.*

CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.medical.theconferencewebsite.com/conferences/obstetrics-and-gynaecology)

September 11-14, 2019	**14th World Congress of Perinatal Medicine 2019, İstanbul, Turkey**
September 18-20, 2019	**French Society of Gynecologic and Pelvic Surgery 2019, Lille, France**
September 18-20, 2019	**International Society for the Study of Vulvovaginal Disease 25th Congress 2019, Torino, Italy**
September 20-22, 2019	**Asia-Pacific Association for Gynecologic Endoscopy and Minimally Invasive Therapy 20th Annual Congress 2019, Chongqing, China**
September 24-28, 2019	**International Urogynecological Association 44th Annual Meeting 2019, Nashville, United States**
September 25-28, 2019	**North American Menopause Society 30th Annual Meeting 2019, Chicago, United States**
September 26-28, 2019	**Society of European Robotic Gynaecological Surgery 11th Annual Meeting 2019, Sofia**
October 6-9, 2019	**European Society for Gynaecological Endoscopy 28th Annual Congress 2019, Thessaloniki, Greece**
October 12-16, 2019	**American Society for Reproductive Medicine Annual Meeting 2019, Philadelphia, United States**
October 12-16, 2019	**29th World Congress on Ultrasound in Obstetrics and Gynecology 2019, Berlin, Germany**
October 16-18, 2019	**12th Annual Congress of the European Urogynaecological Association 2019, Tel Aviv, Israel**
October 16-19, 2019	**European Society of Gynecology 2019, Austria**
October 24-26, 2019	**20th World Congress on In Vitro Fertilization 2019, Barcelona, Spain**
October 31-November 2, 2019	**Middle East Fertility Society 26th Annual Meeting 2019, Cairo, Egypt**
November 2-5, 2019	**European Society of Gynaecological Oncology State of the Art Conference 2019, Athens, Greece**
November 9-13, 2019	**48th AAGL Global Congress on Minimally Invasive Gynecology 2019, Vancouver, Canada**
November 21-23, 2019	**27th World Congress on Controversies in Obstetrics, Gynecology & Infertility 2019, Paris, France**
November 28-30, 2019	**29th Congress of the German Society of Perinatal Medicine 2019, Berlin, Germany**

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2019.com)

September 11-14, 2019	**14. World Congress of Perinatal Medicine, İstanbul, Turkey**
September 20-26, 2019	**5. KED Kongresi, İzmir, Turkey**
October 2-6, 2019	**Obstetrik ve Jinekoloji Zirvesi, Antalya, Turkey**
October 3-6, 2019	**7. Üreme Tıbbı Cerrahisi Derneği Kongresi, Antalya, Turkey**
October 11-13, 2019	**15. TJOD Asistan Okulu, Antakya, Turkey**
October 17-20, 2019	**15. Ulusal Meme Hastalıkları Kongresi, Antalya, Turkey**
November 22-24, 2019	**7. Uluslararası Ürojinekoloji Kongresi, İstanbul, Turkey**
November 23, 2019	**TMFTP Tıbbi Uygulamalar ve Hukuk Kongresi, Ankara, Turkey**
December 5-8, 2019	**İstanbul Üniversitesi 9. Kadın Doğum Günleri, İstanbul, Turkey**

NEOFORTİL®M

TAKVİYE EDİCİ GIDA

SPERMATOGENEZ'de Etkin ve Ekonomik Seçenek

Bileşenler (Her bir Tablet için)	
L-Carnitine Tartrate	300 mg
L-Arginine Hydrochloride	125 mg
Vitamin C	60 mg
Vitamin E	36 mg
Zinc Sulfate Monohydrate	20 mg
Coenzyme Q10	7,5 mg
Vitamin B9 Folic Acid	400 mcg
Selenium	30 mg

NEOFORTİL®M 180
180 Tablet 2x1
3 Aylık Tedavi

NEOFORTİL®M 60
60 Tablet 2x1
1 Aylık Tedavi

İhtiyaç duyulan anda gereği kadar destek... **Ne eksik, ne fazla...**

NEOFORTİL® WM & DHA

TAKVİYE EDİCİ GIDA

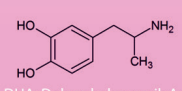
TEK DOZDA GÜÇLÜ KOMBİNASYON

30 Tablet WM

30 Kapsül DHA

Onay Numarası ve Tarihi: 000563-23.03.2016

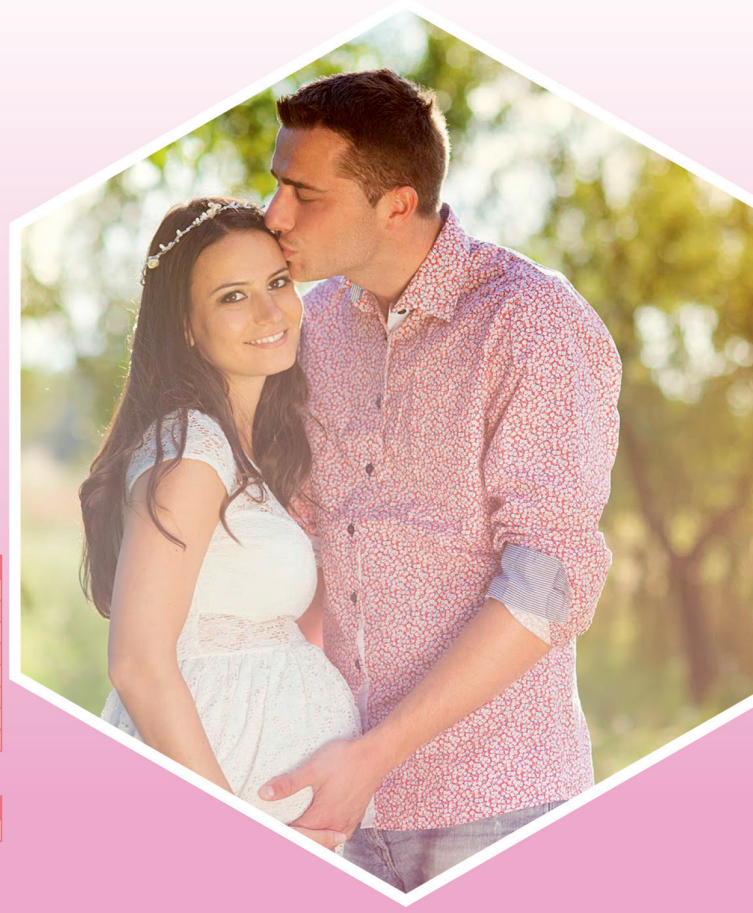
- İçeriğindeki Vejeteryan DHA, Vitaminler, Mineraller ve Bitkisel Ekstraktlarla birlikte eşsiz bir üründür.
- Aynı ambalajın içinde 1 aylık kullanıma uygun 30 tablet ve 30 kapsül bulunur.
- Vejeteryan DHA, direk olarak mikroalglerden (yosunlardan) elden edildiği için bu şekilde adlandırılır ve mevcut balık yağlarından ayrılır.



DHA: Dokosaheksaenoik Asit

Bileşenler (Her bir Tablet için)	
Folik Asit	400 mcg
E Vitamini	12 mg
Çinko	10 mg
Magnezyum	100 mg
Selenium	27.5 mcg
Damiana Yaprağı	90 mg
Ginseng Kökü	60 mg
Maca Kökü	50 mg

Bileşenler (Her bir Kapsül için)	
Vejeteryan DHA	200 mg



Tanı Pharma

0850 532 8264
www.tanipharma.com


Gebelik ve emzirme dönemi boyunca
Her şey yolunda
Omega 3, folik asit, iyot, demir dahil anne ve bebeğin ihtiyacı olan vitamin ve mineraller
VİTAMİN
MİNERAL
Hepsi 1 arada
OMEGA 3
FOLİK ASİT
Günde 1 kapsül
reGenesis MAX
Omega Vita Mineral
OMEGA-3 YAĞ ASİTLERİNİ İÇEREN TAKVİYE EDİCİ GIDA
30 kapsül
Exeltis
Exeltis
Rethinking healthcare
14052019-584767