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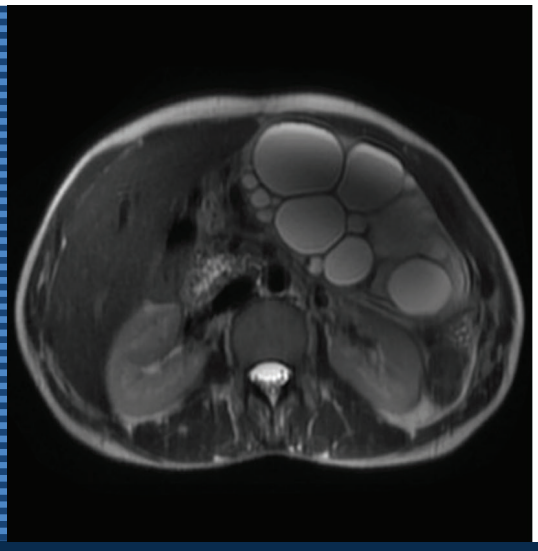

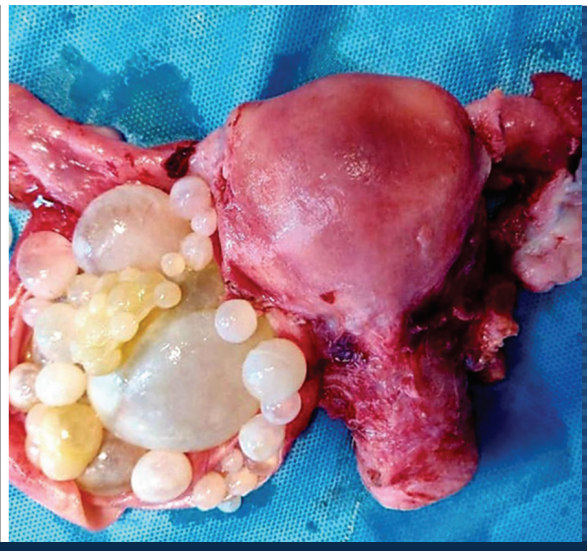

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Cover Picture: Bahadur et al. Hydatidosis with Endo-myometrial involvement

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Şiddetli menstrüel kanama yaşayan kadınların
SORUNLARI AYNI FAKAT İHTİYAÇLARI FARKLI

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- Şiddetli menstrüel kanama miktarında **%88 oranında,** hızlı ve uzun süreli azalma sağlar.

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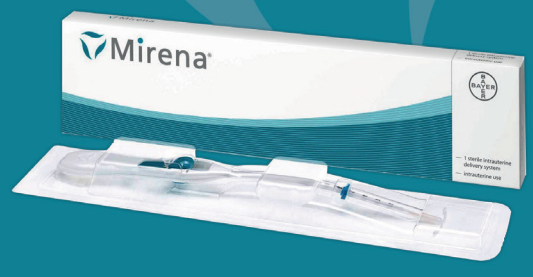

Referanslar: 1. Qlairista® Kısa Ürün Bilgisi **2.** Mirena® Kısa Ürün Bilgisi

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 Pozolojiyi uygulama şekli, süresi ve şekli: Tablet almına doğal sıklusun (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 hormonlan esas olarak, hem intestinal mukoza hem de karaciğerde bulunan sitokrom P450 3A4 (CYP 3A4) sistemi tarafından metabolize edilirler. Bu nedenle, fenitoin, barbitüratlar, primidon, karbamazepin, rifampisin ve muhtemelen oksikarbazepin, 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 kontrasseptifler belirli başka ilaçların (örn. lamotrijin) 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 tablolarn 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,vaskküler 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 görüşülmelidir. Estradiol/estradiol valerat içeren KOK'larn 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 bağlrıtnın 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, ayrı 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 kullanlarda 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 kullanlarlara tanısı konulan meme kanseri, hiç kullanmamış kadınlarda tanısı konulanlardan, klinik olarak daha az ilerlemiş olma eğilimindedir. KOK kullanlarında 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 eritematozus, hemolitik üremik sendrom, Sydenham koresi, herpes gestasyonis, otosklerioza 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 rejimiz 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 istenmeden 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. Kullanım 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 oluştuğunda şekilde alınması sonucunda olışabilecek semptomlar bulantı, kusma ve genç kızlarda hafif vajinal kanamadır. Antidotu yoktur ve tedavi semptomatik olmalıdır. **Raf ömrü:** 60 ay. Saklanışa yönelik özel tedbirler: 30°C'nin altında, oda sıcaklığında saklanmalıdır. Ambalajın niteliği ve içeriği: Polivinil klorürden yapılı transparan filmler ve ısıyla işlenmiş alumiyumdan yapılı metalik folyolardan oluşan blister ambalajda 28 tablet. **Ruhsat sahibi:** Bayer Türk Kimya San. Ltd. Şti., Çakmak Mah. Balkan Cad. No:53 34770 Umraniye - Istanbul 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. **Fiyatı:** 55,46 TL (19.02.2020)

MİRENA® Levonorgestrel rahim içi sistemi **Formülü: MİRENA®** 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 hiperplazıye 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; **MİRENA®**'nın içeriğine karşı olabilecek aşırı duyarlılık durumu. **Uyarılar / Önlemler:** Aşağıdaki durumlardan herhangi biri varsa ya da ilk kez ortaya çıkıyorsa, **MİRENA®** 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 tansival ve terapötik girişimlerde bulunulmalıdır. Varikoz venlerin ve yüzeyel tromboflebitin venöz tromboembolideki olası rolü konusunda görüş birliği yoktur. **MİRENA®** enfekte endokardit riskine yol açan konjenital kalp hastalığı ya da valvüler kalp hastalığı olan kadınlarda dikkatle kullanılmalıdır. Bu hastalarda rahim içi sistem takılır veya çıkartılırken antibiyotik profilaksisi yapılmalıdır. Düşük-doz levonorgestrel glukoz toleransını etkileyebileceğinden, **MİRENA®** kullanan diyabetik kadınlarda kan şekeri izlenmelidir. Düzensiz kanamalar, endometriyum poliplerinin ve kanserinin bazı belirtilerini gizleyebilmektedir. Bu olgularda tansival girişimlerde bulunulmalıdır. **MİRENA®** genç ve doğum yapmamış kadınlarda ve ileri uterus atrofisi olan postmenopozal kadınlarda ilk seçenek değildir. **Uygulama ve çıkarma/tekrar uygulama:** Uygulamadan önce, kadın **MİRENA®**'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. **MİRENA®**'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 **MİRENA®** uterus boşluğuna menstruasyonun ilk yedi günü içinde yerleştirilmelidir. **MİRENA®** bir yenioylie sıklusun herhangi bir gününde değiştirilebilir. Sistem ilk trimestr düşüklerini takiben hemen uygulanabilir. Postpartum uygulamalar doğum sonrası altıncı haftaya kadar ertelenmelidir. **MİRENA®**'nın post koital bir kontraseptif olarak kullanılması uygun olmayabilir. Estrogen replasman tedavisi sırasında endometriyal koruma için kullanılacaksa, **MİRENA®** 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 **MİRENA®** takılmadan önce endometriyal patolojinin ekarte edilmesi önerilir. **MİRENA®** bir forseps yardımıyla iplikleri nden nazikçe çekilerek çıkarılır. Eğer iplikler görülemiyorsa ve sistem uterus boşluğu içindeyse ince bir tenekulum 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, **MİRENA®** fertil yaşlardaki kadınlarda bir sıklusun varlığından emin olunması amacıyla menstruasyon sırasında çıkarılmalıdır. Eğer sistem sıklus 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: MİRENA®** kullanan fertil kadınların %20'sinde zamanla oligomenore ve/veya amenore çalışmaktadır. Bir önceki menstruasyonun başlangıcının 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. **MİRENA®**'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 **MİRENA®** çıkarılmalıdır. Enfeksiyon düşürüldüren en kritiçik bir belirtide bile bakteriyolojik tetkikler ve ölem önerilir. Yeniden oynama/çıkma: **MİRENA®**, yerinden oynamışsa çıkarılmalıdır. İsteniyorsa o sırada yenisi takılabilir. Kullanıcıya **MİRENA®**'nın ipliklerini nasıl kontrol edeceği öğretilmelidir. **Perforasyon:** Uterusun gövdesinin ya da serviksin bir rahim içi araç tarafından perforasyonu ya da penetrasyonu nadiren görülebilir ve sıkıkla yerlestirme 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 serviksde geri çekme iplikleri görülmüyorsa, gebelik ekarte edilmelidir. **Geciken foliküller atrezi: MİRENA®**'nın kontraseptif etkisi başlıca lokal etkisine bağlı olduğundan, fertil yaştaki kadınlarda folikül çatlamasının görüldüğü ovulatıar siklolar sıklıkla gerçekleşir. Bazen folikülün atrezisi geçikr 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 **MİRENA®** kullanıcılarında görülür. İyi huylu ovaryal kist görülme oranı kullanılan tansival yönteme bağlıdır. Klinik çalışmalarda **MİRENA®** kullanan kadınların %12'sinde büyümüs folikullere rastlanmıştır. Folikullerin çoğu asemptomatiktir ve üç ay içinde kaybolur. **İstenmeyen etkilerden bazıları:** duygu durum değişkenliği, başağrısı, migren, abdominal ağrı, abdominal şişkinlik, akne, saç dökülmesi, hirsutizm, kasıntı, kızarıklık, ürtiker, sırt ağrısı, pelvik ağrı, dismenore, pelvik enflamatuvar hastalık, uterus perforasyonu, vaginal akıntı, vulvovajinit, servisit, endometrit, memede gerginlik, mastitiji, dişan atılma, uterus perforasyonu. **İlaç etkileşmeleri:** Progestagenlerin metabolizması, özellikle sitokrom P450 enzimleri gibi ilaçlan metabolize eden enzimlerin indüksiyonunu yapan maddeler (fenobarbital, fenitoin, karbamazepin gibi antikonvülsanlar ve rifampisin, rifabutin, nevirapin, efavirenz gibi antiinfektifler) ile birlikte kullanılmaları sonucu artar. **MİRENA®**'nın kontraseptif etkisinin bu tür ilaçlar ile etkileşimi bilinmemektedir, ancak lokal etki mekanizması nedeniyle büyük bir öneme sahip olduğu düşünülmemektedir. **Kullanım şekli ve dozu: MİRENA®** 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 **MİRENA®** progestagen içermeyen oral veya transdermal preparatlarla birlikte kullanılabilir. **MİRENA®** takılacağı zamana kadar açılmaması 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. **MİRENA®** aplikatörü hastane atığı, ambalajlar ise evsel atık kabul edilir. **MİRENA®** uygulaması ile ilgili ayrıntılı bilgi "Teknik Bilgiler" bölümünde bulunmaktadır. 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Aims and Scope

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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/),

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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.

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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.

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Editorial

Dear Colleagues,

I am delighted to introduce the first issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2020.

J Turk Ger Gynecol Assoc displays articles on ongoing hot topics and treatments related to obstetrics and gynecology. With hundreds of citations per year, J Turk Ger Gynecol Assoc's influence extends to over 2.309 subscribers globally. With over 155 submissions a year from over 20 countries, each issue of J Turk Ger Gynecol Assoc includes original clinical research articles, reviews, editorials, quiz and video articles.

Here you may read many good quality manuscripts from all around the world like Mexico, Germany, Iran, Northern Cyprus and India as well as Turkey.

Urinary tract injuries (bladder and ureter) are among the most common complications associated with laparoscopic hysterectomy. All gynecological surgeons should be able to perform diagnostic cystoscopies for evaluating bladder and ureteral integrity. You will read a paper about the use of intravenous sodium fluorescein in the cystoscopic assessment of bladder and ureteral integrity to determine the time of ureteral ejection in patients undergoing laparoscopic hysterectomy.

Tadalafil which is a selective phosphodiesterase type-5 inhibitor has a dual function in ischemic and re-perfused tissues, i.e. vasodilatation and anti-oxidant effects. You will also get the occasion to read an interesting paper investigating the dual effect of tadalafil on ischemia and reperfusion injury in the rat ovary.

Pelvic lymphadenectomy is a supplementary part of staging and treatment in gynecologic oncology. You will watch a video which demonstrates a right-side systematic pelvic lymphadenectomy in a cadaveric model.

Dear Reviewers,

Your reviews are valuable contributions to research, thank you for your valuable efforts and expertise in peer-review.

Dear Researchers,

We are looking forward to receiving your valuable submissions, also we kindly ask you to cite our previous issues which you may easily find in Pubmed and thank you in advance for your contributions.

Best regards,

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

Obituary

Cologne, November 2019

On August 8, 2019, the co-founder of our society passed away in Cologne after a long and serious illness. Dr. İsmet Turanlı was born on September 20 1930 in Malatya, Turkey.

After his state examination and his doctoral thesis in Istanbul in 1955, he worked as an assistant doctor at the University Women's Hospital Ankara with Prof. Canga until 1957. After spending two years abroad at the Hammersmith Hospital in London, at the Karolinksa Institute in Stockholm and at the State Women's Hospital in Wuppertal under Prof. Anselmino, Dr. Turanlı passed the specialist examination for gynecology and obstetrics in Ankara. In 1960, Dr. Turanlı moved to Germany, where he first worked at the State Women's Hospital in Wuppertal after approval of his specialisation in Germany. Starting in 1964, he became a managing Senior Physician at St. Hildegardis Hospital in Cologne. In 1965, Dr. Turanlı settled in a private practice in Cologne. From the beginning of his ambulatory work, his focus was on the field of reproductive medicine. In 1982 he founded an IVF center where he attained the first Turkish IVF child in Germany. In 1993 he founded the German-Turkish Gynecological Society in Cologne together with Prof. Broer, with whom he remained close until his death. For his many years of service as an established colleague, but especially for his extraordinary commitment to German-Turkish relations, he received the Federal Cross of Merit on ribbon, First Class, in 1997.

In addition to his work as a gynecologist and reproductive physician, Dr. Turanlı had many interests. Three-hundred and fifty non-medical publications, four short stories, and 250 poems in Turkish and German and eight compositions, several of which were also performed during the meetings of the German-Turkish Gynecological Society, are testimony of his extraordinary passion.

With Dr. Turanlı we have lost a valuable colleague of extraordinary commitment who has earned special merit for his work for German-Turkish relations and our society. We will always keep him in honorable memory and our thoughts are with his wife and his large family.

Prof. Peter Mallmann, M.D.

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association

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Long-term outcome of endometrial ablation therapy with Cavaterm Thermal Balloon in patients with abnormal uterine bleeding

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Abstract

Objective: The purpose of this study was to evaluate the long-term outcome of endometrial ablation (EA) therapy with Cavaterm Thermal Balloon in patients with abnormal uterine bleeding (AUB).

Material and Methods: The retrospective cross-sectional study was performed on 209 patients who referred to Shahid Sadoughi Hospital in Yazd, Iran between March 2010 and September 2017 with AUB undergoing EA therapy. The data was collected by a questionnaire from the medical records of patients and phone call. The primary and secondary outcomes post EA therapy (from six months to seven years post-operatively) were assessed in patients.

Results: The mean age of participants was 45.9±5.9 years and the mean follow-up duration was 21.2±13.2 months. The rate of treatment response was 95% in the first six months and 92.1% thereafter. The prevalence of amenorrhea was 41.2%. The patient satisfaction rate at the end of follow-up duration was 81.3%. Dysmenorrhea completely resolved in 32.6%. Moreover, 1.4% of patients became pregnant during follow-up. By the end of follow-up, four (1.9%) patients had a hysterectomy due directly to treatment failure.

Conclusion: This study showed that EA surgery with Cavaterm Thermal Balloon was an effective treatment for AUB. The procedure was safe and was associated with a very low rate of postoperative adverse events. The patient satisfaction rate was favorable. (J Turk Ger Gynecol Assoc 2020; 21: 1-9)

Keywords: Abnormal uterine bleeding, endometrial ablation, hysterectomy, amenorrhea

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Introduction

Abnormal uterine bleeding (AUB), which refers to any irregularity in the menstrual cycle, is one of the most common causes of women of childbearing age being referred to clinics (1). Approximately 16% of hysterectomies occur due to AUB (2). Hysterectomy is a definitive treatment for AUB and has been reported to be the second most common major surgical procedures in the United States (3). A strong preference for preservation of the uterus in developed countries has recently led to greater use of minimally invasive drug therapies, including Mirena intra-uterine device (also known as the levonorgestrel releasing device or LNG-IUS) and endometrial ablation (EA),

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even in cases where there is no desire for future pregnancy (4,5). There is also a contraindication for drug therapies in cases with co-existing diseases such as diabetes and cardiovascular disease (6). EA therapy is preferred to hysterectomy due to the benefits of being outpatient based, being quicker, with fewer complications, any hospital stay is usually shorter and recovery is faster too (7). EA is performed using two methods: hysteroscopic endometrial ablation (HEA); and non-HEA (NHEA). HEA uses laser, electric current, or heat energy for coagulation or evaporation of the tissue. The NHEA approach is performed using EA computer systems with the aid of electric current, hyperthermia, cryotherapy or microwaves (8). The purpose of this study was to evaluate the long-term outcomes of EA therapy with the Cavaterm Thermal Balloon in patients with AUB.

Material and Methods

This was a retrospective cross-sectional study which was performed at Shahid Sadoughi Hospital in Yazd, Iran in 2018. All aspects of this research were approved by Ethics Committee of the Yazd Shahid Sahoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1396.186).

In this study, we reviewed medical record of 256 patients who had undergone EA between March 2010 and September 2017. These patients had been referred to Shahid Sadoughi Hospital with AUB, who did not respond to drug therapies or had an impediment to drug and surgical treatment or were reluctant to perform hysterectomy. All participants had completed informed consent before surgery.

Enrollment criteria were: 1) premenopausal women ≥18 years old; 2) unwillingness to maintain fertility and no desire for pregnancy; 3) no urogenital infection; 4) natural history of cervical cytology; 5) negative Beta human choronionic gonadotropin test; 6) no contraindication for EA surgery; 7) underwent EA (Cavaterm Thermal Balloon) after March 2010; and 8) had documented follow-up ≥6 months.

Ablation procedure and follow-up

Vaginal ultrasound was performed before surgery and the thickness of the myometrium, uterine cavity length and myometric length were measured. Endometrial curettage was then carried out to reduce endometrial thickness and the samples were sent for pathological examination. After placing an anesthetic mask, the patient was placed in a lithotomy position. The lower abdominal region, vulva, femoral region, and vaginal cavity were sterilized with iodine. The cervix was initially opened using a 6 mm dilator, followed by using a cavaterm system comprising a silicon balloon connected to a catheter with a width of 6 mm and a unit (thermal balloon EA device and catheter, Plus cavaterm TM model, (Veldana Medical SA Co., Switzerland). The silicone balloon length was set based on the measurements of each individual uterine cavity. After emptying the air from the cavaterm system, the catheter end was inserted into the fundus, and the balloon was filled by glucose 5% fluid until the pressure reached 230±10 mmHg, and this pressure was maintained until the end of the treatment. Then, the circulation of fluid and heat was begun. EA started after reaching a temperature of 70±10 °C. The treatment was continued at this temperature for 10 minutes and then the heating was stopped, the fluid was pumped out and the catheter was removed. For removal the EA catheter was surrounded by an insulator to prevent thermal damage of the cervix and vaginal canal. The patient was then transferred to the recovery ward.

Patients were followed up for six to 90 months after EA therapy. In this study follow up period of patients was divided into four periods of up to six months, six to 12 months, twelve to 24 months and more than 24 months after surgery.

Outcome measures

The primary outcomes were changes in duration and interval of menstruation, amenorrhea rate, and bleeding reduction of at least 50% after surgery. It should be noted that amenorrhea rate and bleeding reduction of at least 50% six months after surgery were considered as the criterion for treatment response.

The secondary outcomes were the prevalence of anemia, dysmenorrhea, patient satisfaction, secondary intervention (medical or surgical) for recalcitrant AUB, adverse effect of EA therapy, and comparison variables in two groups of treatment respond and treatment failed. Anemia was defined if hemoglobin levels were lower than 12 mg/dL (9). Dysmenorrhea had been recorded using a 10-point visual analog scale in the medical record of patients, which higher points of three being considered as a dysmenorrhea (10), adverse effect of EA therapy including of blood discharge, fever (defined as body temperature of >37.5 °C), extreme and prolonged suprapubic pain, urinary tract infection, vaginosis, malodorous discharge, vomiting, and uterine rupture.

The primary and secondary outcomes of post EA therapy (from six months to seven years post- operatively) were assessed in patients.

Data collection was performed by means of a questionnaire and data was extracted from the medical records of the patients, telephone consultation with the patients.

Statistical analysis

The collected data were entered in the statistical software program IBM SPSS Statistics for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean ± standard deviation, frequency, and percent) were used to present the data. Categorical variables were assessed with chi-squared

and Fisher's exact test. Continuous variables were compared by Student's t-test. For all tests, p-values <0.05 indicated statistically significant differences.

Results

Of 256 existing medical records of patients with EA between March 2010 and September 2017, one patient was omitted due to hysterectomy during an initial examination. The reason of her hysterectomy was suspicion of endometrial cancer which proved to be metastatic sarcoma and was treated with radiotherapy after surgery. A further 17 patients had not attended a postoperative follow-up. Ten patients did not answer the phone call, and nineteen patients did not accept to participate in the study. Ultimately, the analysis was performed with the data of 209 patients.

The mean age of the patients was 45.94±5.9 years. The reasons for undergoing EA were: desire to preserve the uterus and ovaries, and age conditions in 153 patients (73.2%); and the presence of underlying disease as an obstacle to more invasive surgery, such as hysterectomy, in 56 patients (26.8%). All patients had a chief complaint of excessive menstruation and a history of drug treatment. Most patients (75.1%) had normal (proliferative or secretory) pathological results. Patient characteristics pre-EA surgery are presented in Table 1.

The result of primary outcomes in patients before and after EA surgery are presented in Table 2. The mean duration of menstruation was significantly decreased to 3.7±4.3 days in the first six months (p=0.001) and 3.1±3.3 days 24 months after EA surgery (p<0.001). The mean interval of menstruation cycle was significantly increased to 38.5±32.6 days 24 months after EA surgery (p=0.003).

Amenorrhea and bleeding reduction occurred in 193 (95%) in the first six months and in 187 (92.1%) after the first six months. At the end of follow-up, 84 (41.2%) had amenorrhea (Figure 1). Preoperatively, 146 (69.9%) patients had anemia before surgery and this proportion was significantly reduced after surgery to 61 (29.2%) patients (p=0.001). Of 89 (44.1% of the whole cohort) women who initially experienced dysmenorrhea, only 24 (11.5%) reported that their symptoms had not changed or had worsened, a reduction of 32.6% (Table 3) while the other 65 women reported that their symptoms were "much improved" or "somewhat improved". A comparison of anemia and dysmenorrhea in patients before and after EA is shown in Table 3.

When patients were queried about overall satisfaction with the EA treatment 89.2% of them reported being either "very satisfied" or "satisfied" versus feeling "neutral" or expressed any degree of "dissatisfaction" (Table 4).

Following EA surgery 62 (29.7%) patients had received secondary intervention for recalcitrant AUB until follow-up. Of that number 38 patients (18.8%) required drug therapy, of which 29 responded (76.3%), mostly to 20 or 40 mg megestrol acetate per day. In addition, 24 (11.5%) patients underwent

Table 1. Patient characteristics of the whole cohort (n=209)

Variables		**Mean ± SD**	**Minimum-maximum**
Age, years		45.94±5.9	30-60
Gravidity; n		4.2±2.1	1-14
Parity, n		3.57±1.7	1-12
Weight, kg		73.73±9.9	40-125
Height, cm		158.2±5.3	148-171
BMI, kg/m^2		29.6±3.7	17.8-48.2
Bleeding per month before the EA surgery, day		12.1±5.7	3-30
Interval of menstrual cycles before EA surgery, day		15.9±7.4	0-40
Follow-up duration, month		21.2±13.2	6-90
		n	**%**
Diagnosis	Normal (proliferative or secretory)	157	75.1
	Simple endometrial hyperplasia	15	7.2
	Complex endometrial hyperplasia	2	1
	Myoma	6	2.9
	Endometrial polyps	21	10
	Adenomyosis	8	3.8
Previous curettage		120	57.4
History of medical drug treatment for AUB		209	100

SD: Standard deviation, BMI: Body mass index, AUB: Abnormal uterine bleeding, EA: Endometrial ablation

hysterectomy following EA surgery, 23 of these were in the first three years after the EA procedure.

The most common adverse events after the surgery were blood discharge of more than 14 days in 182 (90.6%) patients. Other adverse events included vaginosis, malodorous discharge, uterine rupture, extreme and prolonged suprapubic pain. The results of patient satisfaction, secondary intervention and adverse events after EA surgery are presented in Table 4.

Up to the end of the follow-up period, four (1.9%) patients were treated by hysterectomy due to direct result of treatment failure [uterine perforation (n=3), device dysfunction (n=1)] (Figure 2).

The mean age of patients in the treatment failure group was significantly higher than in the treatment response group (49.7 vs 41.2 years; p=0.006). In addition the uterus size (p<0.001) tended to be significantly larger in the treatment failure group. There was no significant relationship between body mass index, gravidity, parity, intrauterine pressure and intrauterine temperature, and result of pathology with treatment failure. The results of comparison of variables in the treatment response and failure groups are presented in Table 5.

The pathology result after surgery was reported to be normal endometrium (secretory or proliferative) in 157 patients (75.1%). There was no significant relationship between the pathology type and the treatment response nor was there a significant relationship between the pathology type and the risk of future hysterectomy (p=0.084) (Figure 3).

It is noteworthy that three (1.4%) patients became pregnant in the follow-up period.

Discussion

In this retrospective study, the outcomes of EA therapy using Thermal Balloon and Plus CavatermTM technique were evaluated in 209 patients with AUB. Study results indicated duration of menstruation, a primary outcome, decreased significantly after treatment and the interval between menstrual cycles also increased significantly. These results are consistent with those of Asgari et al. (11) who reported the duration and

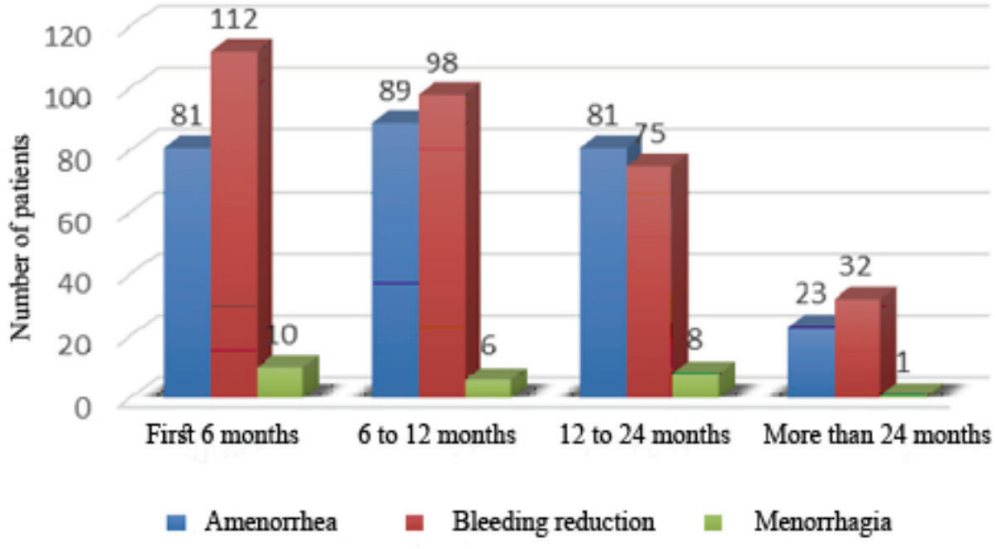

Figure 1. Bleeding state of patients after endometrial ablation therapy

Table 2. Primary outcomes in patients before and after endometrial ablation surgery (n=203*)

Variables	Before	6 m	6-12 m	12-24 m	≥24 m	p**
Duration of menstruation (d), mean ± SD	12.1±5.6	3.7±4.3	3.3±3.9	3±3.7	3.1±3.3	<0.001†
Interval of menstruation (d), mean ± SD	17.2±7.1	24.8±12.4	27.5±16.6	28.7±16.4	38.5±32.6	0.003†
Amenorrhea, n (%)	0 (0)	81 (39.9)	89 (46.1)	81 (39.9)	84 (41.2)	0.003††
Bleeding reduction, n (%)	-	112 (55.2)	98 (48.2)	75 (37)	32 (15.8)	-
Treatment response, n (%)	-	193 (95)	187 (92.1)	156 (76.8)	55 (27)	-

*Hysterectomy was immediately performed for six patients after endometrial ablation [uterine perforation (n=3), pathologic result (complex endometrial hyperplasia, n=2), and device dysfunction (n=1)]. **Reported p-value compares pre-operative and >24 months after surgery data. †Student's t-test. ††Fisher's exact test
SD: Standard deviation

intervals of menstruation after EA was significantly decreased and increased respectively. In the Famuyide (12) study the menstrual bleeding rate in the patients with AUB treated with an EA method was reduced, which was associated with lower risk of hysterectomy in the future. In the present study, the rate of amenorrhea was 41.2% at the end of follow-up, which falls into the previously reported rate for amenorrhea, between 19.4 and 58%, in studies of patients with AUB treated with an EA method (11,13-18).

In this study, the rates of treatment responses ≤6 and >6 months were 95% and 92.1% respectively which are higher than that in the study of Sharma et al. (19) of 80% and 76% for the first six months and later, respectively. While some studies support the therapeutic role of EA (13-16,19), unfortunately in some studies recurrent vaginal bleeding had occurred immediately or years after EA surgery (20-22). Although the recurrence of vaginal bleeding following EA is attributed to inadequate destruction of the endometrium (20,21), unsuspected deep adenomyosis (22), and development of benign (myomas), or malignant diseases (endometrial hyperplasia, or cancer) may be responsible (23). Therefore, it is suggested that, despite EA rapid treatment response, patients need long follow-ups after surgery due to the risk of bleeding recurrence.

Most of the patients presented in this cohort were anemic before the EA surgery. Bernardi et al. (24) found that a significant percentage of women who report heavy menstrual bleeding are not only iron deficient, but also anemic, although most of their patients with anemia resolved after EA surgery. This was thought to be due to the high rates of amenorrhea and significant bleeding reduction as a result of EA (25). Kim et al. (26) suggested that EA is an effective alternative to hysterectomy for women with persistent menorrhagia and anemia when supportive measures fail.

Dysmenorrhea, defined as a complaint of pain experienced during or immediately before menstruation, improved in the majority of our patients after EA surgery, which is consistent with previous studies (11,17,27). Prostaglandins (PG) and arachidonic acid metabolites play an important role in the pathogenesis of dysmenorrhea, being elevated in women with dysmenorrhea (28). However PGs, together with endothelin, which are powerful, vasoactive substances play a key role in the control of menstrual blood loss (28). Cameron et al. (29) showed the concentration of Prostaglandin E (PGE) and "total" PGs, defined by these authors as PGE + 6oxo PGF1 alpha + PGF2 alpha, was greater in the endometrium of those women with heavy menses than in those individuals with a normal menstrual loss. Therefore, it may be expected that dysmenorrhea will be improved by reducing menstrual bleeding.

The rate of patient satisfaction with treatment was high (86.6%) in our study, consistent with other studies (1,11-14,18,30). It has previously been reported that the resulting reduction in blood loss and increase in patient satisfaction rates leads to improved quality of life (30,31).

In the present study, following EA surgery 24 (11.5%) patients had subsequent hysterectomy. This is similar

Table 3. The comparison of anemia and dysmenorrhea before and six months after endometrial ablation ablation (n=209)

Variable	Preoperative	Postoperative	p*
Anemia, n (%)	146 (69.9%)	61 (29.2%)	<0.001
Dysmenorrhea, n (%)	89 (44.1%)	24 (11.5%)	<0.001
*Chi-squared test			

Table 4. The result of patient satisfaction, secondary intervention and adverse events after endometrial ablation surgery (n=209)

Variables		Number (%)
Patient satisfaction	Very satisfied	170 (81.3)
	Satisfied	11 (5.25)
	Neutral	14 (6.7)
	Unsatisfied	10 (4.8)
	Very unsatisfied	4 (1.9)
Secondary intervention for recalcitrant AUB	Medical	38 (18.8)
	Hysterectomy	24 (11.5)
Adverse events	Blood discharge	182 (90.6%)
	Fever	0 (0)
	Extreme and prolonged suprapubic pain	1 (0.5)
	Urinary tract infection	0 (0)
	Nausea	0 (0)
	Vaginosis, malodorous discharge	9 (4.3)
	Vomiting	0 (0)
	Uterine rupture	3 (1.4)
AUB: Abnormal uterine bleeding		

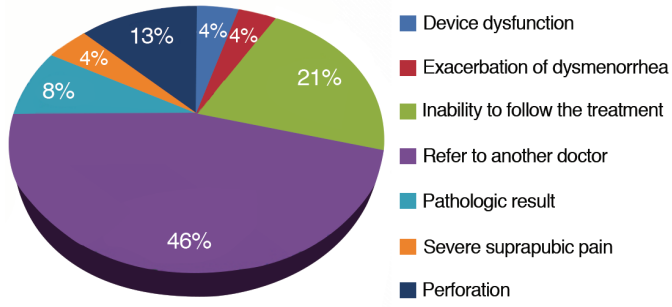

Figure 2. Causes of hysterectomy in patients

to the rates of hysterectomy subsequent to EA therapy, from 10% to 13%, which have been reported previously (16,17,30,32-34) although higher rates (18%-25%) have been reported by some studies (30,34). This variability in reported hysterectomy rates may be due to differences in study population and method or technique applied for EA therapy. For example Comino and Torrejón (34) reported an association between the presence of myoma and the need for subsequent hysterectomy.

Four (1.9%) cases of hysterectomy resulted directly from treatment failure, one patient due to impaired function of the device and three others due to perforation of the uterus. One of these latter three patients required hysterectomy only four minutes after EA surgery due to the rupture of an arteriovenous malformation (AVM). Although AVM is a contraindication for EA, the 34-year-old patient desired uterine preservation and thus underwent EA therapy after giving informed consent for the hysterectomy, if required, so that the surgical team were prepared for the need for hysterectomy while undertaking the EA surgery. Rosati et al. (14) reported that of 5.2% of hysterectomies, 3.9% were directly due to treatment failure. Similarly, Comino and Torrejón (34) found that half of the 18% of hysterectomies occurring in their study were directly due to treatment failure. In our study, 95.8% cases of hysterectomy were performed in the first three years subsequent to EA, the majority within the

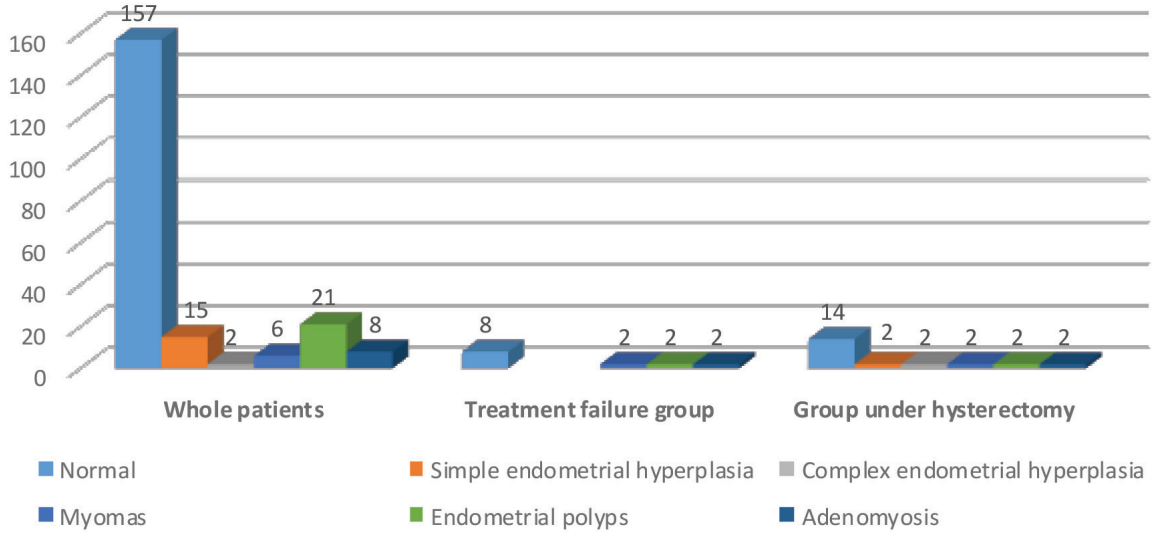

Figure 3. Results of pathology for patients

Table 5. Comparison of variables between treatment responders and treatment failure groups

Variables		**Treatment response group (n=195)**	**Treatment failure group (n=14)**	**p**
Age (year); mean ± SD		41.2±5.8	49.7±4.7	0.006*
BMI (kg/m^2); mean ± SD		29.6±3.7	29.1±4.11	0.591*
Parity; mean ± SD		3.6±1.7	3.2±1.1	0.421*
Intrauterine pressure, (mmHg); mean ± SD		225.15±15.6	226.1±15.9	0.891*
Intrauterine temperature (°C); mean ± SD		74.2±3.3	73.35±4.1	0.315*
Uterus size	<10 cm, n (%)	131 (67.2)	2 (14.3)	<0.001**
	10-12 cm, n (%)	64 (32.8)	12 (85.7)	
Results of pathology	Normal (proliferative or secretory); n (%)	149 (76.4)	8 (57.1)	0.38***
	Simple endometrial hyperplasia; n (%)	15 (7.7)	0	
	Complex endometrial hyperplasia; n (%)	2 (1)	0	
	Myomas; n (%)	4 (2.1)	2 (14.3)	
	Endometrial polyps; n (%)	19 (9.7)	2 (14.3)	
	Adenomyosis; n (%)	6 (3.1)	2 (14.3)	

*Student's t-test. **Chi-squared test. ***Fisher's exact test.
BMI: Body mass index, SD: Standard deviation

6 months and 12 months, which is consistent with the results of Longinotti et al. (35) study.

In this study, the most frequent adverse events were blood discharge (90.6%), vaginosis, malodorous discharge (4.3%), uterine rupture (1.4%), and extreme and prolonged suprapubic pain (0.5%). These were not unexpected given previous research (11,32-34). A study audit of more than 10,000 EA surgery patients from the UK found an overall complication rate of 4.4%. The most frequent complications were hemorrhage (2.4%), uterine perforation (1.5%) and cardiovascular and respiratory complications (0.5%) (36). In the Gimpelson (37) study, the only complication was uterine perforation (0.4%).

In the present study, the likelihood of a lack of treatment response and the risk of hysterectomy was higher in older patients, both of which can be related to the hormonal causes of AUB and is consistent with the literature (17,19,38). Nakamura et al. (39) showed that age was associated with recurrence of menorrhagia and re-surgery. These authors also suggested that the EA surgery may be less effective for younger women with myomas, despite the longer period of time until the onset of menopause (17,19,34,38).

The perioperative uterus size was greater than 10 cm in 85.7% of EA treatment non-responders and in 100% of perforation cases in our series. This suggests that uterine size may be an important criterion for selecting patients for EA to reduce the risk of treatment failure. Nakamura et al. (39) showed uterine cavity length (≥10 cm) was an independent risk factor for recurrence of menorrhagia and re-surgery. Larger uterine cavity length may be associated with more aggressive characteristics of myomas and thus it is not surprising that they are associated with an increased risk for recurrence and re-surgery (39). Furthermore, our series included six patients (42.85%) with myomas, endometrial polyps, and adenomyosis who proved resistant to EA treatment. We found that EA tended to be less effective in this patient population, than in women with normal, simple and complex endometrial hyperplasia. Nakamura et al. (39) showed that EA was less effective in women with myomas and adenomyosis. This study suggested that the thickened myometrium in women with adenomyosis impaired the effectiveness of EA treatment and suggested that multiple rounds of EA treatment may more successfully control menorrhagia in cases with adenomyosis.

The incidence of pregnancy after EA surgery in our study was 1.4%, in which two of three pregnancies were successful. In contrast Kohn et al. (40) reported that 85% of pregnancies following EA were terminated with abortion or due to ectopic pregnancy. This contradiction may simply be an effect of small sample size of this group in our study. It is important to make EA patients aware that EA surgery is not a contraceptive method and should apply reliable or permanent contraceptive techniques until menopause.

Conclusion

The results of this study showed that the EA surgery with Cavaterm Thermal Balloon was an effective treatment for AUB and had satisfactory results in terms of amenorrhea and treatment response levels. In addition, the patient satisfaction rate was favorable and the procedure is safe and is associated with a very low rate of postoperative adverse events. However, our findings indicate that EA surgery may be more effective for younger patients. Also, our findings indicate EA surgery may be less effective for women with myomas, endometrial polyps, adenomyosis and a larger uterus. Further research with larger sample sizes are needed to confirm which of these clinical parameters affects the success of EA surgery in AUB and may then be used to select the most appropriate patient groups for this type of treatment.

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Informed Consent: *All participants completed informed consent before surgery.*

Peer-review: *Externally peer-reviewed.*

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Time of ureteral ejection of sodium fluorescein in the cystoscopic assessment of ureteral patency in patients undergoing total laparoscopic hysterectomy

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Abstract

Objective: To evaluate the time of ureteral ejection of intravenous sodium fluorescein in the assessment of ureteral patency in patients undergoing total laparoscopic hysterectomy (TLH).

Material and Methods: Fifty-four women undergoing TLH were studied in a public teaching hospital in Culiacan, Sinaloa, Mexico. They underwent cystoscopic evaluation of ureteral patency after intravenous administration of 100 mg of sodium fluorescein. The present study analyzed the time elapsed in minutes from the intravenous administration of fluorescein to the outflow of stained urine by one or both ureteral meatus, the degree of urine staining, and the impact of body mass index (BMI) (BMI; normal, overweight, and obesity) on ejection time.

Results: The overall average time elapsed to visualize the ejection of fluorescein through at least one ureteral meatus was 7.5 minutes [95% confidence interval (CI): 6.3-8.7]. There were no significant differences in the time of ureteral ejection of fluorescein taking BMI into account (p=0.579), with a mean time for normal BMI of 8.1 minutes (95% CI: 5.1-11.2), for overweight of 7.0 minutes (95% CI: 5.5-8.5), and for obesity of 7.8 minutes (95% CI: 5.3-10.3).

Conclusion: Intravenously administered 10% sodium fluorescein dye is rapidly eliminated and strongly stains urine, which makes it useful for identifying ureteral patency during cystoscopy after TLH. Fluorescein excretion is not affected by patient BMI. (J Turk Ger Gynecol Assoc 2020; 21: 10-4)

Keywords: Sodium fluorescein, ureteral patency, ejection time, laparoscopic hysterectomy

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Introduction

After cesarean section, hysterectomy is the surgical procedure most commonly performed for benign indications. In the United States (US), approximately 600,000 hysterectomies are performed per year using one of three approaches: abdominal, vaginal, and laparoscopic (1).

Although laparoscopic hysterectomy (LH) has many advantages over laparotomic hysterectomy, it also has disadvantages, and there is an increased risk of complications when surgeons with little experience perform the procedure. Urinary tract injuries (bladder and ureter) are among the most common complications associated with LH (2-4). The frequency of urinary tract injuries reported for total laparoscopic hysterectomy (TLH) (0.31%) is roughly similar to that reported for laparotomic hysterectomy (0.03-2.0%), with hematuria as the main sign of injury (5-7).

Although the risk of injuring both the bladder and ureter can be high during TLH, most injuries can be identified by cystoscopy (8).

Gynecologic surgery causes 75% of iatrogenic injuries to the bladder and ureter. Visual inspection alone will miss many of these injuries. Furthermore, visual evaluation of ureteral peristalsis during the procedures is not reliable. Less than 50%

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and 25% of cases of ureteral and bladder injuries respectively are detected by visual inspection when intraoperative cystoscopy is not performed (8).

Due to this low rate of detection of ureteral injuries during gynecological surgery, the American College of Obstetricians and Gynecologists recommends that all gynecological surgeons should perform diagnostic cystoscopies for optimal patient care, with the aim of evaluating bladder and ureteral integrity (9).

When performing cystoscopy, it is advisable to use dyes to better evaluate ureteral integrity. For this purpose, many stains have been used, including indigo carmine, methylene blue, 10% sodium fluorescein, phenazopyridine, and vitamin B12, among others (10-16). Several studies have shown that the use of indigo carmine during cystoscopy is useful for detecting ureteral injuries, but since 2014, this drug has not been marketed in the US (10-12). Methylene blue in solution for intravenous use at a dose of 50 mg (5 mL of a 10 mg/mL solution) is mainly eliminated in urine, which stains blue and is easily visible during cystoscopy. One disadvantage of methylene blue is that it interferes with pulse oximetry by altering oxygen saturation readings and can result in a serotonergic syndrome when administered concomitantly with serotonin reuptake inhibitors or monoamine oxidase inhibitors (13). Another intravenous agent that promises to be useful to stain urine during diagnostic cystoscopy after a gynecological procedure and that has been used extensively in ophthalmology is 10% sodium fluorescein. It is fast acting and well tolerated, but there are few reports on its use in gynecological procedures. It can be used intravenously at doses of 0.25 to 1 mL (25 to 100 mg) and is rapidly eliminated in urine, giving urine a bright yellow color easily visible during ureteral emptying (14).

The purpose of the present study was to evaluate the use of intravenous sodium fluorescein in the cystoscopic assessment of bladder and ureteral integrity and to determine the time of ureteral ejection in patients undergoing TLH.

Material and Methods

After approval from the Local Research and Ethics Committee of the Civil Hospital of Culiacan, Sinaloa, Mexico (decision no: 306), and after obtaining the written informed consent of the patients, a prospective, descriptive, and observational study was conducted in 54 healthy patients submitted for TLH, who underwent cystoscopic evaluation of bladder and ureteral integrity after intravenous administration of 100 mg of sodium fluorescein diluted in 10 cc of saline solution (1 mL of 10% sodium fluorescein containing 0.1 g of fluorescein; Alcon Laboratories Inc., Fort Worth, TX). Fluorescein was administered after laparoscopic port closure. All patients were asked about history of allergic reactions before starting the surgical procedure.

Cystoscopy was conducted with the patient in the lithotomy position, under general anesthesia, and after injection of 200 mL of saline solution through the bladder catheter. After bladder distention with saline solution, a 5 mm lens connected to an endoscopic camera was introduced to evaluate bladder integrity, identify the ureteral meatus, and visualize the ejection of urine through both meatus.

The primary variable was the time elapsed from the administration of fluorescein to the cystoscopic observation of the outflow of dye-stained urine through at least one ureteral meatus (Figure 1). Secondary variables were patient age, body mass index (BMI), surgical time, rate of bladder and ureteral injuries identified during cystoscopy, frequency of hematuria and rate of adverse events associated with the drugs including nausea, vomiting, headache, gastrointestinal conditions, syncope, hypotension, severe shock, seizures, thrombophlebitis at the injection site and other symptoms and signs of hypersensitivity. Adverse events and urinary complications were evaluated for at least four weeks after the surgical procedure. To analyze if the time of ureteral ejection of fluorescein could be affected by selected variables, it was compared in relation to BMI (normal, overweight, and obesity) and the surgical time of the procedure.

Statistical analysis

To compare time of ejection of fluorescein between the BMI groups, the log-rank test was used with 95% confidence intervals. A p-value <0.05 was considered statistically significant. The data were analyzed with SPSS v24 (IBM Inc., Armonk, NY, USA) statistical software.

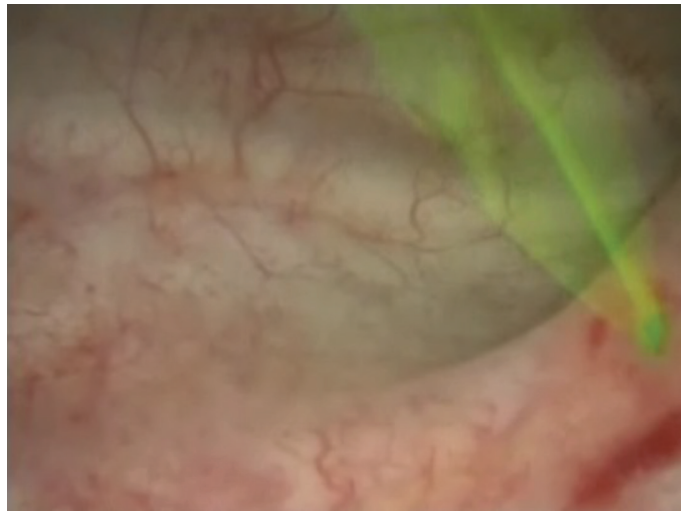

Figure 1. Observation by cystoscopy of the ejection of fluorescein through the left ureteral meatus

Results

Fifty-four patients with a mean age of 45.3 years [standard deviation (SD) ±5.5] and mean BMI of 28.8 kg/m^2 (SD ±4.5) were included. The number of patients with normal BMI was 12 (22.2%), with overweight 25 (46.3%), and with obesity was 17 (31.5%). Mean parity was 2.9 (SD ±1.3); the number of patients with at least one previous cesarean section was 38 (70.4%), of which 22 (57.8%) had a history of three cesarean sections.

Table 1. Demographic and clinical characteristics of the studied population

Characteristic	Mean (SD) or Frequency (%)	95% CI
Age (years)	45.3 (5.5)	43.8-46.7
BMI (kg/m^2)	28.8 (4.5)	27.6-30
Normal	22.2 (n=12)	11.1-33.3
Overweight	46.3 (n=25)	33-59.6
Obesity	31.5 (n=17)	19.1-43.9
Number of pregnancies	2.9 (1.3)	2.55-3.25
One or more cesareans	70.4 (n=38)	58.2-82.6
Main indications for TLH		
Anormal uterine bleeding/ Uterine leiomyomas*	96.3 (n=52)	91.27-101.3
Endometrial hyperplasia	3.7 (n=2)	-1.3-8.7

*All patients with abnormal uterine bleeding undergoing laparoscopic hysterectomy had uterine leiomyomas.
SD: Standard deviation, CI: Confidence interval, BMI: Body mass index, TLH: Total laparoscopic hysterectomy

Table 2. Operative characteristics and time of ureteral ejection of sodium fluorescein during cystoscopy of the studied population

Characteristic	Mean or Frequency (%)	95% CI
Operative time (min)	104.2	94.2-114.2
Operative bleeding (mL)	114.4	104.4-124.4
Uterine weight (gr)	262.3	217.7-306.9
Intraoperative complications	3.7 (n=2)	-1.3-8.7
Major bleeding	1.8 (n=1)	-1.7-5.3
Bladder injury	1.8 (n=1)	-1.7-5.3
Time of ureteral ejection of sodium fluorescein at cystoscopy (min)		
Overall (min)	7.5	6.3-8.7
BMI group[a]		
Normal	8.1	5.1-11.2
Overweight	7.0	5.5-8.5
Obesity	7.8	5.3-10.3

[a]No significant differences between the groups (p=0.56).
CI: Confidence interval, min: Minimum, BMI: Body mass index

The main indication for hysterectomy was abnormal uterine bleeding (96.3%) (Table 1). All patients with abnormal uterine bleeding were given medical treatment before performing LH. Mean surgical time for hysterectomy was 104.2 minutes (SD ±37.5), mean operative bleeding was 114.4 mL (SD ±37.5), and mean uterine weight was 262.3 g (SD ±167.2).

There were no significant differences in the time to ureteral ejection of fluorescein between the BMI groups (log-rank=1.093, p=0.579). Mean overall time of ureteral ejection was 7.5 min [95% confidence interval (CI): 6.3-8.7] (Table 2). By BMI group, the mean time for the normal BMI group was 8.1 min (95% CI: 5.1-11.2), for the overweight group was 7.0 minimum (95% CI: 5.5-8.5), and for the obese group was 7.8 min (95% CI: 5.3-10.3), (p=0.560) (Table 2, Figure 2).

There was only one bladder injury in a patient with a previous cesarean section repaired laparoscopically in two planes with vicryl 000 suture; the integrity of the suture line was previously corroborated with the retrograde instillation of 200 mL of physiological solution plus 1 mL of 10% sodium fluorescein. No ureteral injuries were observed during the study period. There were no adverse effects after the administration of fluorescein.

Discussion

Lower urinary tract injuries are serious potential complications related to TLH due to the anatomical closeness between the bladder, ureter, and uterus. A recent study on LH, in which the ureter was identified prior to the procedure, reported a frequency of 0.31% in lower urinary tract injuries, which included six bladder injuries and four ureter injuries (4). In this

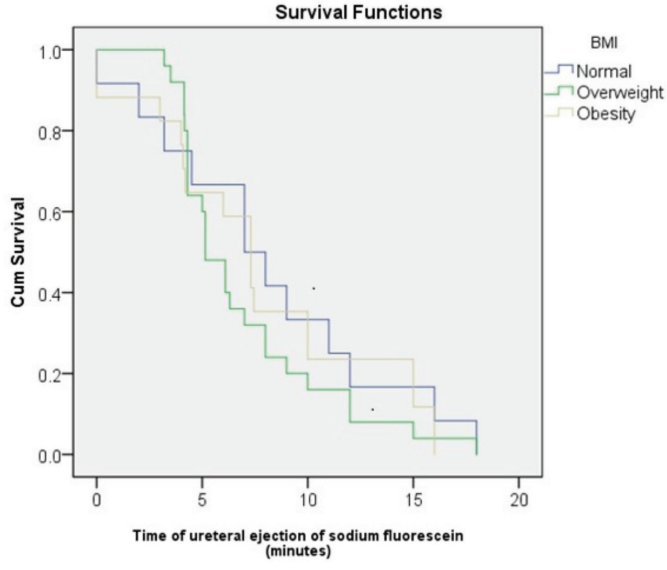

Figure 2. Survival curve showing the time of ureteral ejection of fluorescein by body mass index groups

BMI: Body mass index

series of 54 patients, there were no ureteral injuries, and there was only one case of bladder injury in a patient with bladder adhesions from previous cesarean sections. This complication rate is similar to that reported for laparotomy hysterectomy (0.03-2.0%) in other studies (5,6).

Hematuria is one of the signs that may suggest lower urinary tract injury, mainly bladder injury, but not of the ureter, as the latter may be asymptomatic and manifest late. In one study, the frequency of hematuria was 2.1%, and that of lower urinary tract injury was 1.6% (7). In the present study, 26 patients had hematuria, and there were no cases of ureteral injury. Therefore, the results of the present study suggest that hematuria is not a good indicator of bladder or ureteral injury.

The most widely used stains to evaluate bladder and ureteral integrity during intraoperative cystoscopy in gynecological procedures are indigo carmine and methylene blue, which are scarce in Mexico. Therefore, it was necessary to evaluate other available alternatives to determine if they are effective for staining urine and determining ureteral patency.

A dye that has been evaluated for urine staining is 10% sodium fluorescein (widely used as a fluorescent tracer in many fields, mainly in retinal angiography), which is easily seen during cystoscopic evaluation, but there are no reports on the average time of ureteral ejection in patients undergoing TLH (17,18). Doses ranging from 0.5 to 1.0 cc of 10% sodium fluorescein result in good visualization of ureteral jets (14).

Fluorescein is a hydroxyxanthene dye with a fluorescence motif-unlike most organic dyes and has been used in ophthalmology to demarcate retinal, choroidal, and iris vessels and help detect retinal and vascular abnormalities. It is administered intravenously at an adult dose of 500 mg/5 mL of 10% sodium fluorescein; the dye may take 10 to 15 seconds to appear in the choroidal and retinal vessels, although this may vary depending on the site, rapidity of the injection, and state of the systemic circulation (19). In ophthalmology, the doses of sodium fluorescein used for intravenous angiography are generally higher than those used in the present study, in which lower doses were used (500 mg vs 100 mg) (19).

Fluorescein and its metabolites are actively excreted by the kidneys and they can be detected in the urine after the first circulatory pass with excretion being completed within six to 12 hours after injection, although urinary fluorescence can be detected up to 36 hours after administration in patients with normal renal function (19).

In the present study, the time of ureteral ejection of 10% sodium fluorescein in the urine was not affected by the BMI of the patients, as no significant differences were found between patients with normal weight, overweight, and obesity. Nevertheless, the mean time of ureteral ejection of 10% sodium fluorescein tended to be higher in patients with normal weight compared to patients with overweight and obesity, which may be due to the greater impact of the pneumoperitoneum on plasma and renal flow in normal-weight or thin patients. However, without management to force diuresis in patients undergoing TLH, the times of ureteral ejection of fluorescein were variable, which may also reflect patients responding differently to physiological changes induced by the pneumoperitoneum. It is notable that in all of the patients in this series of cases, the pressure was maintained at 14 mmHg during the entire surgical procedure.

Sodium fluorescein is not free of adverse effects with headache, nausea, vomiting, hypotension, and anaphylaxis being the most common side effects reported (18). Anaphylaxis is a rare event, reported with a frequency of 0.083% in patients undergoing intravenous angiography. However, physicians who use intravenous sodium fluorescein should be aware of this complication and be prepared to manage it (19). In a series of 12 patients in which 1 mL (100 mg) of 10% sodium fluorescein was used, one patient experienced a transient yellowing of the palms and sclera (14). This differs from the results of this series of 54 patients undergoing LH, in which no adverse events occurred. This may be due to the use of very low dose intravenous sodium fluorescein compared with the doses used in retinal angiography (19).

Ten percent sodium fluorescein (dye) administered intravenously is rapidly eliminated and strongly stains urine with a yellowish-green color, making urine outflow easily visible on its ejection through the ureteral meatus during cystoscopy after TLH. As BMI does not interfere with the time of ureteral ejection of the stained urine during cystoscopy, it can be used in patients undergoing TLH to evaluate ureteral patency and bladder injuries.

Ethics Committee Approval: *The study was approved by the Local Research and Ethics Committee of the Civil Hospital of Culiacan, Sinaloa, Mexico (decision no: 306).*

Informed Consent: *Informed consent was obtained of the patients.*

Peer-review: *Externally peer-reviewed.*

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Obstetric and perinatal outcomes in pregnant women with Takayasu's arteritis: single centre experience over five years

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Abstract

Objective: To study obstetric and perinatal outcomes among pregnant women with Takayasu arteritis (TA), attending our hospital for pregnancy and childbirth between January 2011 to December 2016.

Material and Methods: Retrospective study was carried out by abstracting clinical charts on all pregnant women with TA who underwent antenatal care and/or delivery in our hospital during this period. American College of Rheumatology criteria was used for diagnosis of TA. Sixteen women with TA were included in the study. Maternal demographic data, stage of disease, complications related to disease, details of treatment taken prior to pregnancy, pregnancy outcomes, and neonatal outcomes were studied.

Results: Forty-four percentage (7/16) belonged to type 5 angiographic type, however the same proportion (7/16) had undergone surgical corrections prior to pregnancy and the majority (15/16) were on medical management. Only three women (19%) were diagnosed during pregnancy. Most did not have active disease measured by Kerr's criteria (n=12; 75%), and Indıan Takayasu clinical activity scores A. Chronic hypertension was the commonest antenatal complication (56.2%), nearly one-third had growth restricted babies and 25% had preterm labour. There were no cardiovascular events, no maternal deaths, nor fetal or neonatal deaths. Two-thirds of our women were delivered by caesarean section.

Conclusion: Preconceptional counselling is of paramount importance in women with TA. Good maternal and fetal outcomes are observed with close antenatal surveillance and multidisciplinary care. Pregnancy should be planned during disease remission, with good antenatal care, close monitoring of clinical symptoms, early diagnosis and treatment of complications. (J Turk Ger Gynecol Assoc 2020; 21: 15-23)

Keywords: Takayasu's arteritis, periconceptional counselling, vasculitis, chronic hypertension, high risk pregnancy

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Introduction

Takayasu arteritis (TA), also called pulseless disease, is a chronic vasculitis that affects large vessels, mainly the aorta and its important branches (1). It was first described by Japanese ophthalmologist Mikito Takayasu in 1908 (2). The incidence of TA is 2,3 per million persons per year, with male to female ratio being 1:9 (3). Since young women are more commonly affected than men, one may encounter this condition in pregnancy, although it is still rare. Hence TA is also known as "young female arteritis" (2).

Management of pregnant women with TA is challenging because of the physiological increase in blood volume and cardiac output during pregnancy, which worsens the cardiovascular complications associated with the disease (4). Although the course of the disease per se is not affected by

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pregnancy, it has the potential to cause serious maternal and neonatal morbidity (5,6).

The inflammation of the aorta and its branches leads to stenosis, occlusion and aneurysm formation. Compliance of these blood vessels is also reduced leading to vasoconstriction, which in turn, leads to hypertension.

Pregnancy related increase in blood volume makes matters worse in the presence of "fixed" cardiac output, leading to increased cardiac strain. This often results in aortic regurgitation (AR) and congestive heart failure. Vasoconstriction also leads to chronic uteroplacental insufficiency, resulting in worsening of pre-existing hypertension superimposed pre eclampsia and/or fetal growth restriction (6,7).

There is a lack of recognized robust guidelines for management of such pregnancies and much of the evidence available in the medical literature is in the form of case series or case reports (6-10).

The aims of this study were to study the obstetric and perinatal outcomes among pregnant women with TA's, attending our hospital for pregnancy and childbirth between January 2011 to December 2016.

Material and Methods

This was a retrospective study carried out in the departments of Obstetrics, Neonatology and Rheumatology at Christian Medical College and Hospital, in Vellore, a tertiary care perinatal centre in India, which has an average of 15,000 deliveries per year. This study was approved by the institutional review board and ethics committee: IRB Min No. 10665 (Retro) dated 19.04.2017. The consent of pregnant women was not taken given the retrospective nature of the study.

Clinical charts of pregnant women with TA who underwent antenatal care and/or delivery in the Hospital between January 2011 to December 2016 were retrieved from the medical records department. American College of Rheumatology criteria were used for diagnosis of TA (Table 1).

Maternal demographic data, stage of disease based on angiographic classification, complications related to disease, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values, details of treatment taken (medical/surgical) prior to pregnancy, pregnancy outcomes, and neonatal outcomes were obtained.

Pregnancy outcomes studied were: existence of chronic hypertension and/or development of gestational hypertension; superimposed pre eclampsia; fetal growth restriction; any cardiovascular events in pregnancy; preterm labour; and the mode of delivery.

Neonatal outcomes included gestational age at birth, birth weight and any other neonatal complications.

Figure 1 shows the selection of patients for the study and clinical management of these women.

Operational definitions

1. Active disease was defined as the presence of features of vascular ischemia or inflammation (such as carotodynia), claudication, diminished or absent pulse, bruit, asymmetric blood pressure in either upper or lower limbs or both, elevated ESR, systemic features, such as fever, musculoskeletal abnormality (without any other cause identified) and typical angiographic features.

New onset or worsening of two or more features indicated "active disease." (Kerr's Criteria 1994) (2).

2. Disease remission was defined as when there was complete resolution or stabilization of all clinical features and fixed vascular lesions (Kerr's Criteria 1994) (2).

3. Angiographic types (11):

Type-1: Involves the branches from aortic arch.

Type-2 a): Involves the ascending aorta, aortic arch and its branches.

Type-2 b): Involves the ascending aorta, aorta arch and its branches and thoracic descending aorta.

Type-3: Involves thoracic descending aorta, abdominal aorta and or renal arteries.

Type-4: Involves abdominal aorta, and or renal arteries.

Type-5: Combined features of type 2B and 4.

4. Chronic hypertension: Blood pressure ≥140/90 that predates conception or presents before 20 weeks of gestation and persists >12 weeks postpartum (12).

5. Gestational hypertension: Blood pressure ≥140/90 in two occasions 15 minutes apart, identified for the first time after 20 weeks of gestation and normalizes by 12 weeks post-partum (12).

6. Preeclampsia: Presence of elevated blood pressure with protienuria (24 hrs protein >300 mg, urinary protein creatine ratio >0.3, urine dipstick $>1^{+}$) or creatinine >1.1, platelets <1,00,000, elevated liver enzymes twice the upper limit of normal range (12).

7. Superimposed preeclampsia: In women with chronic hypertension, new onset proteinuria after 20 week gestation, or a sudden inrease in proteinuria in those with pre-existing proteinuria, before 20 weeks or development of low platelets (12).

8. Secondary antiphospholipid antibody syndrome (APS): Antiphospholipid antibody, occurring secondary to an autoimmune disease (13).

9. Intrauterine growth restriction: Fetal weight less than the 10^{th} centile for that gestational age (14).

10. Intra uterine death: Baby born after 28 weeks of gestation without any signs of life as defined by the World Health Organisation (15).

11. Indian Takayasu clinical activity scoring (ITAS): A clinical scoring system formulated by the Indian rheumatology association vasculitis group in March 2010, to study disease activity. Any new clinical manifestations of flare that has occurred over the previous three months are documented. A score ≥2 is considered disease activity (16).

12. ITAS.A scoring (ibid Oct 2012), ITAS including acute phase reactants (ESR, CRP). The score values of these are individually added to the original ITAS score, which gives an ITAS A-ESR or an ITAS A-CRP. A score of 5 or more is considered active disease. The cutoff ranges for CRP and ESR were taken from ITAS.A. CRP <5 mg/dL had a score of 0, CRP of 6-10 mg/dL had score of 1, 11-20 mg/dL score of 2 and >20 mg/dL score of 3. Similarly ESR <20 mm/hr score of 0, 21-39 mm/hr score of 1, 40-59 mm/hr score of 2, and >60 mm/hr score of 3 (16). A higher score increases the likelihood of disease activity.

Results

Maternal characteristics

There were sixteen pregnant women with TA who were seen and delivered between January 2011 and December 2016. All women fulfilled the American College of Rheumatology 1990

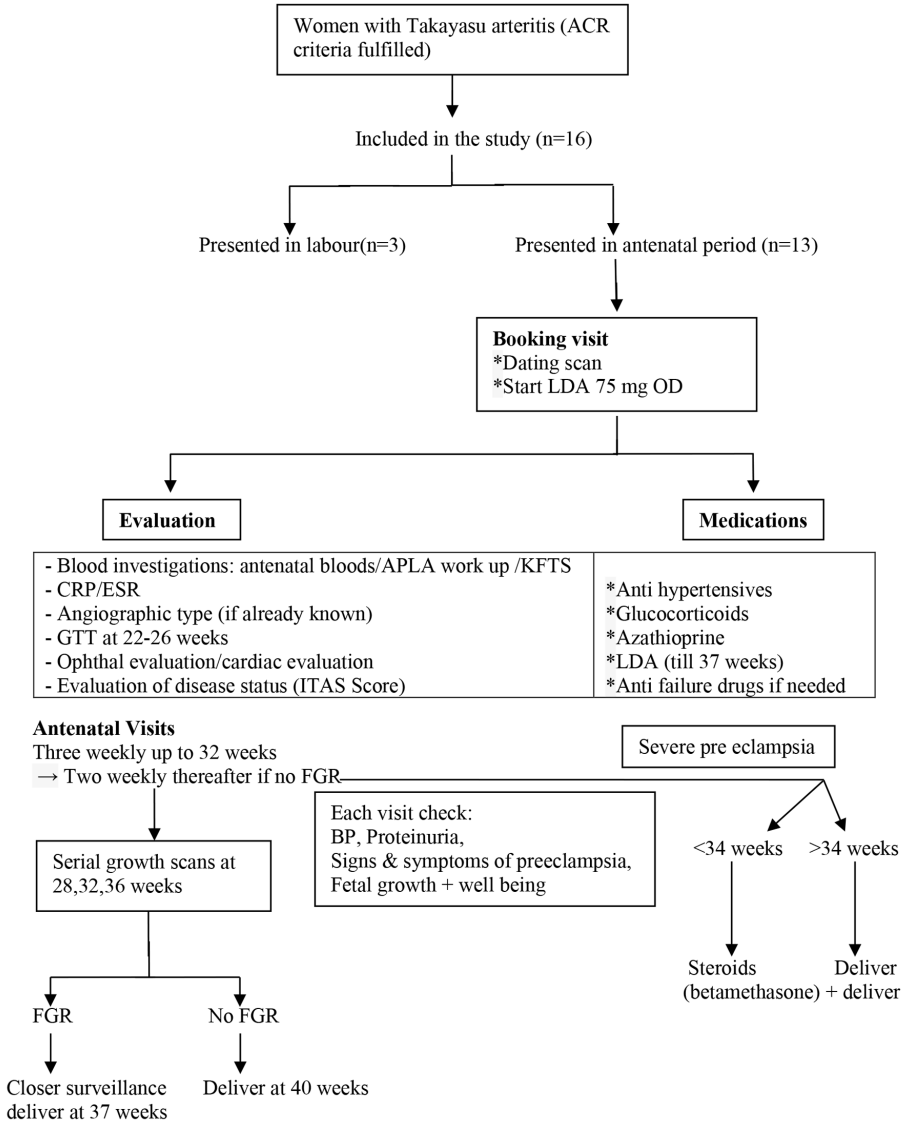

Figure 1. Flow diagram of clinical management in pregnant women with TA

ACR: American College of Rheumatology, APLA: Anti-phospholipid antibody, KFTS: Kidney function tests, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDA: Low dose aspirin, ITAS: Indian Takayasu arteritis society, FGR: Fetal growth restriction, GTT: Glucose tolerance test, FGR: Fetal growth restriction

criteria for diagnosis of TA. Three women were first diagnosed with TA during their pregnancies, or during intrapartum period when they presented in labour (Table 2). Remaining thirteen women who had been diagnosed with TA prior to pregnancy, were under regular follow up and treatment with rheumatologist, cardiologist or cardiothoracic surgeons, however they did not have any formal preconceptional counselling prior to becoming pregnant.

Nearly three quarters of the subjects did not have active disease, as per Kerr's criteria, probably because they were under multidisciplinary care before pregnancy. However, the periconceptional disease status of 19% (3/16) women who either presented in advanced stage of pregnancy or were diagnosed to have the disease during pregnancy itself was unknown.

The majority (75%) were between 20-30 years of age (Table 2). The median (range) age of diagnosis was 23.5 (22.0-25.5) years. Median (range) diagnosis-to-pregnancy interval was 4.5 (2.25-8.00) years.

Disease characteristics

The majority of subjects in whom the diagnosis of TA had been made prior to pregnancy (7/13; 54%), belonged to angiographic type 5 and none of them showed disease activity in pregnancy. We however did not know the angiographic type in three women who presented in advanced pregnancy without any pre-pregnancy evaluation having been performed earlier. As angiography is an invasive procedure, this was not performed during pregnancy solely for the purpose of diagnosis. The majority of women with hypertension had involvement of renal arteries too (6/9; 67%). Occular involvement was the next most common complication related to disease (see Table 3).

Nearly half the women in our cohort had undergone surgical intervention for TA prior to conception. Percutaneous transluminal angioplasty (PTA) with stenting of stenosed vessel was the most common surgical procedure carried out. Three women had stenting of the descending aorta, two of the common carotid artery, one underwent stenting of the subclavian artery and one had stenting of renal arteries along with the common carotid and subclavian artery. Two women required restenting following PTA due to restenosis of the arteries. One patient underwent nephrectomy for kidney failure; in this case renal function was 8%.

Almost all (15/16; 94%) were on medical therapy. These also included seven women who had also undergone PTA, with or without stent. All women were on multiple drugs, the most common combination (9/16; 56%), being steroids, immunosuppressants and anti-hypertensives. Seven women were on antiplatelet medications. One woman was on anti-cardiac failure drugs due to severe AR.

ITAS score was known for only half of cases, (n=8). The majority of them (n=7; 87.5%) had a score of <2 indicating lack of active disease, one had a score of 6. Using the ITAS.A criteria taking into account the values of acute phase reactants, ITAS.A-ESR/ITAS.A-CRP were calculated. The median (Inter Quartile range) for ITAS.A-ESR and ITAS.A-CRP were 2.50 (2.3) and 0.50 (0.2.75) respectively.

Obstetrics and neonatal implications

Six (37.5%) women had miscarriages, prior to a successful pregnancy (Table 2). The reasons for miscarriages are not clear since they occurred elsewhere, without proper medical records. Nine women (56.2%) had chronic hypertension. Chronic hypertension was seen especially in the nine women in whom descending abdominal aorta and the renal arteries were involved (6/9; 66.7%). Two of these women developed superimposed preeclampsia (22.2%). None had secondary APS. Cardiovascular events, such as congestive heart failure and worsening of AR were not encountered during pregnancy. One woman was on anti-cardiac failure medication prior to pregnancy due to severe AR, but did not have further deterioration of cardiac function during pregnancy. There were no maternal deaths in our cohort (Table 4).

In two women in our cohort no obstetric complications manifested. One was angiographic type 1, not on any treatment, and was in remission. The angiographic type of the other was unknown although she had bilateral ocular ischemic syndrome with dense cataract and was on steroids and aspirin.

Of the babies delivered nearly one third had fetal growth restriction and a quarter were born preterm. However, there were no intrauterine fetal deaths, either antepartum or intrapartum (Table 4).

Of the six women who delivered vaginally, two went into spontaneous labour whereas the rest had induced labour. Labour was induced in two women at term due to disease related complications of fetal growth restriction and superimposed preeclampsia whereas labour was induced for obstetric reasons, the preterm premature rupture of membranes, in the remaining two. Median (range) gestational age at delivery was 37 (36.00-38.75) weeks and median (range) birth weight was 2.6 (2.33-2.86) kg (Table 2).

Ten of the 16 (62%) deliveries were made by lower segment caeserian section (LSCS). Three of the LSCS were carried out as a result of disease condition per se: two had dilated aortic roots, at risk of aortic dissection during labour; and one had type 5 disease. The remainder of the LSCS (n=7) were done for obstetric indications, of which three for fetal distress, one for breech, one for arrest of descent, one for previous preterm LSCS with severe preeclampsia and one for previous LSCS not willing for Trial of labor (Table 4).

Discussion

TA is a chronic idiopathic inflammatory disease affecting the aorta and large arteries. Etiology, though unknown, is probably autoimmune and is associated with diminished pulses, claudication, hypertension, stroke and cardiovascular complications. Histology shows panarteritis with acute exudative and chronic granulomatous inflammation associated with hyperplasia neovascularization. Aneurysms are caused by metalloproteases released from inflammatory cells, while infiltration by leukocytes and proliferation of myofibroblasts causes stenosis of vessels and its associated symptoms (17).

Since this condition is predominantly seen in young women, it is not uncommon to come across pregnant women with TA. In addition women with TA are more likely to become pregnant than other forms of vasculitis, since TA does not affect fertility (2,6,7). Mean age of diagnosis in our cohort was 24 years which was similar to other previous reports (18,19). Most of our patients were in the second decade of life as is classically described in the literature (2).

TA, being a Th1 mediated vasculitis, does well in pregnancy with successful outcomes (20). There have been many theories postulated for this such as an immunomoduatory effect of progesterones, release of cytokines by helper T cells and immunologic changes seen in pregnancy as part of an adaptive process (4,21,22). However it is associated with poor perinatal outcome, especially in patients with complicated disease and relapses (6-8,23).

Outcomes are affected by the type of arterial involvement. The incidence of hypertension, preeclampsia, and growth restriction in the fetus is found to be higher when renal artery and abdominal aorta are involved (24). Renin production is reported to increase when there is partial occlusion of the renal artery, which would explain the hypertension and decreased uteroplacental circulation resulting in growth restriction (24).

Relapses have also been found to be associated with preeclampsia and growth restriction, which could be the result of impaired placentation and fetal perfusion because of injury to the syncytiotrophoblast, endothelium of spiral veins, endovascular trophoblasts of the spiral arteries and glandular cells of the decidua by autoimmnune inflammatory processes (23). In addition the increase in blood volume and cardiac output during pregnancy can deteriorate the already existing vascular lesions of TA which could be fatal (4,21,24,25). The course of the disease however is not altered by pregnancy (20).

Pre-pregnancy counseling to stabilize the disease, is of paramount importance in women with TA (24,25). Presence of chronic hypertension, vasculitis and active disease six months prior to conception are factors associated with poor pregnancy outcomes (26). The main objective of periconceptional counselling is to assess disease activity; optimal control of blood pressure and changing over to safer drugs (20). There are various scores for assessing the disease activity such as Kerr's score and ITAS score which will aid in counselling.

In our cohort although most of the women did not have periconceptional counselling, we had successful outcomes, secondary to good disease control prior to conception, and multidisciplinary management during pregnancy.

Suppression of the inflammatory process of TA and thus suppression of placental inflammation during pregnancy has been found to improve outcomes. Low dose corticosteroids and immunosuppressants are considered as the mainstay of treatment (23,27). Hidaka et al. (28) observed good pregnancy outcomes in their cohort on these medications. They had ten patients and nine of them were on steroids (28) One-fourth (n=4;25%) of our women were on corticosteroids alone and almost half (n=9:56%) on both steroids and immnunosupressants.Overall an 81% (13/16) of them were on steroids.

In our cohort, the preconceptional disease activity status was not known in 19% (3/16) cases as these presented in advanced pregnancy or in labour. This could be partially attributed to lack of patient awareness about the need for preconceptional counselling as well as the prolonged diagnosis to pregnancy interval. Unfortunately, this is not an uncommon scenario in the developing world where women do not have easy access to specialized health care .These women were diagnosed in the last trimester of pregnancy, one after 32 weeks when she first presented to our hospital, other two at 40 weeks when they presented in labour, and was incidently found to have diminished pulse in one limb. Singh et al. (18) showed that early assessment of disease status prior to conception and effective intervention prior to embarking on pregnancy, resulted in successful pregnancy outcomes. Other studies have noted increased rates of abortions in these women (24,25).

Though elevation of acute phase reactants may not be a very reliable marker for disease activation (29), it is considered a mode of assessing disease progression by ITAS.A (2012). This in turn would necessitate close antenatal surveillance with multidisciplinary involvement. Similar observations were included in other case reports and studies (2,8,10).

Almost half of our women were hypertensive and most of them required antihypertensive medication. Optimal control of hypertension is the key to successful pregnancy outcome since uncontrolled hypertension can cause: miscarriages; superimposed preeclampsia; abruption; fetal growth restriction; and ultimately intrauterine demise. Hypertension can also lead to catastrophic complications such as aortic dissections

in women with dilated aortic roots. Thus hypertension, together with the autoimmune pathology of TA can directly or indirectly aggravate medical and/or obstetric complications (2,6,9,20,25,30).

Garikapati et al. (7) observed hypertension in 90% of their patients. In another similar study Singh et al. (18) found hypertension in 90% of patients with renal involvement. This however dropped to 50% following treatment for underlying pathology. Their rate of superimposed preeclampsia was only 10%. This is somewhat similar to our findings.

Although most of our women had type 5 TA, the severity of complications in terms of hypertension and superimposed preeclampsia was much lower than those mentioned by some others (7), since most of our women had already undergone treatment for the underlying disease prior to embarking upon pregnancy. Four of our patients with type 5 TA underwent PTA prior to pregnancy. The rates of hypertension reported by Kirshenbaum and Simchen (24) in his cohort who had antenatal counselling and stabilization of disease was 60%, which was very similar to our finding.

Pregnancy can also aggravate the already existing complication of TA, such as renal insufficiency, retinopathy, myocardial infarction, AR, aortic aneurysm, increasing maternal morbidity and mortality (2,20). One third of our cohort had renal involvement, 10% had cardiac and 15% had ophthalmic involvement. Although some of our women were diagnosed with AR prior to pregnancy, there was no deterioration in maternal cardiac function during pregnancy.

AR was the most significant cardiac problem as has been reported previously (7,18). In our cohort, two women had severe pre-pregnancy AR, with one being on anti-cardiac failure drugs. However, none of them had any worsening of symptoms during pregnancy. Aortic aneurysm and aortic dissection is a known complication of TA, and its occurrence in pregnancy with uncontrolled hypertension could cause maternal death, especially in the third trimester and during labour. We did not have any severe adverse outcomes such as any mortalities in our cohort. Close antenatal, intrapartum and postpartum monitoring, with a strict control of hypertension, and immediate surgical intervention whenever required, could prevent maternal deaths, as was observed by Lakhi and Jones (6) and Shafi et al. (8) in their case reports.

Delay in diagnosis, hypertension early in pregnancy and degree of vascular involvement (type 3, 4 and 5 TA) are considered predictors of poor outcomes in pregnant women with TA (4,9,10,30). We also noted similar findings. Women with type 5 disease had the most obstetric complications in terms of superimposed preeclampsia, preterm labour, fetal growth restriction and need for caesarean delivery.

Table 1. American College of Rheumatology 1990 criteria (31)

Criteria	Definition
Age at disease onset (<40 yrs)	Development of symptoms or findings related to TA at age <40 yrs
Claudication of extremities	Development and worsening of fatigue and discomfort in one or more muscles of extremities, while in use especially in the upper extremity
Decreased brachial artery pulse	Decreased pulsations of one or both brachial artery
Blood pressure difference of >10 mmHg	Difference of >10 mmHg in systolic blood pressure in both arms
Bruit over subclavian artery or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriogram narrowing or occlusion of entire aorta, it primary branches, or large arteries in proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes, changes usually focal or segmental

Table 2. Maternal characteristics

Variables	Number (n)	Percentage (n/16)
Age (years)		
10-20	2	12.5
20-30	12	75
30-40	2	12.5
Domicile		
Tamil Nadu	9	56.3
Rest of India	7	43.7
Gravidity		
Primigravida	8	50
Multigravida	8	50
Diagnosed during pregnancy		
Yes	3	18.75
No	13	81.25
History of miscarriages		
Yes	6	37.5
No	10	62.5
Age at diagnosis (years)		
Mean +/- SD	24.25 +/- 4.59	-
Median IQR	23.50 (22.0, 25.75)	-
Diagnosis pregnancy interval (years)		
Mean +/- SD	5.19 +/- 2.97	-
Median IQR	4.50 (2.25, 8)	-
SD: Standard deviation, IQR: Interquartile range		

Table 3. Disease characteristics

Variable	Number (n)	Percentage (n/16)
Angiographic findings		
Type 1	2	12.5
Type 2	1	6.3
Type 4	3	18.8
Type 5	7	43.8
Unknown	3	18.8
Complication*		
Ophthalmic	3	18.75
Hypertension	9	56.25
Cardiac	2	12.5
Renal	6	37.5
Others	1	6.25
CRP at booking		
<5	4	25.0
6-10	5	31.25
11-20	4	25.0
>20	2	12.5
Unknown	1	6.25
ESR at booking		
<20	0	0
21-39	3	18.75
40-59	6	37.5
>60	6	37.5
Unknown	1	6.25
Treatment		
Medical	9	56.25
Medical & Surgical	7	43.75
PTA with stenting	5	-
PTA without stenting	1	-
Nephrectomy	1	-
Unknown	2	12.5
Medications**		
Steroids	4	25.0
Immunosuppressant alone	0	0
Steroids + immunosuppressant	9	56.25
Antihypertensive	6	37.5
Antiplatelet	7	43.75
Antifailure	1	6.25
Antiepileptics	2	12.5

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PTA: Percutaneous transluminal angioplasty

Disease activity at onset of pregnancy by Kerr's criteria

Absent	12	75.0
Present	4	25.0
Not known	0	0
ITAS score		
<2	7	43.7
>2	1	6.3
Unknown	8	50.0
ITAS A-ESR Median IQR	2.50 (2.3)	-
ITAS A-CRP Median IQR	0.50 (0.2.75)	-

*Some women had two or more than two complications. **Most women were on steroids + immunosuppressants and antihypertensive
ITAS: Indian Takayasu clinical activity score, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, IQR: Interquartile range

Table 4. Maternal and neonatal outcomes

Variables	Numbers	Percentage
Antenatal complications		
Chronic hypertension	7	43.75
Superimposed preeclampsia	2	12.5
FGR	5	31.25
Preterm labour	4	25.0
Abruption	1	6.25
Maternal death	0	0
Congestive cardiac failure	0	0
Antiphospholipid antibody	0	0
Intrauterine fetal demise	0	0
None	2	12.5
Mode of delivery		
LSCS	10	62.5
NVD	6	37.5
Neonatal morbidity		
Jaundice	1	6.3
Nil	15	93.8
Birth weight		
Mean +/- SD	2.58 +/- 0.34	-
Median (IQR)	2.6 (2.33, 2.86)	-
GA at delivery		
Mean +/- SD	37.06 +/- 1.06	-
Median (IQR)	37.0 (36.0, 38.75)	-

FGR: Fetal growth restriction, LSCS: Lower segment caesarian section, NVD: Normal vaginal delivery, SD: Standard deviation, IQR: Interquartile range

Table 5. Obstetric and neonatal outcomes in different angiographic classification over period of January 2011 to December 2016

Type	None	Chronic hypertension	SPE	PTL	IUGR	LSCS	Neonatal complication
1	1	-	-	1	-	-	-
2A	-	-	-	-	-	-	-
2B	-	-	-	-	1	-	-
3	-	-	-	-	-	-	-
4	-	2	-	-	1	3	1
5	-	5	2	3	2	5	-
Not known	1	-	-	-	1	2	-

PTL: Preterm labour, IUGR: Intrauterine growth restriction, LSCS: Lower segment caesarian section

The severity of the angiographic type determines the obstetric and perinatal outcomes, with more severe ones having a greater degree of adverse outcomes (7). This was also consistent with our findings (Table 5).

In our cohort, 31% babies were found to be growth restricted. The most common cause for fetal growth restriction was the presence of maternal hypertension, leading to uteroplacental insufficiency. Similar findings were noted previously by other authors (6-8,10,18,25). Women who had stenting and surgical corrections prior to pregnancy had well grown babies.

Involvement of infra-diaphragmatic arteries, especially the renal arteries is associated with adverse pregnancy outcomes (18,24,26). In our study, only one third women with involvement of the renal arteries had fetal growth restriction since most of these women were in remission. Disease activity was controlled with a combination of drugs such as immunosuppressants, steroids and anti-hypertensives in order to achieve optimal control of blood pressure. Singh et al. (18) had also reported improved outcomes in women who had angioplasty of the renal artery before conception.

Although mean gestational age at delivery was 37 weeks, 25% of our cohort had preterm birth, which was due to preterm premature rupture of membranes. This is somewhat more than the rate reported in the literature which is in the range 6-16% (18). We are unable to explain the increased incidence of preterm premature rupture of membranes in our cohort. Around 38% (6/16) of women had a history of miscarriages in our cohort. This is much higher than that found by Hauenstein et al. (2) who reported 12% rate. We are not aware of the cause of miscarriages in prior pregnancies as most of these were managed elsewhere with few clinical details available. It is quite possible that these would have been related to greater disease activity (Table 2). There was no intrauterine fetal demise, a severe and unfortunate complication of TA in the third trimester, nor any neonatal deaths, unlike in other studies were lack of multidisciplinary approach and uncontrolled disease status led to these unfortunate events (2,18).

Vaginal birth at term is recommended for all patients with TA (2,6). Most of our patients experienced spontaneous labour, whereas 25% underwent induction of labour. We had 60% LSCS rate in our cohort, the majority of which were done for obstetric indications. The rate of LSCS was similar to some previous reports (24,25). Women were more likely to have LSCS in severe disease types (type 4, 5) (Table 5). This is because the more severe angiographic types are more likely to have obstetric complications. Intrapartum fluctuations of blood pressure and increased cardiac output can worsen the already existing maternal complications of TA (24,25,28). It can further deteriorate the already existing uteroplacental insufficiency, leading to fetal compromise.

Strengths

We had collected data over a period of five years with 16 patients included in the study. Ascertainment of data was very good with very few lost data.

Study Limitation

This was a retrospective study and the clinical information obtained from the charts depended on the recordings of various clinicians.

Conclusion

Periconceptional counselling is ideal in women with TA, however it may not be feasible in the developing world. Though most of our cohort conceived without preconceptional counseling, good outcome was achieved because of close antenatal surveillance and multidisciplinary care of such pregnancies. It is advised to plan pregnancy during disease remission, with good antenatal care and close monitoring of clinical symptoms. Early diagnosis of complications and its treatment result in good maternal and fetal outcome.

Ethics Committee Approval: *This study was approved by the institutional review board and ethics committee: IRB Min No. 10665 (Retro) dated 19.04.2017.*

Informed Consent: *The consent of pregnant women was not taken given the retrospective nature of the study.*

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Post-partum tubal ligation at time of cesarean delivery or via laparoscopy as an interval sterilization has similar effects on ovarian reserve

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Abstract

Objective: To observe and compare the effect of postpartum tubal ligation (TL) procedures on ovarian reserve at women desiring TL as a contraceptive method at the end of pregnancy.

Material and Methods: Eighty-one women were included in the prospective study. TL was performed at the time of cesarean delivery (CD) (n=49) and as an interval procedure by laparoscopy (LS) in the postpartum period (n=32). Anti-müllerian hormone (AMH) was used to determine ovarian reserve. Blood samples were taken twice from each subject; the first sample was taken before delivery from all subjects and the second sample was taken 4 months after sterilization. AMH level differences were compared in each group and between groups.

Results: The preoperative AMH values of CD and LS groups were similar 2.30 (maximum: 5.20, minimum: 0.42) ng/mL and 1.80 (maximum: 3.50, minimum: 0.40) ng/mL, respectively (p=0.262). The postoperative AMH values of the CD and LS groups were 1.30 (maximum: 2.60, minimum: 0.30) ng/mL and 0.90 (maximum: 2.50, minimum: 0.20) ng/mL, respectively (p=0.284). When the preoperative and postoperative values of each group were compared the change was statistically significant for both groups p<0.001. The decrease in mean AMH values in the CD and LS groups were 37.83% and 44.15%, respectively. The percentage changes of AMH values were not statistically significant (p=0.286).

Conclusion: TL at the time of CD and interval sterilization with LS have similar effects on ovarian reserve. (J Turk Ger Gynecol Assoc 2020; 21: 24-8)

Keywords: Tubal ligation, ovarian reserve, anti-müllerian hormone, cesarean section, laparoscopy

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Introduction

Tubal ligation (TL) is a permanent contraceptive method preferred mostly by women with more than one child (1). It is known to be safe procedure but utero-ovarian blood flow disruption has been considered as an adverse effect of the procedure (2-6). The debate on this issue has continued since the 1950s (2). Several studies were designed to observe the effect of TL on ovarian function (3-21). The first studies were primarily based on observational data (3-6). It has been reported that TL may result in menstrual irregularity, mainly shortening of menstrual bleeding due to disruption of ovarian function (3,4). However, all previous studies were observational and needed to be checked by objective measurements.

For the last decades, more objective parameters were used to measure ovarian reserve and function; namely, follicle-stimulating hormone, luteinizing hormone, estradiol (E2), anti-müllerian hormone (AMH), and ultrasound (Doppler blood flow and antral follicle count) for determining the effect of TL (9,11-22). Until recently, AMH was mainly used to assess ovarian reserve status (21-23).

Controversial results regarding the effect of salpingectomy on ovarian reserve measured by AMH have been reported (7,8). Ye et al. (7) reported decreased ovarian reserve after salpingectomy. However, Venturella et al. (8) reported that

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surgical excision including the removal of mesosalpinx with salpingectomy did not cause any negative effect on ovarian reserve. Bipolar coagulation was thought to create less tissue damage; however, laparoscopic TL using bipolar electrocoagulation was reported to cause lower AMH values (11,12).

It is certainly the case that most women usually express their desire for TL in their pregnancy period (24). In the case of TL at the time of cesarean delivery (CD), there must be an indication for the CD. However, to the dissatisfaction of some patients, physicians may be reluctant to proceed with cesarean delivery for the sole purpose of sterilization; these patients are referred for interval sterilization with laparoscopy (LS).

In the present retrospective cohort study, we aimed to compare the effects of two different postpartum TL modalities on ovarian reserve in women desiring TL at their pregnancy period; TL at the time of CD and interval sterilization with LS.

Material and Methods

Patients who had a desire for TL during pregnancy at the obstetrics and gynecology clinics of a university hospital between November 2011 and May 2013 were enrolled in this retrospective cohort study. The study was approved by the Institutional Review Board (IRB approval no: 16-624-13, date: 11/11/2013).

Patient selection

The first study group consisted of women who underwent TL during a scheduled or emergency CD. The second study group consisted of women who underwent laparoscopic TL in the postpartum period, 2-4 months after vaginal delivery (interval sterilization). The inclusion criteria were women aged between 30 and 40 years who had a desire for TL at the end of their current pregnancy. The exclusion criteria were previous ovarian surgery, polycystic ovary syndrome, any type of cancer and/or pelvic radiotherapy history, and any medication affecting ovarian response (oral contraceptive pills, danazol, gonadotropin-releasing hormone analogues).

A total of 90 patients were assessed for eligibility. After application of the inclusion and exclusion criteria, 84 patients were found to be eligible. Four of the excluded patients had polycystic ovaries and two had previous ovarian surgery because of endometrioma. Three more patients, one from the CD group and two from the laparoscopic TL group were lost during the follow-up period. As a result, 49 patients from the first group and 32 patients from the second group were included in the final analyses. Figure 1 shows the flow-chart of patients who were assessed, excluded, and followed up.

Surgical procedures

In our clinic, the Pomeroy technique is preferred for TL during CD. In this technique, the fallopian tube is inspected and held from the isthmic portion, then ligated using a number 0 absorbable suture by penetrating the avascular part of the mesosalpinx. The upper part of the ligated portion is cut with scissors and the remaining ligated part is checked for hemostasis. Then, the same procedure is repeated for the contralateral fallopian tube (25). Laparoscopic TL is performed under general anesthesia with the insertion of two to three ports. First, the pelvic anatomy is inspected. Then the fallopian tube is held from the avascular isthmic portion and cauterized using bipolar forceps until it becomes white, and subsequently cut with scissors without using electro-cautery. The cut portion is checked for hemostasis. The same procedure is repeated for the contralateral fallopian tube. There is no intervention with the ovaries during either of the procedures.

Main outcome parameters

The main outcome measure was preoperative and postoperative AMH changes. The percentage change between preoperative and postoperative AMH values were calculated for both groups for intergroup comparison.

Anti-müllerian hormone assay

The first blood samples were collected in the third trimester for each group when pre-labor assessment took place. The second blood samples were collected four months after sterilization. Blood samples were centrifuged at 4000 rpm for 10 minutes and stored at -80 °C until required for analysis. Upon collection of all samples, serum AMH levels were determined on the same day by using a commercially available enzyme-linked immune sorbent assay kit (Beckman Coulter Inc., Paris, France) with a lowest detection limit of 0.14 ng/mL. Intra- and inter-assay coefficients of variation were 12.3% and 14.2%, respectively.

Statistical analysis

Data analyses were performed using the SPSS Version 21.0 statistical software package (IBM Corporation, Armonk, NYC, USA). Samples were tested using Kolmogorov-Smirnov test to determine normality of distributions. Continuous variables were compared using the Mann-Whitney U test according to the distribution of each variable. The Wilcoxon signed-rank test was used for the comparison of preoperative and postoperative AMH values. A p value of <0.05 was considered statistically significant. In determining the difference of two methods by time, a p value of <0.025 was considered statistically significant, according to Bonferroni's correction.

Results

A total of 81 participants were evaluated, 49 patients underwent TL during CD, and 32 patients underwent TL with LS. The mean age of the CD group and LS group was 34.4±2.25 and 35.1±2.27 years, respectively. The median parity value of both groups was 3. The body mass index (BMI) of the CD group and LS group was 28.8 and 29.1 kg/m^2, respectively. Both groups were similar with consideration to age, parity, BMI, and live birth numbers (Table 1). The median preoperative AMH value for the CD group was 2.30 (maximum: 5.20, minimum: 0.42) ng/dL and 1.80 (maximum: 3.50, minimum: 0.40) ng/dL for the LS group. Both groups were similar according to preoperative median AMH values (p=0.262). The median postoperative AMH value for the CD group was 1.30 (maximum: 2.60, minimum: 0.30) ng/dL and 0.90 (maximum: 2.50, minimum: 0.20) ng/dL for the LS group. Both groups were similar according to the median postoperative AMH values (p=0.284). The median postoperative AMH values of both groups were lower than the preoperative median AMH values; this difference was statistically significant for both groups (p<0.001). The percentage change of the median AMH value of the CD group and LS group was 37.83% and 44.15%, respectively. The percentage change of the AMH values was similar between the groups (p=0.286) (Table 2).

Discussion

The present study was conducted to compare the effects of two different postpartum TL methods on ovarian reserve. According to our results, both TL at the time of CD and interval TL with LS were detected to significantly decrease serum AMH levels. However, when preoperative and postoperative percentage changes were compared between the groups, similar changes were detected.

The speculated mechanism of the adverse effect of TL on ovaries was blood perfusion disturbances (2-6). However, studies evaluating utero-ovarian Doppler blood flow changes were unable to demonstrate any difference, either on blood perfusion or follicular phase hormonal values after TL (12-18). Nevertheless, two studies demonstrated decreased mid-luteal progesterone levels contributing menstrual disturbances after TL (13,14). Surgical sterilization can result in subtle changes in ovarian function, even though ovulation itself is not affected (16,17). Kelekci et al. (18) and Kutlar et al. (19) demonstrated increased resistivity index of utero-ovarian blood flow without statistical significance. In addition, the negative impact of TL on ovarian reserve was histologically confirmed in an animal study (20). In a recent study that compared the effect of TL and salpingectomy at the time of CD on ovarian reserve, similar AMH changes were detected 6-8 weeks postoperatively (21).

In this study, we detected statistically decreased postoperative AMH levels in both procedures. The percentage change of AMH was lower in the CD group, but we failed to demonstrate a significant difference between the groups.

The mesosalpinx is one of the blood perfusion sources for ovaries (2). When tubal patency is disrupted for sterilization, blood perfusion on the mesosalpinx may be intervened (1,2). Salpingectomy is an invasive procedure compared with TL. Ganer Herman et al. (21) reported that even salpingectomy during CD resulted with similar AMH changes when compared with TL performed during CD. In the present study, the decrease of AMH percentage was lower in the CD group, but this change was not statistically significant. The intervention of the avascular mesosalpingeal part of the uterus may be simpler compared with interval sterilization through LS. This might be a reason for this percentage difference.

Previously, Ozyer et al. (22) compared AMH values in women who underwent TL at the time of CD and TL with mini-laparotomy approximately 1 year after surgery. They found

Table 1. Patient characteristics

	Cesarean group (n=49)	Laparoscopy group (n=32)	p
Age (mean)	34.4±2.25	35.1±2.27	0.926
Parity (median)	3	3	0.637
Live birth (median)	3	3	0.714
Body mass index	28.8	29.1	0.846

Values are mean ± standard deviation and median values for parity and live birth. There was no statistical significance between the groups (p>0.05 for all)

Table 2. Change of the anti-müllerian hormone values for both groups

	Number	AMH preop[a] (median) ng/mL	AMH postop[b] (median) ng/mL	% Change[c]
Cesarean	49	2.30 (max: 5.20, min: 0.42)	1.30 (max: 2.60, min: 0.30)	37.83%
Laparoscopy	32	1.80 (max: 3.50, min: 0.40)	0.90 (max 2.50, min 0.20)	44.15%

Values are mean and minimum and maximum values are presented for the variable range.
[a]Comparison of preoperative AMH values of both groups p=0.262. [b]Comparison of postoperative AMH values of both groups p=0.284. Comparisons of [a-b] for both groups are statistically significant p<0.001. [c]Comparison of percentage change of preoperative and postoperative values are without significance p=0.286
AMH: Anti-müllerian hormone, max: Maximum, min: Minimum

higher AMH levels in women who underwent TL at the time of CD. Interestingly, different from Ozyer et al. (22), postoperative AMH values in both groups were prominently decreased in the present study. This may because of our study population. Our study cohort was constituted by pregnant women and women in the early postpartum period, as the major strength of this study. None of the patients started to menstruate during the study period. The sharp fall of AMH could be a result of the inability to create a new AMH secreting follicle cohort after TL. In the long term, AMH levels may probably be compensated after ovarian function recruitment. The classic dogma regarding ovarian physiology dictates that the number of primordial follicles is constant and cannot be replenished. AMH is expressed by granulosa cells; its expression is initiated in the smallest growing follicles and declines in the early antral stages as one follicle is selected for dominance and the rest become atretic. Sönmezer et al. (23) proposed a theory of a compensatory mechanism following surgical ovarian damage. It is possible that any acute damage may stimulate more primordial follicles from the stockpile start to growing (23). This may be possible without any inhibitory situation such as pregnancy and lactation. In our study, there was no compensatory mechanism because all patients were pregnant or in the early postpartum period, and the sharp decrease might be due to the absence of this compensatory mechanism.

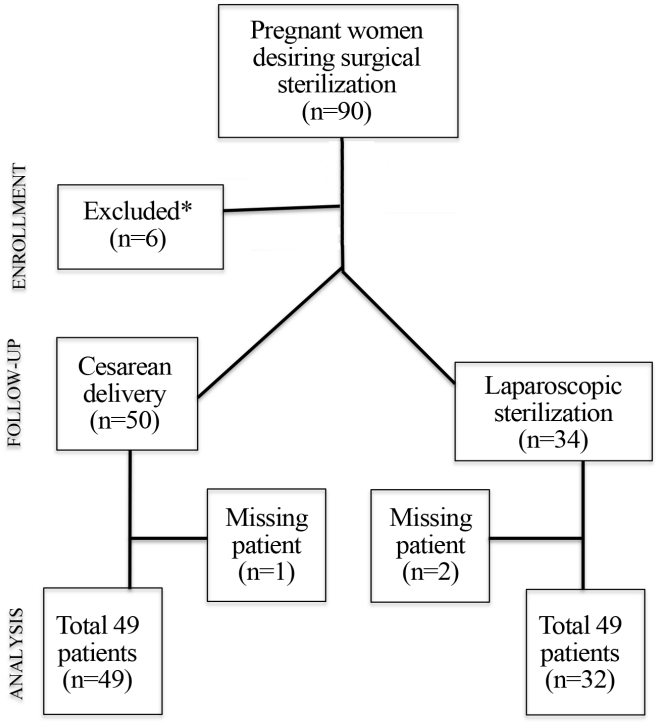

Figure 1. Flow-chart of patients
***Four of the excluded patients had polycystic ovaries and two had previous ovarian surgery because of endometrioma**

The other strength of our study was the comparison of the effects of the two most frequently used TL methods by assessing preoperative and postoperative AMH values. To the best of our knowledge, this is the first survey to compare two different TL procedures and is therefore a pioneer for similar studies.

Study limitations

The long-term postoperative values were not evaluated in our study. Also, cesarean section itself might have a negative effect on ovarian reserve, which could not be determined in our study. The effect of pregnancy on the bioactivity of AMH is still unknown. There are studies stating that AMH is invariant during the pregnancy period (9,26). In contrast, some studies reported a decrease of circulating AMH levels during the pregnancy period, but the observations are inconsistent (27,28). It could be better if the ovarian reserve markers were assessed before the pregnancy period, but it could only be possible for intrauterine insemination or in vitro fertilization patients who we may not be offered a surgical contraceptive technique in the postpartum period. Another limitation of our study was the low number of patients in the study groups. Moreover, the lack of a power analysis before data review can be noted as a limitation.

In conclusion, this study showed that both management techniques for TL had similar but negative impacts on ovarian reserve. These data can be beneficial for both patients and physicians, that the timing of TL may not have different effects on ovarian reserve. However, further studies are needed with larger cohorts evaluating long-term AMH values, particularly after recovery of normal menstrual periods.

Ethics Committee Approval: *The study was approved by the Institutional Review Board (IRB approval no: 16-624-13, date: 11/11/2013).*

Informed Consent: *It was obtained.*

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Effect of vaginal douching on vaginal flora and genital infection

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Abstract

Objective: This study aimed at examining the effect of vaginal douching (VD), which is a traditional and cultural application, on the vaginal flora and genital infections.

Material and Methods: This descriptive study included 190 women including those who did or did not perform VD. A questionnaire survey and vaginal sampling were employed. The collected samples were transported within 8 h for laboratory testing.

Results: There was no significant difference between the two groups in terms of vaginal flora. In the VD group, only a few patients reported a history of Sexually Transmitted disease (STD), but none in the non-VD group had STDs ($p<0.05$). No significant difference in infections was noted. However, there was a significant relationship between the history of infections and VD ($p<0.01$).

Conclusion: Women who performed VD are at risk for vaginal infections. Further studies are warranted in the future for clinical application. (J Turk Ger Gynecol Assoc 2020; 21: 29-34)

Keywords: Vaginal douche, vaginal flora, infection

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Introduction

Vaginal douching (VD) is the process of washing the vagina with water or other liquid solutions (1,2). VD can be widely seen in cultures that define the female body, menstruation, and sexual relations as dirtiness. In Turkish culture, women define menstruation as dirtiness (3). In Turkey, the rate of VD was 43.9-64.5% (2,4-8,9). In a 2014 study by the Republic of Turkey Ministry of Health Department, 79.20% women were found to be douching for hygiene (96.26%), religious belief (52.86%), and pregnancy prevention (12.74%) (10). These women stated that douching helped them feel clean, healthy, and good, treated infections, provided ablution, enhanced their appeal to partners, and prevented pregnancy. Moreover, women performed VD for vaginal cleaning following coitus to protect themselves from diseases, during menstruation, to feel clean before sexual intercourse and gynecologic examinations, to decrease unpleasant odours, to imitate others who performed VD, to gain experience, or out of curiosity (2,4-6,8,9,11-14).

Various researchers have evaluated the effects of VD on the health of women. Although some studies emphasised that VD caused important health issues, others revealed no such correlation. Some studies have indicated an effect of VD on vaginal flora and on the ascension of microorganisms into the upper genital tract (15,16). In the past, VD was associated with bacterial vaginosis, human immunodeficiency virus (HIV), and chlamydial infections, pelvic inflammatory disease (PID), preterm birth, low-birth-weight infants, infertility, ectopic pregnancy, cervical cancer, and AIDS (14,17-19). Vaginal dryness, burning in the vaginal area, genitourinary infection, and irritation have been reported in women who douche frequently (18). In a past study, the rates of genital infections were 53.5% and 33.8% in women who did

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and did not douche, respectively (19). In 1990, Brinton et al. (20) found that the risk of cervical cancer and PID increased with the use of commercial products instead of water and soap solutions during douching. In 2006, Akın et al. (6) detected the rate of VD in women with a history of infertility (40.0%), miscarriage (47.3%), preterm birth (40.0%), and low-birth-weight infants (57.1%) ($p>0.05$). These results indicate the variation in the reported findings on VD. Martino and Vermund (16) emphasised that VD was harmful. The World Health Organization has also indicated the adverse effects of VD in 2012. In a study by Sunay et al. (22), women who douched demonstrated an increased risk of abnormal vaginal discharge (about 3.9 times more; $p=0.001$) than women who did not douche.

Some studies support the positive effect of douching on health. For instance, some studies reported the alleviating effect of VD on HIV and human papilloma virus. In fact, antiseptic douche solutions have been shown to decrease the incidence of HIV (23,24). In a study on the effect of douching on vaginal flora, douching with saline or acetic acid once daily was found to reduce the structure and number of vaginal bacteria within 10 min. Moreover, douching with povidone-iodine-like bactericidal agents reportedly induced over-reproduction of pathogenic organisms that repress *Lactobacillus* (25,26). Hence, this study aimed to detect the effect of VD on vaginal flora and genital infection in women aged >18 years.

Material and Methods

This study was conducted at the Ministry of Health Hospital and the Maternal and Infant Health Centre of Family Planning. Study subjects included women who had been referred to these centres. The sample size was calculated using the NCSS Pass 2008 program, which required 190 women. Sen and Mete (2) reported a VD frequency of 47.2%. The ratio of VD was predicted as 27.2-67.2% using 95% confidence interval (CI) values, 80% power, and 20% standard deviation. On the basis of their douching behaviour, subjects were divided into two study groups: douching and non-douching groups. The VD group consisted of women who had douched in the last 3 days because the effects of douching on vaginal flora continue for 3 days.

The sample selection criteria were age ≥18 years; not being pregnant; no delivery date in the first 42 days; non-diabetic; not in their menstrual cycle during the study period; not using immunosuppressive drugs, antibiotic, antifungal, antiviral, corticosteroid or chemotherapy use in the past 2 weeks and no sexual intercourse in the past 3 days.

A questionnaire developed by the researchers based on the literature was used for data collection. Written informed consent was obtained from the subjects before data collection. After administering the questionnaire, vaginal samples were collected by the researcher in a private room. Vaginal samples were taken from the posterior wall of the vagina and lateral fornix without contacting the vulva using a sterile and disposable cotton swab.

A single-blind study was conducted for the cultivation and examination of vaginal samples by a microbiologist. The samples were transported in Stuart Transport Medium to the Laboratory of Bolu Abant İzzet Baysal University Health Research and the Application Center Microbiology Laboratory within 8 hours of sample collection. Before analysis, the samples were stored at room temperature (transport medium is stable at room temperature). Direct examination and cultivation were performed under laboratory conditions.

Ethical aspect of the study

Ethical permissions were obtained from the Governorship of Bolu city; Bolu Abant İzzet Baysal University, Health Research and Application Center, Microbiology Laboratory; Bolu Abant İzzet Baysal University Faculty of Medicine, Clinical Research Ethical Committee (decision no: 2011/26). Before applying questionnaire, written consent was taken from the women by giving information about the study. The expenses of the laboratory and stationery equipment were met by the financial support of Selçuk University, Coordination Office of Scientific Research Projects.

Statistical analysis

The SPSS 15.0 program was used for the statistical analysis of the study data. Study data were evaluated using the chi-square and logistic regression tests. A p value <0.05 was considered statistically significant.

The presence of vaginal infection pathogens and women's health-related factors were considered dependent variables. Factors including age, educational background, working status, health insurance, and the level of income were the independent variables.

Results

The rate of douching was much higher in women aged ≥50 years (61.1%). All women in the non-VD group were in the 20-29 years age group (57.4%), and they were all secondary school graduates. The educational level was higher for women in the non-VD group (76.6%). Among the employed women, 61.1% reported not douching, and 56.8% of unemployed women reported douching. The income range of douching women was 120-320 United States Dollar (USD) (59.6%) and <120 USD (59.3%), whereas that of women in the non-VD group was ≥500 USD (80.0%) and 320-500 USD (61.2%).

Of the total, 41.1% women reported having heard about VD from their social group, 37.9% decided to douche by themselves, and

9.5% learnt it from their mothers. The frequency of douching was 3-4 times/week by 35.8% and 1-2 times/week by 33.7% of the women. The frequency of douching was the highest after sexual intercourse in 69.5% of women.

Most women performed VD for personal hygiene. The reasons for douching were reported to be personal hygiene by 83.2%, religious reasons by 26.3%, protection from diseases by 9.5%, family planning by 5.3%, and ignorance by 2.1%. Moreover, 75.8% of women douched with water, whereas 17.9% douched with soap.

A statistically significant difference was found regarding vaginal infection history ($p<0.01$) between the two groups. In the VD group, 2.1% of women had Sexually Transmitted disease (STD) previously, whereas no women in the non-VD group had STD. Hepatitis B was reported in two women. The previous incidence of vaginal infection was 57.9% in VD subjects and 37.9% in non-VD subjects. A statistically significant difference was found between women with vaginal infection and those performing VD ($p<0.01$). In women with vaginal infection, the reason for infection was unknown in 78.7% in the VD group and 63.9% in the non-VD group.

No statistically significant difference was found between the two groups with respect to vaginal flora ($p>0.05$). The microbiologic evaluation results of vaginal flora revealed that the rate of women with normal vaginal flora (the primary colonising bacteria of a healthy individual is *Lactobacillus*) was 57.9% in the VD group and 70.5% in the non-VD group ($p>0.05$) (Table 1).

According to the result of logistic regression, a statistically significant difference was determined between the working status, profession, education level, and income status of the women ($p<0.01$) (Table 2). The probability of VD was found to be higher in housewives and workers in comparison with that in employed women and civil servants [odds ratio (OR)=2.064, 95% confidence interval (CI): (1.136-3.753); OR=4.185, 95% CI: (1.520-11.521), respectively]. When the education levels were similarly investigated, the probability of VD was found to be much higher in women had or had not graduated from

Table 1. Distribution of female vaginal specimens according to microbiologic examinations (infection effect-normal flora presence) according to vaginal douching status (n=190)

	Practicing VD		Not practising VD		Total number		χ^2	p
	n	%	n	%	n	%		
Vaginal microbiologic examination								
Vaginal infection factors present	40	42.1	28	29.5	68	35.8	3.298	0.069
Normal vaginal flora	55	57.9	67	70.5	122	64.2		
VD: Vaginal douching								

Table 2. Investigation of some variables affecting women's vaginal douching behaviours using logistic regression

Variables	β	Odds ratio	95% Confidence interval	p
Employment status				
Employed	-	1	-	
Not employed	0.725	2.064	1.136-3.753	0.017
Profession				
Officer	-	1	-	
Worker	1.431	4.185	1.520-11.521	0.006
Education status				
University	-	1	-	
High school	1.567	4.792	2.092-10.976	<0.001
Secondary school	1.716	5.564	1.981-15.623	0.001
Primary school and lower education	1.399	4.052	1.669-9.837	0.002
Income*				
>500	-	1	-	
320-500	2.168	2.533	0.735-8.730	0.141
120-320	8.824	5.895	1.829-19.003	0.003
<120	6.656	5.818	1.527-22.172	0.010
*Income in United States Dollars				

primary school [OR=4.052, 95% CI: (1.669-9.837)] and who had graduated from middle school (OR=5.564, 95% CI: 1.981-15.623) and high school [OR=4.792, 95% CI: (2.092-10.976)] in comparison with that in university graduates. Women with low income were likely to douche more often than women with high income [OR=5.895, 95% CI: (1.829-19.003)].

In the logistic regression analysis (reference, douching; risk factor, non-douching), the incidence of genital infection was higher in the VD group than in the non-VD group [OR=2.253, 95% CI: (1.260-4.029)].

Discussion

In the VD group, 59.4% of women had primary school and lower education, and 63.0% had graduated from middle school. The education level in the non-VD group was determined to be high school in 44.7% and higher education in 76.6% of women ($p<0.01$); these findings are supported by other studies (2,4-7,16,19). On the basis of these results, a reverse correlation exists between the education level and VD frequency.

Among the employed women, 61.1% reported not performing VD, whereas 56.8% of the unemployed women reported performing douching ($p<0.05$). In studies performed by Karaer et al. (5) and Ege et al. (19), employed women were less likely to perform VD. Another study, Yanikkerem and Yasayan (11) reported that 81.9% of the women who performed VD were housewives. The similarity between this study and other studies was revealed in terms of the working status of the women. A relationship was reported between VD and the socioeconomic levels of women. In the present study, the incidence of VD was higher in women with low income ($p<0.01$). Karaer et al. (5) also reported a statistically significant relationship between the level of income and VD, as in our study ($p<0.01$). On the contrary, Sunay et al. (22) found that the frequency of performing VD was higher in married and low-income women.

Women had learnt VD from their social groups (41.1%), by themselves (37.9%), through their mothers (9.5%), through healthcare personnel (9.5%) and through the media (2.1%). Thus, the sources of learning VD were elders, media, mothers, family members, their friends, healthcare personnel, and relatives (2,4,6-8,11,12,14,27). A study by Rosenberg et al. (28) showed that douching had a strong cultural component. The frequency of VD was 35.8% for 3-4 days/week and 33.7% for 1-2 days/week. Overall, the frequency of VD ranges between 1 and 2 times per day and between 1 and 2 times per week/month (4,6-8,9,11,13,29). The factors affecting the frequency of VD were determined as their cause, practice time, belief, and cultural response. It was believed that the high incidence of VD was related to avoiding infection from the toilet, menstruation, and sexual intercourse.

Most women used water (75.8%) and a solution of soapy water (17.9%) during VD. Various materials were identified for douching, primarily with water, and the second most commonly used product was water with soap (4,7-9,11,19). Similar studies performed in other countries revealed that water containing vinegar and commercial solutions were used more frequently for VD (1,13). With respect to the need for maintaining personal hygiene, it may be thought that VD was performed using only water or a solution of soapy water after taking a bath and using the toilet without the use of other solutions. Moreover, the incidence of VD was higher among women with low socioeconomic status. Therefore, the reason for using a solution of soapy water was considered related to their low costs.

The effects of these VD solutions on the vaginal flora remain unknown. In 2004, Zhang et al. (30) identified the incidence of bacterial vaginosis in women using water with vinegar for VD. In 1992, Onderdonk et al. (25) found that povidone-iodine caused a significant reduction in the normal flora (lactobacilli, the dominant bacteria in the vagina) and an increase in the incidence of vaginal infections. In 2000, Pavlova and Tao (31) reported that the inhibitory effect of solutions containing vinegar on pathogens caused vaginal infections, except on *Lactobacillus*. In this study, when the effects of solutions used for VD were investigated, the rate of using a water and soap solution was 14.5% in women with a normal vaginal flora and 22.5% in women with vaginal infection in the VD group. Moreover, 80% of the women with a normal vaginal flora used water and 70% of women with vaginal infection also used water.

In this study, the frequency of using water and soap solution was higher in women with vaginal infection than in women with normal vaginal flora. The rate of using water alone by women with normal vaginal flora was higher than that by women with vaginal infections. According to these results, the rate of using water alone for douching was lower than that of using water and soap solution. Van Royen et al. (32) determined that women with bacterial vaginosis used greater amounts of soap for hygiene purposes. However, it remains unknown whether the use of soap causes any change in the vaginal flora and the reason for frequent bathing may be the presence of a fishy odour in the vaginal discharge.

In this study, 57.9% of women in the VD group had an infection history, whereas 62.1% of women in the non-VD group had no infection history ($p<0.01$). Similar results were obtained by other studies; for instance, the rates of vaginal infections were higher in VD groups than in non-VD group (4,6,7,9,11,19). Although these findings support that VD may be a risk factor for vaginal infections, the frequency of VD was 1-2 days/week in 40% of the women with vaginal infection compared with

3-4 days/week in those with normal vaginal flora. Women evaluated in terms of the rate of performing VD did not have any effect on the change in flora.

The incidence of having normal vaginal flora was 57.9% in the VD group and 70.5% in the non-VD group ($p>0.05$) (Table 1). When the reasons for douching and factors affecting these reasons were evaluated, profession, education, and income levels were statistically significant ($p<0.01$). The probability of VD was higher in housewives and unemployed women than in employed women and civil servants [OR=2.064, 95% CI: (1.136-3.753)]; OR=4.185, 95% CI: (1.520-11.521), respectively). Similarly, when the education levels were investigated, the probability of VD was much higher in women who did or did not graduate from primary school [OR=4.052, 95% CI: (1.669-9.837)] and those who graduated from middle school [OR=5.564, 95% CI: (1.981-15.623)] and high school [OR=4.792, 95% CI: (2.092-10.976)] than those in graduates. Women with low income were likely to douche more frequently than women with high income (Table 2). Sen and Mete (2) and Arslantas et al. (8) reported that education level was statistically significant when VD-related parameters were evaluated through logistic regression analysis ($p<0.009$ and $p<0.001$, respectively). The former found that the probability of VD was higher among illiterate women than in educated women [OR=1.760, 95% CI: (1.154-2.683)]. On the contrary, the latter found that the probability of VD was lower in women with a college or university degree [OR=0.02, 95% CI: (0.005-0.09)]. According to Arslantas et al. (8), a statistically significant relationship was evident between VD and working status ($p=0.004$), and the probability of VD was lower among employed women [OR=0.34, 95% CI: (0.16-0.70)]. The findings of our study, which are similar to those of Sen and Mete (2) and Arslantas et al. (8), imply that the probability of VD was reduced as a result of increasing education level and working outside of the home.

In the present study, logistic regression analysis was performed to determine the effect of VD on genital infection history. The incidence of genital infections was higher in the VD group than in the non-VD group [OR=2.253, 95% CI: (1.260-4.029)]. Therefore, VD may predispose women to vaginal infections. Sunay et al. (22) reported that the risk of vaginal discharge was 3.9 times higher in the VD group than in the non-VD group [$p=0.001$; OR=3.86, 95% CI: (0.651-1.534)]. Consequently, there was no statistically significant difference in terms of infection as a result of microbiologic evaluation of vaginal samples. However, a statistically significant relationship was determined between infection history and VD ($p<0.01$). Therefore, we believe that women who perform VD are at risk for vaginal infections. Further studies are recommended to understand this issue better.

Some of the participating women who presented to the study centres met the sample exclusion criteria.

Ethics Committee Approval: *Ethical permissions were obtained from the Governorship of Bolu city; Bolu Abant İzzet Baysal University, Health Research and Application Center, Microbiology Laboratory; Bolu Abant İzzet Baysal University Faculty of Medicine, Clinical Research Ethical Committee (decision no: 2011/26).*

Informed Consent: *Written consent was taken from the women by giving information about the study.*

Peer-review: *Externally peer-reviewed.*

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Tadalafil attenuates ischemic damage as well as reperfusion injury in the rat ovary

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Abstract

Objective: Tadalafil is a selective phosphodiesterase type-5 inhibitor with a long half-life. It has a dual function in ischaemic and re-perfused tissues, i.e. vasodilatation and anti-oxidant effects. These features of tadalafil distinguish it from other anti-oxidants. We investigated the dual effect of tadalafil on ischaemia and reperfusion injury in the rat ovary.

Material and Methods: We established five study groups. Group 1 (n=6): sham-operated; group 2 (n=6): torsion; group 3 (n=6): torsion and Tadalafil; group 4 (n=6): torsion/de-torsion; and group 5 (n=6): torsion/de-torsion and tadalafil. Ovarian samples were harvested from animals and evaluated in terms of histopathologic changes, tissue malondialdehyde (MDA) concentrations, lactate production, and plasma cyclic guanosine monophosphate (cGMP).

Results: Follicular degeneration, oedema, haemorrhage, and inflammatory cells were significantly decreased in group 5 in comparison with group 4. Group 2 and group 3 were compared in terms of vascular congestion and haemorrhage; these parameters were significantly decreased in group 3. In addition, significantly decreased MDA and lactate concentrations were observed in group 5 in comparison with group 4. Increased cGMP concentrations were detected in group 3 and group 5.

Conclusion: We conclude that tadalafil might be useful in protecting the ovary against ischaemia and reperfusion injury. In the evet of ovarian torsion, it will provide a greater therapeutic effect than only performing de-torsion of the ovary or using other anti-oxidant agents. (J Turk Ger Gynecol Assoc 2020; 21: 35-40)

Keywords: Phosphodiesterase type-5, tadalafil, ischemia-reperfusion injury, vasodilatation; anti-oxidant

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Introduction

Ovarian torsion is an emergency condition in gynaecology practice. It is particularly important when diagnosed in the reproductive period. Ischemia-reperfusion (IR) injury can damage ovarian tissue and also reduce the ovarian reserve (1). The time of diagnosis is important due to the diminishing ovarian reserve. However, it usually takes some time to achieve a diagnosis given the non-specific diagnostic symptoms. In addition, although restoration of the blood supply of ovarian tissue can reduce ischemic damage, it can also cause reperfusion injury.

When the ischemic period is extended, the associated cell damage becomes irreversible. During the ischemic stage, the production of adenosine triphosphate (ATP) decreases and anaerobic glycolysis begins. Decreasing ATP concentrations leads to the cessation of sodium-potassium pump channel function and subsequent water influx into cells, resulting in cell swelling. If ischemia persists, cells proceed to an irreversible stage. At this stage, severe swelling is seen in the mitochondria, as well as cell membrane damage. Cell death usually results in necrosis.

Reinstating the blood supply of ischemic tissue leads to recovery of cells in the reversible stage. However, this situation

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brings another problematic condition, reperfusion damage. The reoxygenation of ischemic tissues results in the production of reactive oxygen species (ROS), including superoxide anions (O_2^-), hydrogen peroxide, and hydroxyl radicals (OH^-), among others. These ROS damage phospholipids and proteins of the cell membrane and promote mitochondrial permeability which can cause a reduction in ATP and lead to cell death (2). At this stage, the use of antioxidant agents helps to support the self-antioxidant defence mechanism of cells.

One of the phosphodiesterase type-5 (PDE-5) inhibitors is tadalafil which has been used in the treatment of erectile dysfunction (3). As PDE-5 catalyses the hydrolysis of 3'5'-cyclic guanosine monophosphate (cGMP), PDE-5 inhibitors cause an increase in cGMP. Nitric oxide (NO) is a potent vasodilator, and works via the secondary messenger cGMP. PDE-5 inhibitors facilitate the accumulation of cGMP within cells, and also facilitate NO-mediated vasodilation of vascular smooth muscle in mammals. Recent studies have demonstrated a potential beneficial effect of PDE-5 inhibitors on IR injury in the brain (4), kidney (5), and heart (6). These authors found that increasing cGMP attenuates lipid peroxidation (7) and nicotinamide-adenine dinucleotide phosphate [NAD(P)H] oxidase activity, which are the main sources of ROS production in oxidative stress (6).

Tadalafil has a dual function as a vasodilator and antioxidant. These characteristics distinguish it from other antioxidants used to prevent IR injury. In the current study, we investigated the effect of tadalafil on the ischemic stage and on reperfusion injury.

Material and Methods

Animals

Thirty mature, female Sprague-Dawley albino rats were used in this study. All rats were aged 12 weeks and weighed 200-220 g. Animals were housed in steel cages maintained in a temperature-controlled room (21±1 °C) under a 12-h light/dark cycle and fed ad libitum. This study was approved by the intuitional animal care committee, and all procedures were performed according to the experimental guidelines of Ege University (SPK-HADYEK 34562/2015/24). Patient approval has not been obtained as it is performed on animals. The oestrous stage was determined by taking a vaginal smear from all animals, and cell types were identified under a microscope using the Papanicolaou staining procedure. Oestrous was confirmed in the smear specimens from 30 rats, which were included in the experiment.

Experimental design

Animals were anaesthetised with 50 mg/kg ketamine and 7 mg/kg xylazine hydrochloride (Alfasan Int. BV, the Netherlands). The skin of the abdominal area was trimmed and cleaned with povidone iodine. A 2 cm midline incision was performed on the abdomen, and the uterus and ovaries were detected.

In the sham-surgery group (group 1, n=6), laparotomy was performed and the abdomen was closed 1 min later without performing any surgical procedures. In the torsion group (group 2, n=6), ischemia was created for 3 h by applying atraumatic vascular clips to the vascular pedicles of ovaries on both sides. The incision was subsequently closed with 3/0 silk sutures. In the torsion and tadalafil group (group 3, n=6), ischemia was performed, as described for group 2, 30 min after administering 20 mg/kg of tadalafil [(Cialis, Lilly, IN, United States of America (USA)] via oral gavage. In the torsion/detorsion group (group 4, n=6), 3 h of ischemia was created, as in group 2, followed by 3 h of reperfusion. In the torsion/detorsion and tadalafil group (group 5, n=6), torsion was created for 3 h, followed by tadalafil administration 30 min prior to 3 h of detorsion/reperfusion. At the end of the reperfusion stage, both ovaries were harvested for histologic and biochemical evaluation.

Histopathologic evaluation of tissue samples

Ovarian samples were evaluated using a light microscope. Specimens were fixed in 10% buffered formalin, then an increasing alcohol series was used to dehydrate samples. Subsequently, samples were cleared with xylene and embedded in paraffin. Tissue sections were sliced at 4-μm thickness and slides were stained with haematoxylin and eosin (H&E) prior to histologic analysis. An Olympus BX51 microscope connected to an Olympus C-5050 digital camera (Olympus Corp., Tokyo, Japan) was used for the analysis and photography of sections. Histologic sections were evaluated in terms of primordial and developing follicles. In the histology of the ovary, primordial follicles are located beneath of the cortex, surrounded by a single layer of granulosa cells. Primary follicles are encircled by a single layer of cuboidal granulosa cells. The identification of stratified granulosa cells indicates secondary follicles, and stratum granulosum and antral space are major features of tertiary follicles. The pyknotic appearance of the nucleus and collapsed ooplasm, with or without irregular granulosa cells, indicate a degenerated follicle.

The rate of vascular congestion, stromal haemorrhage and oedema, follicular degeneration, and infiltration of inflammatory cells in sections for each animal were scored from 0 to 3 according to the severity of injury. A score of 0 represents normal histology, and <33%, 33-66%, and >66% pathologic findings in the ovarian sections were scored as 1, 2, and 3, respectively (8).

Determination of lipid peroxidation and total protein concentrations

Tissue samples were homogenised in KCl (150 mM) and centrifuged at 5000 g for 10 min. Lipid peroxidation was determined by analysis of the supernatant, with malondialdehyde (MDA) concentrations measured as thiobarbituric acid-reactive substances in each tissue sample (9). Trichloroacetic acid and thiobarbituric acid reactive substances reagents were mixed with tissue samples and incubated at 100 °C for 60 min. The samples were centrifuged at 3000 rpm for 20 min after cooling on ice, and the absorbance of the supernatant was read at 535 nm. The standard calibration curve obtained using tetraethoxypropane was used to calculate tissue MDA concentrations, which were expressed as nmol/μg protein. Bradford's method was used to determine the total protein level in the tissue samples, with bovine serum albumin used as the standard (10).

Measurement of plasma cGMP and lactic acid concentrations

After administering tadalafil, plasma samples were collected and stored at -80 °C until use for the cyclic nucleotide assay. Enzyme-linked immunosorbent assay (Cusabio, Biotech Co. Ltd. Wuhan, China) was used to determine the plasma cGMP level. The ultraviolet detection method was used to measure the L-lactic acid concentrations in plasma samples.

Statistical analysis

Mann-Whitney U-test was used to compare the biochemical data and histopathologic scores between groups. The results were considered statistically significant if the p-value was <0.05. Statistical analyses were performed using SPSS software version 16.0 (Chicago, IL, USA).

Results

Histopathologic results

The histopathologic results of ovarian tissue samples of the five groups are presented in Figure 1, with no histopathologic changes observed in the group that received sham surgery (group 1). In contrast, increased follicular degeneration ($p<0.05$), oedema ($p<0.05$), vascular congestion ($p<0.001$), haemorrhage ($p<0.05$), and infiltration of inflammatory cells ($p<0.05$) were observed in the torsion group (group 2). When tadalafil was administered before torsion, a statistically significant decrease in vascular congestion ($p<0.05$) and haemorrhage ($p<0.05$) was found for group 3 compared with the torsion-only group (group 2).

When we evaluated the reperfusion effect, severe tissue damage was observed after restoration of the ovarian blood supply in group 4. Follicular degeneration and infiltration of inflammatory cells were more prominent in the torsion/detorsion-only group (group 4), and all abnormal findings were significantly decreased after adding tadalafil (group 5) when compared with group 4. A comparison of scores between groups in terms of histopathologic abnormalities is shown in Table 1.

Biochemical changes

Increased MDA concentrations were found in the torsion (group 2) and torsion/detorsion (group 4) groups compared with the sham-surgery group (group 1, $p<0.01$). Decreased MDA concentrations were measured in the torsion/tadalafil (group 3) and torsion/detorsion/tadalafil (group 5) groups, but this decrease only reached statistical significance in the torsion/detorsion/tadalafil group (group 5, $p<0.001$). Similar findings were also observed for the lactate results. Increased tissue lactate concentrations were found in the torsion (group 2) and torsion/detorsion (group 4) groups. Importantly, lactate concentrations were normalised in the groups that received tadalafil (groups 3 and 5). Plasma cGMP concentrations reflected the effect of tadalafil treatment, and a statistically significant increase in cGMP concentrations was found in the groups that were administered tadalafil (groups 3 and 5, $p<0.01$). The biochemical results are presented in Table 2.

Discussion

The aim in cases of ovarian torsion is to reduce the extent of necrotic tissue and preserve ovarian function. For this purpose, the ischemic period should be shortened and reperfusion

Table 1. Histopathologic findings in the groups

	Group 1	Group 2	Group 3	Group 4	Group 5
Follicular degeneration	0.16±0.16	1.0±0.25*	0.5±0.22	2.66±0.21	0.66±0.21††
Vascular congestion	0.33±0.21	2.66±0.21**	1.5±0.22#	2.5±0.34	1.83±0.30
Oedema	0.5±0.22	1.16±0.27*	1.33±0.21	2.16±0.30	1.16±0.16†
Haemorrhage	0.16±0.16	1.83±0.30*	0.66±0.33#	2.33±0.33	1.0±0.25†
Infiltration by inflammatory cells	0.16±0.16	0.83±0.16*	1.0±0.25	1.66±0.21	0.83±0.16†

Group 1: Sham operation, Group 2: Torsion, Group 3: Torsion and tadalafil, Group 4: Torsion/detorsion, Group 5: Torsion/detorsion and tadalafil, *: P<0.05, group 1 vs group 2, **: P<0.001, group 1 vs group 2, #: P<0.05, group 2 vs group 3, ##: P<0.001, group 2 vs group 3, †: p<0.01, group 4 vs group 5, ††: P<0.001, group 4 vs group 5

injury should be prevented. Many antioxidant drugs have been investigated for their efficiency in preventing oxidative damage during the reperfusion period (11,12). One of them, tadalafil, has antioxidant activity, and attenuates the generation of ROS under oxidative stress (6). In addition, tadalafil also possess a vasodilation effect, leading to an increase in cGMP concentrations. These functions provide a valuable effect during the ischemic period of certain organs, such as the heart and kidney (13,14). In the current study, we demonstrated decreased vascular congestion and haemorrhage in ischemic ovaries with the use of tadalafil. Our findings are similar to those obtained by Lledo-Garcia et al. (15), who studied the use of sildenafil for renal ischemia and reported the effectiveness of administering sildenafil in warm ischemic kidneys during the immediate post-transplant period. The effectiveness of a PDE-5 inhibitor in ischemic ovaries was also revealed in our results.

Tadalafil has a similar function to other PDE-5 inhibitors like sildenafil; however, it is more selective than sildenafil for the binding of PDE-5 (16) and has a longer half-life (17.5 vs 4.5 h, respectively) (17). These features mean that tadalafil is longer acting. Tadalafil augments the effect of NO by decreasing cGMP degradation. NO plays a major role in inhibiting NAD(P)H oxidase and limiting neutrophil and platelet adhesion, aggregation, and activation (18).

Increased tissue MDA indicates lipid peroxidation because MDA concentrations increase under conditions of oxidative stress (19). MDA impairs the ionic transport and enzymatic activity of cells, causing major changes in cell membrane permeability, resulting in damage and breakages that separate cell and organelle contents (20). In the event of ischemia, energy

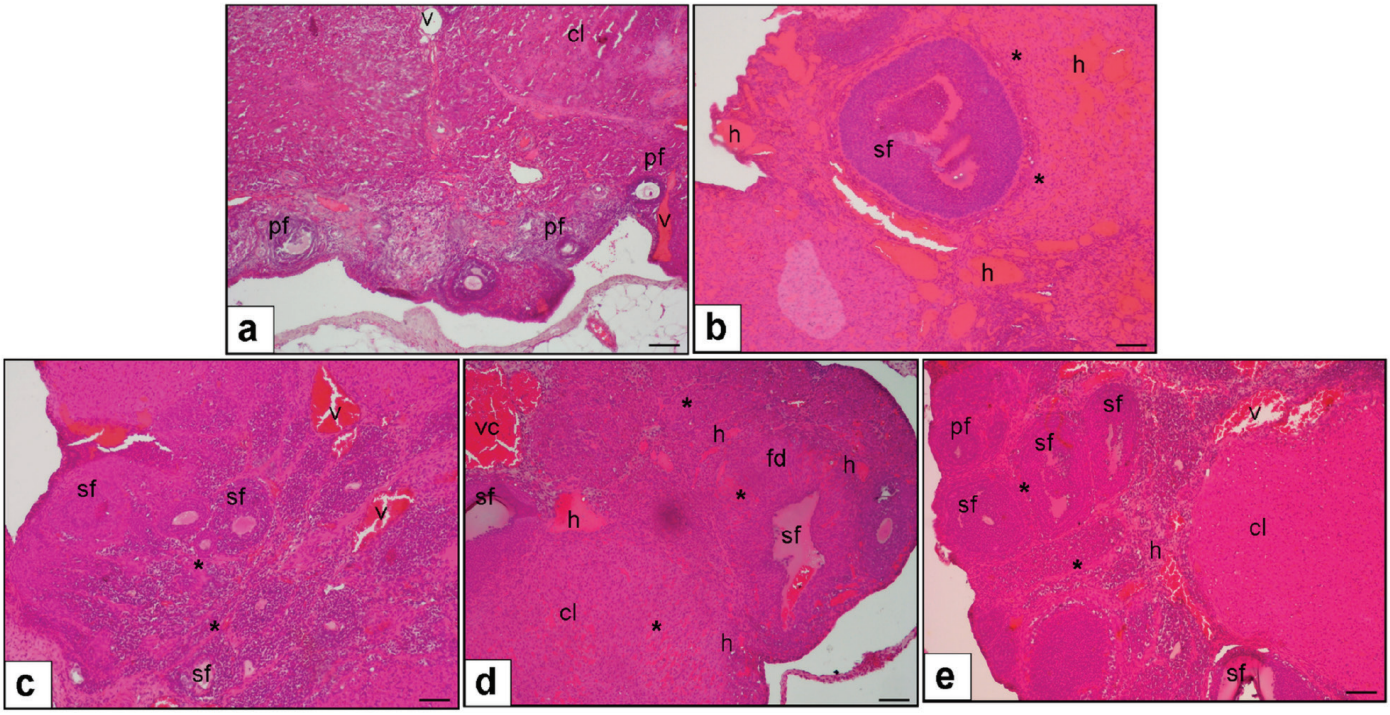

Figure 1. a. No pathologic changes were detected in the sham-operated animals. (v) vessel, (sf) secondary follicle, (pf) primary follicles, (cl) corpus luteum. b. Haemorrhaging (h) and oedema (*) were detected in the 3-h torsion group. c. Decreased vascular congestion (vc), and Haemorrhaging (h) were observed in the torsion and tadalafil group. d. Vascular congestion (vc), haemorrhaging (h), and oedema (*) were observed in the torsion/de-torsion group. e. Decreased oedema (*) and haemorrhaging were detected in the torsion/de-torsion tadalafil group. Haematoxylin and eosin staining was performed. Scale bars represent 250 μm

Table 2. Tissue biochemical parameters in groups

	Group 1	Group 2	Group 3	Group 4	Group 5
MDA, (nmoL/μg protein)	0.06±0.01	0.75±0.21**	0.41±0.15	1.66±0.20	0.29±0.09$^{\#\#}$
L-Lactate Level (mmoL/L)	6.4±0.80	10.7±1.58*	8.72±1.71	21.3±1.66	13.41±1.07$^{\#}$
Plasma cGMP Level (pmol/L)	10.7±1.45	13.7±1.53	29.2±2.7†	17.9±1.6	37.8±5.07$^{\#}$

Group 1: Sham operation, Group 2: Torsion, Group 3: Torsion and tadalafil, Group 4: Torsion/detorsion, Group 5: Torsion/detorsion and tadalafil, *: p<0.05, group 1 vs group 2, **: P<0.01, group 1 vs group 2, †: P<0.01, group 2 vs group 3, #: P< 0.01, group 4 vs group 5, ##: P<0.001, group 4 vs group 5

production is interrupted, which reduces the concentration of ATP in cells. These cells begin anaerobic energy production, increasing the lactic acid content and decreasing the pH level of cells. Arikan et al. (21) previously investigated the effect of tadalafil on IR injury in rat ovaries, and demonstrated decreased MDA concentrations and increased catalase (CAT) and superoxide dismutase (SOD) activities, which are scavenger enzymes for ROS, after using tadalafil (21). Additionally, they observed reduced histopathologic damage in groups that received tadalafil, which led the authors to conclude that tadalafil had a protective effect against IR injury. Similarly, increased MDA and lactate concentrations were ameliorated by tadalafil in our study, and these biochemical findings are supported by the histopathologic results of the tadalafil groups. Another PDE-5 inhibitor, sildenafil, has also been investigated in ovarian IR injury. The authors found changes in MDA, myeloperoxidase (MPO), SOD, glutathione peroxidase (antioxidant enzyme) between treated and untreated groups (22). MPO is secreted by neutrophils and is used as a marker of neutrophil activation in IR injury. These authors observed decreased MDA and MPO concentrations and increased tissue antioxidant enzyme concentrations, as well as an improved histologic appearance, in groups treated with sildenafil (22).

The effectiveness of PDE-5 inhibitors on reperfusion injury in ovaries has been confirmed by two studies (21,22). The investigators demonstrated an antioxidant effect of PDE-5 inhibitors on reperfusion injury. The vasodilator feature of PDE-5 inhibitors also contributes to this effect. Therefore, in the current study, we investigated the vasodilator effect of tadalafil during the ischemic stage and found attenuated vascular damage in the ischemia groups that were administered tadalafil. These findings indicate that tadalafil has a dual function to reduce ischemia and reperfusion damage in the ovary.

A limitation of this study is the absence of long-term observations for both the biochemical and histologic parameters. Thus, future long-term studies should be performed to determine whether the changes in histologic and biochemical parameters are transient or permanent.

The current management of ovarian torsion includes the protection of ovaries after detorsion, and avoids oophorectomy where possible (23). In this situation, prophylactic measures against injury are implemented, which affect ovarian function (24). Sometimes, the diagnosis of ovarian torsion takes time due to its non-specific symptoms. However, prompt diagnosis of ovarian torsion is important to preserve ovarian function. Therefore, the use of tadalafil in patients with suspected ovarian torsion will provide a greater therapeutic benefit than if treatment is only started following ovary detorsion. This treatment resembles the use of acetylsalicylic acid in patients with suspected myocardial infarction in the ischemic stage.

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Can maternal urinary and serum carbohydrate antigen 19-9 concentrations be utilized in the diagnosis of fetal hydronephrosis?

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Abstract

Objective: Fetal hydronephrosis (FH) is the most common fetal renal pathology encountered in daily obstetric practice. Urinary and serum carbohydrate antigen 19-9 (CA 19-9) concentrations are elevated in obstructive renal pathologies. Our aim was to assess maternal urinary and serum CA 19-9 concentrations in pregnancies with FH and compare results with controls.

Material and Methods: Twenty pregnancies with severe FH, 20 pregnancies with mild-moderate FH, and 20 healthy singleton pregnancies were included in this descriptive, case-control study. The diagnosis and classification of FH was based on the anterioposterior diameter of fetal renal pelvis. Maternal urinary and serum CA 19-9 concentrations were measured and compared between groups.

Results: Severe FH cases had significantly higher maternal urinary CA 19-9 concentrations compared to controls (median: 75 vs 24 U/mL; respectively; p=0.014). Concentrations of CA 19-9 did not differ between the mild-moderate FH group and control group. No statistically significant difference was found between the groups with respect to maternal serum CA 19-9 concentrations.

Conclusion: Our results show that maternal urinary CA 19-9 concentration is significantly higher in pregnancies with severe FH. However, no difference was detected in serum CA 19-9 concentrations between pregnancies with severe FH, mild-moderate FH and controls. If the mechanisms of transplacental passage and maternal urinary excretion are clarified, maternal urinary CA 19-9 may be a potential marker for indicating fetal kidney damage. (J Turk Ger Gynecol Assoc 2020; 21: 41-5)

Keywords: Hydronephrosis, pregnancy, CA 19-9

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Introduction

Fetal renal pathologies are frequently encountered in obstetric practice. Fetal hydronephrosis (FH) is the most common antenatally detected renal pathology (1). The severity of hydronephrosis and the need for postnatal treatment are closely associated with the underlying pathology. The most basic and frequently used technique for evaluation of the fetal renal pelvis is the imaging-based measurement from anterior to posterior in the transverse plane. This measurement depends on the operator and is affected by maternal hydration. Furthermore, it does not provide information about renal parenchymal damage (2,3). Given all these factors, the anterioposterior measurement of the renal pelvis has low prognostic value. Other ultrasonographic measures and urinary markers are not sufficient to make an accurate diagnosis and predictive enough for clinically significant FH (4).

Carbohydrate antigen 19-9 (CA 19-9) is a Lewis blood group antigen derivative glycoprotein (5). This antigen is found in the amniotic fluid in high concentrations due to the secretion of amnion and decidual cells (6). In addition to being a tumor marker used in gastrointestinal cancers, this antigen is increased in many benign conditions. Renal epithelium excretes CA 19-9 under physiological conditions. High serum

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and urine concentrations can be detected in patients with severe hydronephrosis (7-9). It has been shown that urinary and serum CA 19-9 can be used as a marker for the diagnosis and management of obstructive renal pathologies (10,11).

This study was based on the hypothesis that increased levels of CA 19-9 could be detected in maternal serum and urine due to increased excretion by the fetus with hydronephrosis. The research aim was, therefore, to evaluate CA 19-9 concentrations in maternal serum and urine in pregnancies with FH.

Material and Methods

Sixty pregnant women who were admitted to the Department of Obstetrics and Gynecology, Manisa Celal Bayar University, between July 2017 and July 2018 were enrolled for this case-control study. Three groups were defined as severe FH, mild-moderate FH and control with each group consisting of twenty cases.

For the diagnosis of mild-moderate hydronephrosis, the criteria of anterioposterior diameter between 4 and 10 mm (second trimester) or 7 and 15 mm (third trimester) were used. Greater than 10 mm and 15 mm were used for the diagnosis of severe hydronephrosis (second and third trimester, respectively) (12). The control group consisted of twenty healthy pregnant women matched for age and gestational age. Obstetric ultrasonography and fetal renal pelvis measurements were performed by a single ultrasonographer with 13 years of experience on grayscale ultrasonography (M.A.). The Health Ethics Board of Manisa Celal Bayar University approved this study (approval number: 20.478.486-23248, date: 28.06.2017). Informed consent was given by all participants and the study was carried out in compliance with the Declaration of Helsinki.

Exclusion criteria were: multiple gestation; any fetal chromosomal or structural anomaly; pregnancies complicated with any type of diabetes mellitus; gestational or pregestational hypertensive disorders; women with inherited thrombophilia, connective tissue disorders, chronic renal or hepatic disease; and history of any proven or suspected malignancy.

A complete obstetric history and demographic data were obtained. Antenatal detailed anomaly scan was performed. Maternal peripheral venous blood and urine samples were collected before 10.00 am following an overnight fast. Store samples tightly stoppered at room temperature and were examined within eight hours. Venous blood samples were centrifuged for 15 minutes at 3000 g. Quantitative measurement of urinary and serum CA 19-9 concentrations was performed using original reagents by a two-region immunoenzymatic immunoassay on the Beckman Coulter Unicel DXI 800 analyzer, [Beckman Coulter, Brea, CA, United States of America (USA)]. The lowest detectable level of CA 19-9 distinguishable from zero with 95% confidence is 0.8 U/mL. This assay exhibits total imprecision of less than 10% across the assay range. One study, using commercially available human serum based control material generating a total of 20 assays, 2 replicates per assay, over 20 days provided 6.4% coefficient of variation for intra-assay precision and 5.7% coefficient of variation for inter-assay precision (13).

Statistical analysis

Statistical Package for the Social Sciences program, version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Distribution of variables was assessed with the Shapiro-Wilk test. Statistical comparisons were performed with the ANOVA test (normally distributed data) and the Kruskal-Wallis test or the Mann-Whitney U test (skewed data). Appropriate post-hoc test was utilized for multiple comparisons between groups (Bonferroni and Dunn's). Chi-square test was utilized for categorical variables. The relationship between the maternal urinary and serum CA 19-9 levels and other parameters were determined with Spearman's rho correlation coefficient. Normally distributed data were reported as mean ± standard deviation, whereas skewed data were presented as median and range. All reported p values are two-tailed. Statistical significance was assumed when the p value was <0.05.

Results

Maternal age, gestational age and fetal gender were not significantly different between groups (Table 1). Male fetuses constituted the majority in all groups (70%, 65%, 65%). Unilateral renal involvement was more frequent in both hydronephrosis groups (80% vs 65%). No statistically significant difference was found for maternal serum CA 19-9 concentrations between the groups ($p=0.353$). However, maternal urine CA 19-9 concentrations were elevated in both FH groups (Table 1 and Figure 1). Post-hoc Dunn's analysis revealed urinary CA 19-9 concentrations were statistically significantly higher in the severe FH group compared to the control group (median: 75 vs 24 U/mL respectively; $U=8.6$, $p=0.014$). There was no significant difference between the mild-moderate and severe FH groups ($p=0.189$). Also, the difference between the mild-moderate FH group and controls did not reach statistically significant level.

To compare the possible diagnostic utility of urinary CA 19-9 for FH, we combined the two FH groups ($n=40$) and compared with the control group ($n=20$) in terms of CA 19-9 levels in urine. The Mann-Whitney U test indicated that urinary CA 19-9 concentrations were significantly higher in all women carrying fetuses with hydronephrosis than for women with normal pregnancies (mean rank: 32.53 vs 21.95, respectively; $U=227$, $p=0.023$) (Figure 1).

As seen in Table 2, the serum and urinary CA 19-9 concentrations were positively and significantly correlated ($r=0.433$, $p=0.001$).

Table 1. Maternal clinical and biochemical characteristics of study groups

	Mild-moderate FH, n=20	Severe FH, n=20	Control, n=20	p
Maternal age (mean ± SD)	27.05±5.5	29.95±6.2	31.1±4.4	0.063[a]
Gestational week (mean ± SD)	24.00±1.9	25.25±2.7	24.55±2.8	0.307[a]
Gravidity (mean ± SD)	1.85±0.9	2.05±1.1	1.90±1.0	0.818[a]
Fetal gender (F/M)	6/14	7/13	7/13	0.928[b]
Affected kidney (B/U)	4/16	7/13	-	0.288[b]
Serum CA 19-9 (U/mL)				
(mean ± SD)	14.4±11.6	19.4±12.3	16.9±8.0	0.353[a]
Urinary CA 19-9 (U/mL)				
(median)	49.00[1-2]	75.002	24.001	0.014[c]*
(range)	1.6-241.0	20.1-485.0	1.0-357.0	

[a]One-Way analysis of variance test was used to compare continuous variables. [b]Chi-square test was used to compare categorical variables. [c]Kruskal-Wallis was used to compare continuous variables. [1,2]: Defined significance between each groups (1<2) (post-hoc test Dunn's). *Correlation is significant at the 0.05 level (2-tailed)
FH: Fetal hydronephrosis, SD: Standard deviation, B: Bilateral, F: Female, M: Male, U: Unilateral, CA: Carbohydrate antigen

Table 2. Correlations between serum and urinary carbohydrate antigen 19-9 levels and the other parameters

	Serum CA 19-9		Urinary CA 19-9	
	r	p	r	p
Maternal age	-0.203	0.12	-0.205	0.125
Gestational age	-0.006	0.966	0.189	0.159
Gravidity	0.089	0.430	0.160	0.220
Fetal gender	-0.185	0.157	-0.077	0.569
Urinary CA 19-9	0.433	0.001*	-	-

*Correlation is significant at the 0.05 level (2-tailed)
CA: Carbohydrate antigen

In addition, maternal serum and urinary CA 19-9 concentrations were not found to be associated with maternal age, gestational age, gravidity or fetal gender.

Discussion

Fetal renal obstruction may be transient or permanent and partial or complete. If the pathological process is persistent in nature, nephrogenic tissue may be affected resulting in cystic dysplasia (14). Therefore, differentiation of renal pathology is important in determining the outcome. Intuitively, FH may be considered as an obstructive pathology. However, in some cases, FH can be the result of non-obstructive processes, such as vesicoureteral reflux or megaureter (15). However, the differentiation may not be possible until delivery. Current diagnostic methods are not adequately predictive to differentiate postnatal clinically significant cases of FH, and in this circumstance, the antenatal management of this condition is challenging and controversial.

Different serum and urine markers have been described for monitoring hydronephrosis and its treatment in children, and utilization of such markers during the antenatal period may be promising in the detection of fetuses requiring treatment (16). CA 19-9 is an antigen of oncofetal origin, produced by amnion cells and decidua. Therefore, the concentration of this antigen in amniotic fluid is high and increases as the gestational period progress (6). Oncofetal antigens may pass from the embryoplacental compartment into the maternal circulation (17). The amount of antigen in maternal circulation depends on factors such as renal function, half-life, molecular weight and protein characteristics. The maternal serum concentration of CA 19-9 is increased throughout pregnancy but does not exceed normal values (0-35.3 U/mL), hence CA 19-9 could be a useful biomarker during pregnancy (18). Maternal serum CA 19-9 levels were found to be significantly higher in primigravidity, female fetus and fetal aneuploidy (19,20). In the current study, groups were homogenous and not significantly different in terms of gestational age, gravidity and fetal gender. Inflammation and persistent obstruction in the kidney can lead to increased concentrations of CA 19-9 in circulation and in urine (21,22). In line with studies indicating increased excretion of CA 19-9 in obstructive renal pathologies, it can be hypothesized that CA 19-9 concentration in amniotic fluid may be higher in cases of FH (10,11). Newborns diagnosed with a posterior urethral valve have been found to show elevated concentrations of CA 19-9 in urine samples taken immediately after birth and high levels were reported to be associated with a poor prognosis (23). In addition, higher concentrations of amniotic fluid CA 19-9 were reported in pregnancies with posterior urethral valves (24). In the light of this information, we aimed to evaluate maternal serum and urine CA 19-9 concentrations in pregnancies with FH.

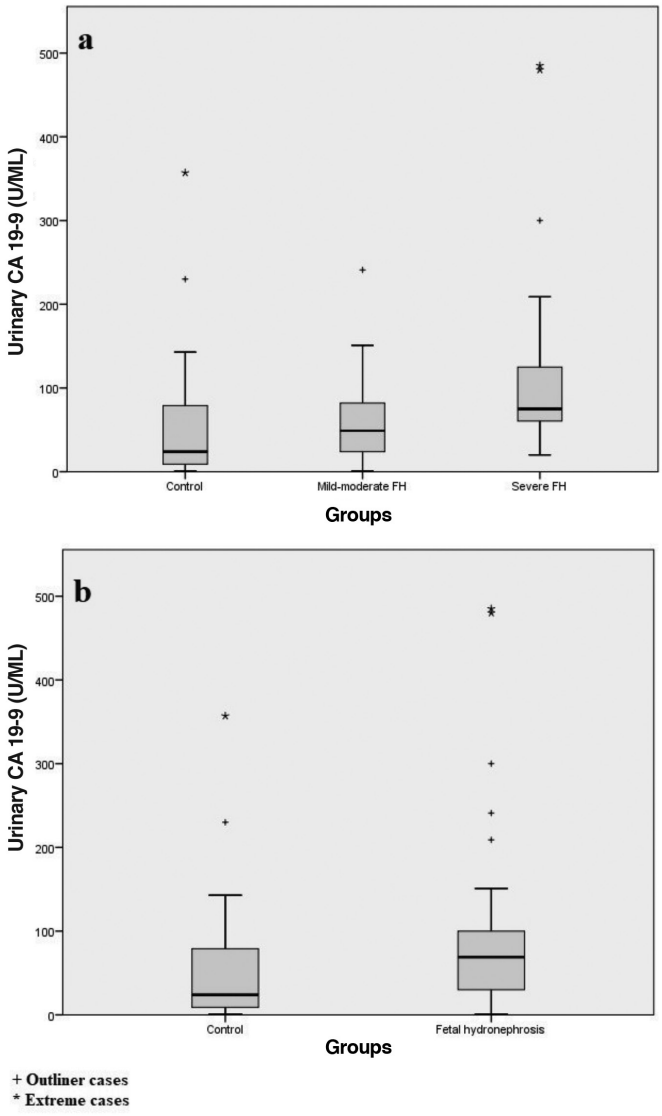

Figure 1. a. Urinary CA 19-9 levels between three groups, b. Urinary CA 19-9 levels between all FH group and controls. Distributions are compared with box plots graphs.

FH: Fetal hydronephrosis, CA: Carbohydrate antigen

In our study, there was a statistically significant difference between severe FH and the control group in terms of urinary CA 19-9 concentration. Our finding was consistent with Kajbafzadeh et al. (25) who reported that CA 19-9 excretion increased significantly in the urine of pregnant women with severe FH. In the current study, the pairwise analysis also revealed an insignificant difference between mild-moderate FH and controls. We did not define a cut-off point for the diagnosis of severe FH because of the small number of cases and skewed distribution. Unspecified maternal renal disease or physiological renal changes due to pregnancy may be the factors affecting urinary excretion of CA 19-9 that led to outlier results and skewed distribution. When we compared the urinary CA 19-9 concentrations between controls and all FH cases (n=40), the difference was still statistically significant. However, the skewed distribution of the data, the very wide ranges of measurements of CA 19-9 even in the control group and insignificant difference between mild-moderate FH and controls make this marker useless to discriminate all FH cases. It was interesting that there was no statistically significant difference between groups for maternal serum CA 19-9 levels. Transplacental passage of CA 19-9 into maternal circulation has been described in previous studies (19,20,26). Our result may be due to the fact that, even though an increased concentration of the antigen may have been present in amniotic fluid it might be eliminated quickly in urine after transplacental passage. Measurement of amniotic fluid CA 19-9 and comparing the results with maternal serum and urine CA 19-9 levels might clarify this fact. Transplacental passage and ultimate maternal urinary excretion of CA 19-9 is intuitive, since, to date, it has not been studied by either in- or ex-vivo studies. Also, the difference in serum concentrations may fail to reach a statistically significant level due to the small sample size in our study. Last but not least, it should be kept in mind that CA 19-9 is not expressed in 7% of people (27). But, elevated levels of CA 19-9 could be found in some pathological conditions regardless of the Lewis phenotype (28). Even so, the unknown Lewis phenotype of mothers nor fetuses would limit the utility of the marker.

The strength of our study was the homogeneity of the groups with regards to maternal age, gravidity, fetal gender and gestational week at sampling. However, our investigation has several limitations. A key limitation was the small number of cases in each group. Although mild FH is not a rare antenatal finding, severe and progressive cases are. In the unilateral FH cases, the diluting function of normal kidney can affect CA 19-9 measurement but due to the small sample size, we could not sub-divide groups further. Another limitation of the study was that amniotic fluid levels of CA 19-9 were not evaluated. Furthermore, cases with progressive hydronephrosis requiring treatment were not identified because of a lack of neonatal outcomes. One future research objective would be to assess the correlation between increased maternal urinary CA 19-9 and neonatal urinary CA 19-9 concentrations.

Conclusion

Our findings suggest that this non-invasive diagnostic method could detect clinically significant severe FH but the descriptive nature of the study prevents us from identifying a clinical significant cut-off concentration for maternal urinary CA 19-9 concentration in FH. Also, there may be many subtle maternal variables affecting urinary excretion of CA 19-9 which may result in high concentrations in maternal urine in the absence of FH, thus interfering with the diagnostic accuracy. It might

be more accurate to improve the ultrasonographic assessment techniques). Therefore, with the available data, we can not make precise comments about the use of CA 19-9 as a reliable diagnostic marker for FH. Further longitudinal and comprehensive studies with much larger sample sizes are needed to identify the clinical significance of maternal urinary CA 19-9 level in cases of FH.

Ethics Committee Approval: *The Health Ethics Board of Manisa Celal Bayar University approved this study (approval number: 20.478.486-23248, date: 28.06.2017).*

Informed Consent: *Informed consent was given by all participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices - M.A.; Concept - M.A.; Design - M.A., F.M.K.; Data Collection or Processing - M.A.; Analysis or Interpretation - F.T., H.Ö.; Writing - M.A., B.A.Ü.*

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The effect of mother-infant skin-to-skin contact immediately after birth on exclusive breastfeeding: a systematic review and meta-analysis

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Abstract

In the new millennium, exclusive breastfeeding plays an important role in national and international policies. The effects of mother-infant skin-to-skin contact (SSC) after birth has been investigated in several studies. Given that there has been no overall estimate of this effects, the present study was conducted with the aim of investigating the effects of mother-infant SSC on the rate of exclusive breastfeeding through a systematic review and meta-analysis of randomized controlled trials. In the present study, the databases of Scopus, PubMed, Cochrane, SID, Magiran, IranDoc, and Google Scholar were searched to identify randomized controlled trials that evaluated the effects of mother-infant SSC immediately after birth on the rate of exclusive breastfeeding. The risk of bias and strength of evidence were examined according to the Cochrane Collaboration's tool and the Grading of Recommendation, Assessment, Development, and Evaluation approach, respectively. The data analysis was performed using Stata software. To assess the publication bias and heterogeneity, Egger's and Begg's tests and I^2 were used, respectively. In addition, the fixed effects model was employed to perform the meta-analysis. The heterogeneity of the factor of effects in the studies was determined as 16.2% ($p<0.303$). There was no publication bias among the studies included; the p values of Egger's and Begg's tests were 0.168 and 0.386, respectively. The effects of mother-infant SSC on exclusive breastfeeding was statistically significant [odds raito (OR)=2.19; 95% confidence interval (CI): (1.66-2); $p<0.001$]. The subgroup analysis results in the normal vaginal delivery group included OR=2.45 [95% CI: (1.76-3.35); $p<0.001$], for the cesarean delivery group the results were OR=1.44 [95% CI: (0.78-2.65); $p=0.24$], the results for the duration of exclusive breastfeeding as of the discharge time up to 3 months were OR=2.47 [95% CI: (1.76-3.48); $p<0.001$], and the results for the 3 to 6 months of exclusive breastfeeding were OR=1.71 [95% CI: (1.05-2.78); $p=0.030$]. The study results showed that mother-infant SSC increased the rate of exclusive breastfeeding. Therefore, this finding could be used by maternal and infant health care providers to develop evidence-based intervention programs. (J Turk Ger Gynecol Assoc 2020; 21: 46-56)

Keywords: Mother-infant skin-to-skin contact, exclusive breastfeeding, systematic review, meta-analysis

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Introduction

Infants are quite vulnerable in the early stages of their life, and due to the higher speed of their growth than at other life stages, it is important that they are provided with sufficient energy, proteins, and other nutrients vital for their future health. Breastfeeding is the most ideal nutrition method at this stage. Hence, breastfeeding plays an important role in formulating national and international policies on general health, child survival, and maternal health, in the new millennium (1-7).

Breastfeeding benefits will be maximized if practiced exclusively in the first 6 months after birth and then continued with supplementary nutrition up to 2 years. However, the reduction in the rate of exclusive breastfeeding is one of the most prevalent and serious problems at the present time. This

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rate is low in many world countries, having also been declining over the past few years in our country. In Iran, according to the Ministry of Health, the rate of breastfeeding has been plunging in recent years, with the exclusive breastfeeding rate having reached 56.8% and 27.9% by the end of the 4th and 6th month, respectively. This fact required the Office of Research and Technology of the Ministry of Health to develop the breastfeeding promotion program as one of the country's research priorities (1,8,9); based on this program, it is required that breastfeeding methods be developed and adopted.

Previous studies have shown that the life environment of infants before, during, and immediately after birth, the measures adopted during pregnancy and after birth, and the hospital policy affect the length of the breastfeeding period. These factors can affect the breastfeeding mechanism and the neonate's primary sucking behaviors, thereby leading to the discontinuation of breastfeeding and a reduction in the exclusive breastfeeding rate (10-12); hence, they are required to be taken into account because the early hours after birth are the most ideal time for a baby to start nutritional behaviors, such as searching and sucking. During this period, most babies respond to the tactile, warm, and olfactory stimuli of their mothers' body and become capable of sucking, and thus they start getting breastfed. Therefore, the early hours after birth are critical for the establishment and continuation of breastfeeding (1,10,13). Research has shown that the separation of the baby from the mother at birth, even for a short time, for the purpose of activities such as the evaluation of the baby, vitamin K injections, as well as the repair of an episiotomy and perineal injuries, could exert negative physiologic effects on the baby, including creating stress and increasing baby crying. As a result, the consumption of stored energy reduces the neonate's success in initiating nutritional behaviors, thereby affecting the stimuli and necessary responses to the development of sucking skills, effective breastfeeding, and the breastfeeding duration (10,13).

The study by DiGirolamo et al. (14) showed that the delay in starting breastfeeding was the major risk factor in the premature interruption of breastfeeding. Hence, skin-to-skin contact (SSC) between the mother and the infant is recommended at the first moments after birth so as to promote breastfeeding. SSC between the mother and the infant is a method in which the naked newborn is placed in the prone position on the mother's bare chest immediately after birth or during the first 24 hours after birth. During mother-infant SSC, the interaction between the mother and infant is enhanced, leading to an increase in the neonate's response to the mother's body stimulation and the development of nutritional behaviors in the baby (15-17).

Most studies have shown that SSC is beneficial for the mother and the baby. Nevertheless, there are conflicting studies on the relationship between mother-infant SSC and breastfeeding. Mahmood et al. (18), Gouchon et al. (19), Marín Gabriel et al. (20), and Vaidya et al. (21) reported that mother-infant SSC immediately after birth increases exclusive breastfeeding significantly. However, in the studies by Moore et al. (32) and Carfoot et al. (22), there was no significant relationship observed between mother-infant SSC and the exclusive breastfeeding rate (13).

Systematic reviews and meta-analyses are essential tools for summarizing the evidence available in a precise, accurate, and reliable manner (23). Despite the fact that several studies have been performed on the effects of mother-infant SSC on exclusive breastfeeding, the contradictory findings of these studies necessitate performing a meta-analysis that provides clear and coherent results and a comprehensive guide for policy makers and researchers. Thus, the present meta-analysis was performed with the aim of investigating the effects of mother-infant SSC immediately after birth on exclusive breastfeeding.

Materials and Methods

In the present systematic review and meta-analysis, all studies on the effects of mother-infant SSC immediately after birth on exclusive breastfeeding were investigated using the following search terms: breastfeeding, breast feeding, lactation, or human milk; SSC, skin-to-skin mother-infant contact, SSC or kangaroo mother care (KMC) methods; KMC; exclusive breastfeeding, breastfeeding exclusivity, and breastfeeding status; and randomized clinical trials, and their Persian equivalents in the electronic databases of SID, Magiran, IranDoc, Scopus, PubMed, ISI Web of science, Cochrane, and Google Scholar from 2000 up to April 2018. In addition, a manual search was performed in the reference section of relevant trials, systematic reviews, and meta-analyses to identify trials missed by the electronic search. The search and selection processes of the trials are shown using the PRISMA flowchart (Figure 1), with the PRISMA checklist used to report the meta-analysis results.

The inclusion criteria were (1) studies with an randomized-control trial (RCT) design, (2) the interventions that consisted of SSC defined as the placing of the naked neonate in the prone position on the mother's bare chest within 10 minutes of birth, (3) the participants consisted of mothers and healthy infants between 37 to 42 weeks of pregnancy, and (4) the primary outcome was exclusive breastfeeding up to six months after birth. There was no secondary outcome included.

To study the selection, first, the abstracts and keywords of relevant articles and their eligibility were examined in view of the inclusion criteria. Secondly, the full texts of the articles were reviewed independently by two authors for eligibility and discussed until consensus was reached.

The risk of bias was examined for each study by two independent evaluators using the Cochrane Collaboration's tool. In the event of a disagreement between the two evaluators, the issue would be resolved by a third researcher. Using the mentioned tool, 6 types of biases were assessed, including selection bias (random sequence generation and allocation concealment), performance bias (examining the blinding of participants and personnel), detection bias (the blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of biases. Based on the degree of each type of bias, the studies were assessed and reported with low, high, and uncertain risks (24,25).

To assess the overall strength of the evidence, the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was adopted.

The extracted data were registered on relevant forms. The two authors extracted data from the full text of the articles independently, based on the data collection form.

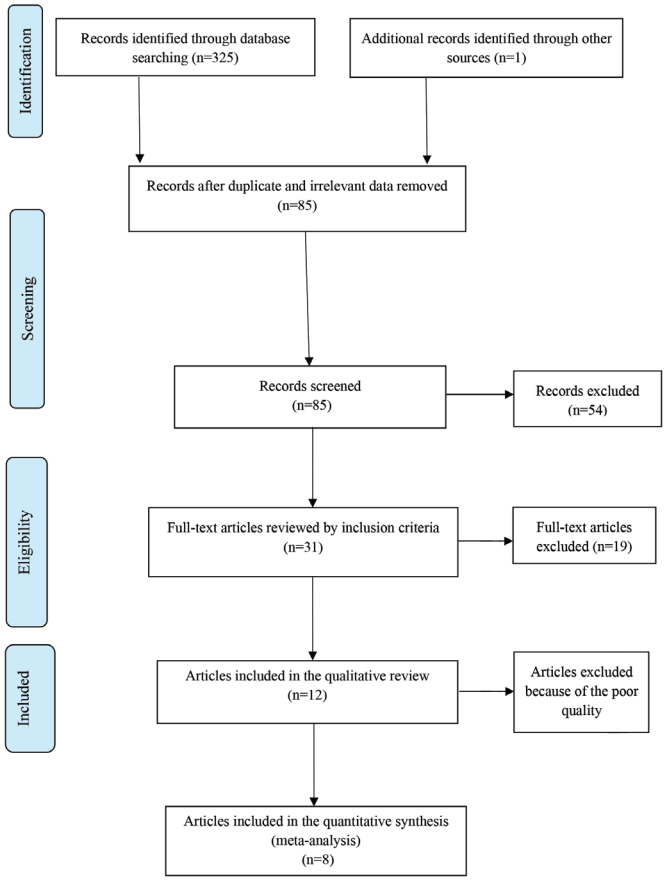

Figure 1. The PRISMA flowchart of the study's selection process

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

The collected data included the authors' names, publication years, study designs, sample sizes, tools, outcomes, and the risks of bias assessment. After data collection, the extracted data were assessed. The data analysis was performed using the STATA 14.1 program. The effect level was calculated as the odds ratio, with the odds of exclusive breastfeeding in the intervention group divided by that of the control group. Next, subgroup analysis was performed based on the type of delivery and duration of exclusive breastfeeding to assess heterogeneity among the studies.

I^2 and its p-value were used to assess heterogeneity among the studies. In addition, a fixed effects model was applied to the pooled data and a meta-analysis was performed. Publication bias among the studies was assessed statistically using Egger's and Begg's tests, and visually using a funnel plot.

Results

In the primary search, 326 articles were obtained, with a total of 12 trials that met the inclusion criteria of the study. Out of the 12 studies, 5 studies were conducted in Iran, 3 India, and the other 4 were conducted in Pakistan, Italy, the United States, and Spain. Exclusive breastfeeding was assessed by asking questions from mothers on the phone or via face-to-face interviews in most studies (n=9). The language of 6 studies was English, and 3 studies were in Persian. The data extracted from the studies included in the meta-analysis are presented in Table 1. The results of assessing the risk of bias in the studies, using the Cochrane Collaboration's tool, are shown in Figures 2, 3.

Publication bias was assessed statistically using Egger's and Begg's tests. The p values of the Egger's and Begg's tests were 0.168 and 0.386, respectively, indicating that no publication bias existed among the studies included. The symmetric pattern of the funnel plot also confirmed the preceding statistical tests visually (Figure 4).

The heterogeneity of the measure of effects among the studies was assessed based on I^2, which was 16.2% ($p<0.303$). However, a random effects model was applied to all calculations because it was assumed that some of the differences between the studies could be factual.

All studies were included in the meta-analysis, which resulted in an odds ratio (OR) of 2.19 with 95% confidence interval (CI) (1.66-2.89), implying that the effects of mother-infant SSC on exclusive breastfeeding were statistically significant ($p<0.001$). The forest plot, the odds ratio, its CI, the corresponding weight of each individual study, the pooled OR, its CI, and the I^2 index are shown in Figure 5.

Next, subgroup analysis was performed based on the type of delivery and periods of exclusive breastfeeding to examine the impact of these two variables on the results (Figures 5, 6). The

Table 1. Features of 12 clinical trials included in study

No	Author year location of the study	Design	Participants	Intervention	Comparison	Dropout rates (%)	Tools	Outcomes
1	Sharma (34) 2016 India	RCT	Two-hundred mother-infant pairs	Mother-infant SSC (n=100)	Routine care (n=100)	0.5	Record breastfeeding status	A significantly higher proportion of neonates was exclusively breastfeed at 6 weeks of age in the SSC group in contrast to the control group (72% vs 57.6%, p=0.04)
2	Khadivzadeh et al. (26) 2016 Iran	RCT	One-hundred fourteen mother-infant pairs	Mother-infant SSC (n=46)	Routine care (n=46)	19.3	Interviews with mothers	The rate of exclusive breastfeeding was significantly higher in the SSC group. There was a significant difference between the two groups in exclusive breastfeeding from birth to day 28 (40.4% vs 20%, p=0.03), and in the last 24-hour report of day 28 after birth (70.2% vs 46.7%, p=0.02)
3	Srivastava et al. (39) 2014 India	RCT	Two-hundred and ninety-eight mother-infant pairs	Mother-infant SSC (n=150)	Routine care (n=148)	10	Direct interviews or telephonic interviews with mothers	At the first follow-up visit (day 4-5), nearly 86.1% of the newborns in the study group were exclusively breastfed whereas only 66.9% of the newborns in the control group received exclusive breastfeeding (p=0.002). Exclusive breastfeeding rates at the 6th week's follow-up visit were 85.2% and 63.6% for the study group and control group newborns, respectively (p<0.0001)
4	Nasehi et al. (38) 2012 Iran	RCT	Hundred and ten women with term babies	Mother-infant SSC (n=54)	Usual post-cesarean breast-feeding (n=56)	0	Patients asked about exclusive breastfeeding	In the follow-up period, 45 individuals (83.3%) of the intervention group and 42 individuals (75%) of the control group had exclusive breastfeeding, with this difference not being significant

Table 1. Continued

No	Author year location of the study	Design	Participants	Intervention	Comparison	Dropout rates (%)	Tools	Outcomes
5	Thukral et al. (40) 2012 India	RCT	Mother-infant pairs n=41	Mother-infant SSC (n=20)	Routine care (n=21)	15	Asked the mothers about the feeding method	EBF[1] rates in 48 hours (95.0 vs 38.1%) and 6 weeks (90 vs 28.6%) were significantly higher in the SSC group than in the control group (p=0.001)
6	Mahmood et al. (18) 2011 Pakistan	RCT	One-hundred and eighty-three mother-infant pairs	Mother-infant SSC (n=92)	Routine care (n=91)	12	IBS[2]	In the SSC group, 85.3% of the infants were exclusively breastfed in one month as against 65.7% in the CC group (p=0.025)
7	Gabriel et al. (20) 2010 Spain	RCT	Three-hundred and fifty healthy mothers with term babies	Mother-infant SSC (n=117)	Routine care (n=113)	34	Telephone calls	Mothers in the SSC group exclusively breastfed babies more frequently upon discharge, but no difference was found in one month of the life
8	Gouchon et al. (19) 2010 Italy	RCT	Ninety-six mother-child pairs	Mother-infant SSC (n=17)	Routine care (n=17)	64	Phone follow-ups	The SSC newborns were attached to the breast earlier (9 SSC newborns and 4 controls after 30 min) were breastfed (exclusively or prevalently) upon discharge (13 SSCs and 11 controls) and in 3 months (11 SSCs and 8 controls)
9	Kamalifard et al. (36) 2010 Iran	RCT	Eighty primipara mothers	Mother-infant SSC (n=40)	Routine care (n=40)	0	Telephone interviews	The mean of the duration of exclusive breastfeeding in the SSC group was 119.8±13.2 days, and in control group, it was 110.75±24 days. The mean difference was statistically significant (p=0.04)
10	Keshavarz and Bolbol Haghighi (35) 2010 Iran	RCT	One-hundred and sixty mother-infant pairs	Mother-infant SSC (n=80)	Routine care (n=80)	0	Telephone interviews	tfeeding up to 6 months (p<0.05) was greater than RC, h (89.3.0 vs 75.3%, p=0.03) 33

Table 1. Continued

No	Author year location of the study	Design	Participants	Intervention	Comparison	Dropout rates (%)	Tools	Outcomes
11	Safarabadi Farahani et al. (37) 2009 Iran	RCT	Hundred mother-infant pairs	Mother-infant SSC (n=50)	Routine care (n=50)	0	Face-to-face interviews	No statistically significant differences was found in duration of exclusive breastfeeding (101.2±27.84 vs 88.7±42.47; P< 0.85) in 4 months)
12	Moore and Anderson (13) 2007 U.S	RCT	Twenty-three mother-infant pairs	Mother-infant SSC (n=12)	Routine care (n=10)	17	IBS	No significant differences was found in breastfeeding exclusivity in one month (1.50±1.1 vs 2.10±2.2; p=0.45)

RCT: Randomized-control trial, SSC: Skin-to-skin contact, [1]EBF: Exclusive breastfeeding, [2]IBS: Infant breastfeeding status

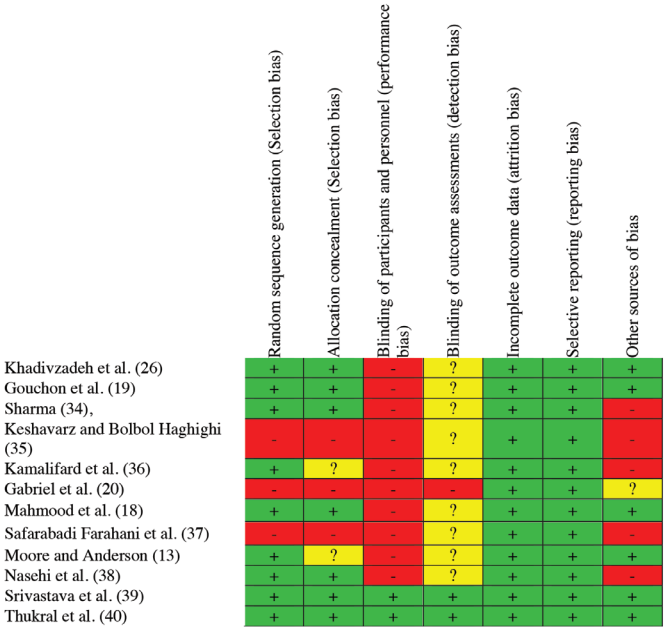

Figure 2. Author's judgments of risk of bias items for each study included

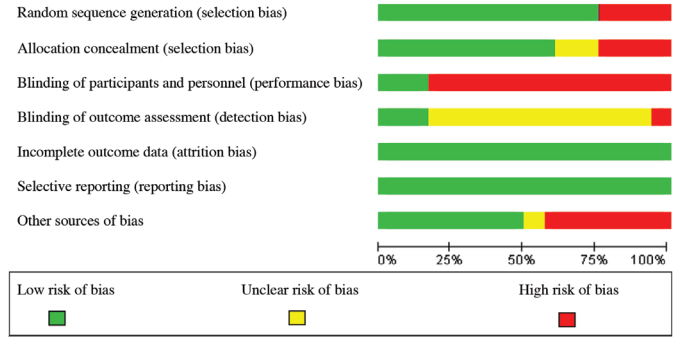

Figure 3. Authors' judgments of risk of bias presented as percentages across all included studies

subgroup analysis, based on the type of delivery, resulted in lower heterogeneity among the studies in the normal vaginal delivery group (I^2=14.9%, p=0.319), yet lower heterogeneity in the cesarean delivery group (I^2=0.0%, p=0.682). However, the measure of the effects OR was 2.45 with a 95% CI (1.76-3.35) for the normal vaginal delivery group and 1.44 with a 95% CI (0.78-2.65) for the cesarean delivery group (Figure 6).

The same pattern was observed when the subgroup analysis was performed based on the duration of exclusive breastfeeding (from the discharge date up to 3 months, as well as 3 to 6 months). In addition, heterogeneity increased in one group (I^2=58.1%, p=0.26) and decreased in the other (I^2=0.0%, p=0.745). Similarly, the subgroup analysis did not change the measure of the effects significantly. The OR values were 2.47 with a 95% CI (1.76-3.48) in the first group, and 1.71 with a 95% CI (1.05-2.78) in the second group (Figure 7).

The sensitivity analysis showed that the restriction of the meta-analysis did not change the results significantly, but improved the quality of the body of evidence evaluated based on the GRADE approach (Table 2).

Discussion

In this systematic review and meta-analysis, 12 RCTs were reviewed that had investigated the effects of mother-infant SSC on exclusive breastfeeding. The results of this meta-analysis indicated that mother-infant SSC had more statistically significant effects on exclusive breastfeeding than routine care. In the analysis of the subgroups performed based on the type

of delivery and duration of exclusive breastfeeding, it was determined that mother-infant SSC had a statistically significant effect on exclusive breastfeeding.

Past research has shown that the life environment of the baby before, during, and immediately after birth, the measures adopted during pregnancy and after birth, and the hospital policy affect the breastfeeding of neonates and are strong predictive factors of the duration of exclusive breastfeeding (26-28). One of the midwifery interventions in hospitals is the separation of the mother from the baby for medical reasons, immediately after birth. The reasons cited by hospitals for isolating the mother from the baby include monitoring the baby quickly after birth to stabilize their physical and medical conditions, preventing mother-to-baby infection transmission, providing more time for the mother's sleep and comfort,

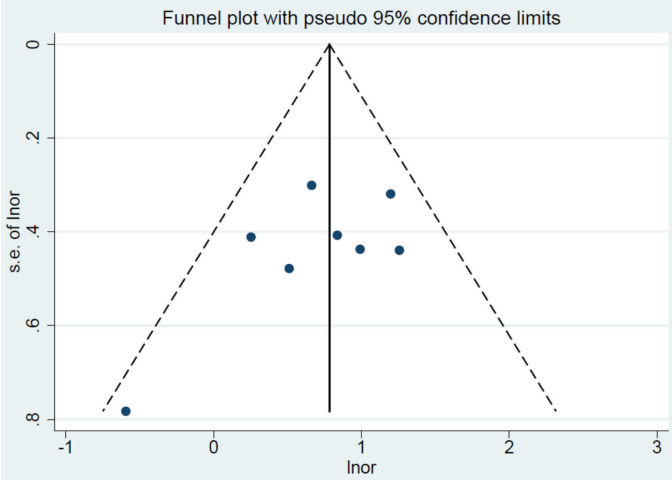

Figure 4. The funnel plot for the publication bias x-axis is the natural logarithm of the odds ratio and the y-axis is the standard error of the natural logarithm of odds ratio

and assessing the baby medically (26). Research in this field showed that the separation of the mother from the neonate after birth could exert adverse effects on the mother and the baby; this could result in reducing the interaction between the mother and the baby, making the baby fail to display nutritional behaviors, causing delays in lactation, reducing the mother's self-esteem and self-efficacy in relation to breastfeeding, impairing breastfeeding, reducing the breastfeeding duration, and finally leading to the use of other foods (1,27,29,30).

To solve the problem, skin contact between the mother and the neonate was introduced, in which the baby was placed on their abdomen in chest-to-chest contact with the mother. The principle of skin contact between the mother and the baby is derived from studies on animals. It has been demonstrated in animal studies that some of the instinctive behaviors seen in neonates are essential for their survival, with the neonates' survival being dependent on close contact with the mother. From the standpoint of ethologists, the early postnatal hours when the fetus is transmitted to the ectopic, undergoing rapid and profound physiologic changes, are critical in the neonate's adaptation in a short time so as to survive. Ethologists believe that the early hours after birth are ideal for starting baby's nutritional behaviors, such as searching and sucking, and are sensitive and critical times for breastfeeding because most babies respond to tactile, warm, and olfactory stimuli of the mother's body. Hence, the separation of the mother and baby immediately after birth could lead to the discontinuation of such instinctive behaviors (31). During SSC, the interaction between the mother and the baby increases, thereby leading to the development of nutritional behaviors that result in the baby's sucking on the mother's breasts and being nourished. It has been reported in relevant research that breastfeeding started

Table 2. The Grading of Recommendation, Assessment, Development, and Evaluation evidence profile for the effects of mother-infant skin-to-skin contact immediately after birth on exclusive breastfeeding for the type of delivery and duration of exclusive breastfeeding

Subgroups	Study results Odds Ratio (95% CI)	Heterogeneity (I^2)	GRADE
Overall	2.19 (1.66-2)	16.20	Moderate: downgraded by one level due to the lack of blinding in most of studies
Normal vaginal delivery	2.45 (1.76-3.35)	14.90	Moderate: downgraded by one level due to the lack of blinding in most of studies
Cesarean	1.44 (0.78-2.65)	0.00	Low: downgraded by one level due to the lack of blinding in most of studies; downgraded by one level due to imprecision
Discharge up to 3 months	2.47 (1.76-3.48)	58.10	Low: downgraded by one level due to the lack of blinding in most of studies; downgraded by one level due to unexplained heterogeneity
3 to 6 months	1.71 (1.05-2.78)	0.00	Moderate: downgraded by one level due to the lack of blinding in most of studies

CI: Confidence interval, GRADE: Grading of Recommendation, Assessment, Development, and Evaluation

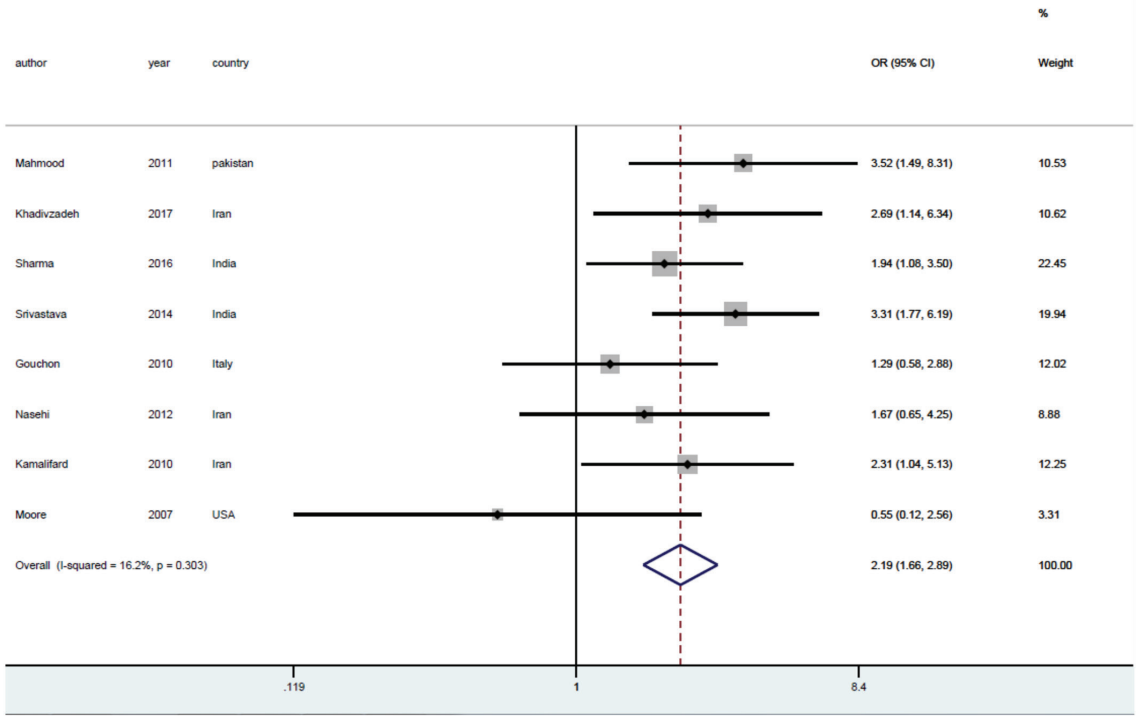

Figure 5. The effects of mother-infant skin-to-skin contact on exclusive breastfeeding based on the odds ratio. The horizontal lines denote the 95% CI, the Square (■) shows the point estimate (the size of the square corresponds to its weight); the diamond shows (◇) the combined overall effects of treatments.

OR: Odds ratio, CI: Confidence interval

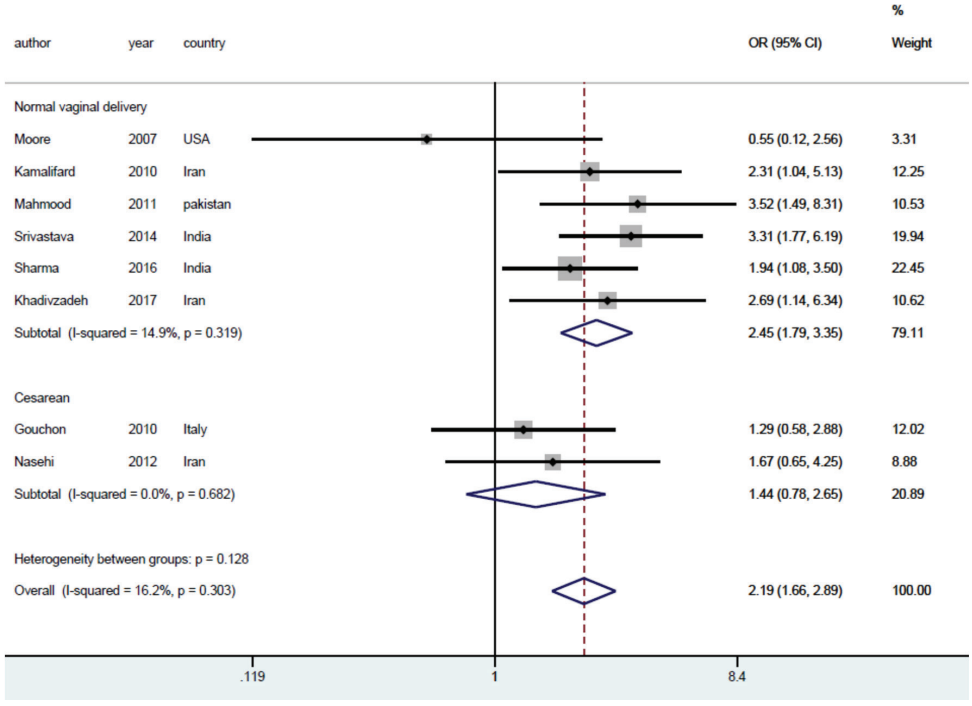

Figure 6. The effects of mother-infant skin-to-skin contact on exclusive breastfeeding based on the type of delivery. The horizontal lines denote the 95% CI, the square shows (■) the point estimate (the size of the square corresponds to its weight); the diamond shows (◇) the combined overall effects of treatments

OR: Odds ratio, CI: Confidence interval

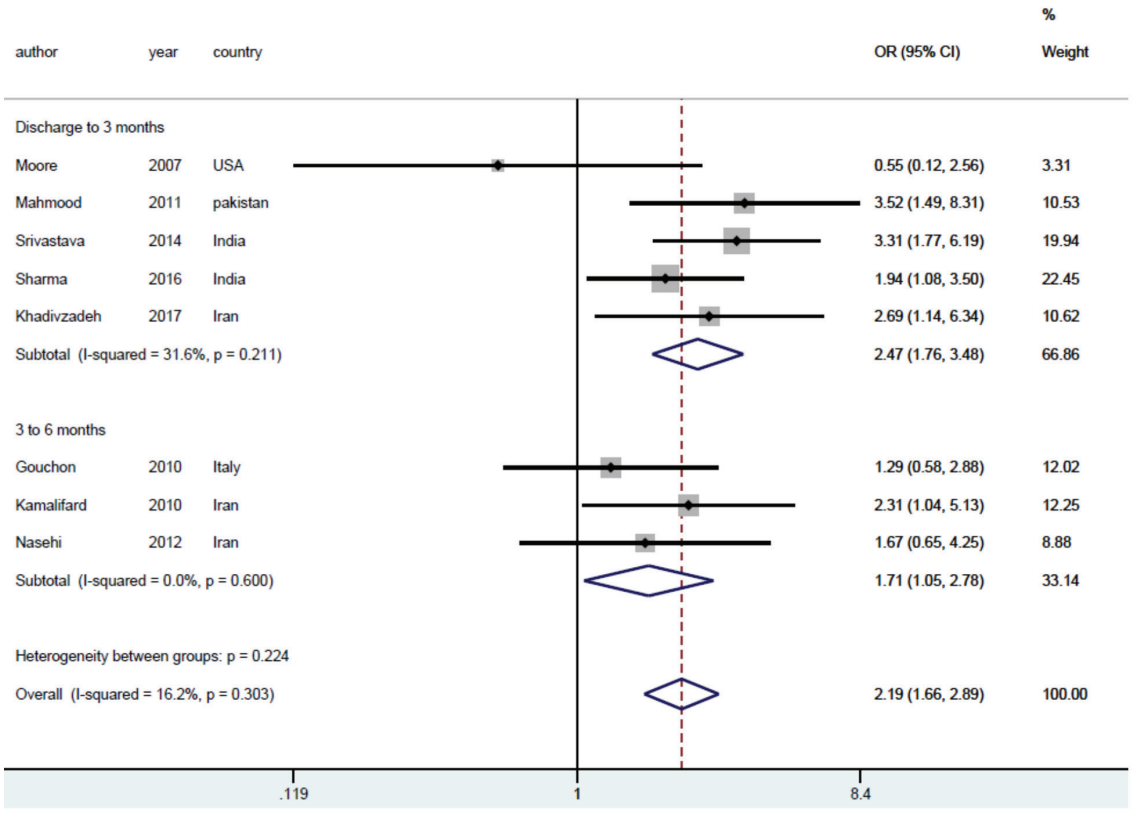

Figure 7. The effects of mother-infant skin-to-skin contact on exclusive breastfeeding based on the periods of exclusive breastfeeding. The horizontal lines denote the 95% CI, the Square (■) shows the point estimate (the size of the square corresponds to its weight); the diamond shows (◇) the combined overall effects of treatment

OR: Odds ratio, CI: Confidence interval

immediately after birth ensures greater continuity. Postnatal skin contact between the mother and the baby is one of the measures recommended by the World Health Organization and UNICEF to increase the rate of breastfeeding because of the importance of this issue and based on the existing evidence (1,13,26,31).

In the same vein, Moore et al. (32) study showed that postnatal skin contact between the mother and the neonate exerted beneficial effects on exclusive breastfeeding. Although this study confirmed the beneficial effects for the mother and neonate, it had some limitations that justified the need for the current study. Some of the limitations included the examining of several different variables in the study that reduced the accuracy of the search, and the non-inclusion of all eligible studies by the data extracted, especially the ones published in Persian, which resulted in a decrease in the input of the final sample size into the meta-analysis and the affect analysis.

Forster and McLachlan (29), in a narrative review, stated that skin contact between the mother and neonate was one of the ways of boosting breastfeeding. In fact, the study by Foster was merely a literature review. By contrast, the present study is a systematic and meta-analytic review; this type of study provides the best evidence for judging the impact of interventions in medicine and their use in clinical settings.

Given that exclusive breastfeeding can provide specific nutrients, both in quality and quantity for the neonate by the end of the 6th month after birth, it provides all the neonate's nutritional needs necessary for normal development. In addition, given that the reduction in the exclusive breastfeeding rate is one of the major public health problems (33), the need for identifying ways of establishing and maintaining exclusive breastfeeding is evident. In this regard, according to the results of the present study, the postnatal skin contact of the mother and neonate could increase the exclusive breastfeeding rate. It is suggested that contact between the mother and baby be adopted as a care method by maternal and child health care providers, such as midwives, doctors, and students responsible in childbirth (34-40).

One of the strengths of the present study is that it is the first systematic and meta-analytic review study in Iran to

investigate the effects of postnatal mother-neonate skin contact on exclusive breastfeeding. One of the limitations of this study is the quality of the studies included in terms of their methodologies. Thus, it is recommended that clinical trials be performed using more qualitative methodologies to obtain more positive evidence.

Conclusion

The articles reviewed in this systematic review and meta-analysis showed that mother-infant SSC increased the exclusive breastfeeding rate. Thus, contact provides the best postnatal care for neonates. In spite of the evidence provided and the benefits of close postnatal contact between the mother and baby, this is not practiced satisfactorily in Iran. In addition, in many cases, the mother and neonate are separated after birth to perform conventional hospital practices, which seems to play an important role in causing lactation disorders. Perhaps this is the reason why, despite the benefits of exclusive breastfeeding in the first 6 months after birth, exclusive breastfeeding rates have declined in our country over the past few years. Thus, the results of the present study could be used in evidence-based decision-making by policy makers and service providers in the field of maternal and child health care as a guide for increasing the exclusive breastfeeding rate.

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

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This article will be credited by TMA within the scope of CME/CPD.

The International Urogynecological Association/ International Continence Society classification of complications of prosthesis and graft insertion: Pros and cons and a review of the literature

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Abstract

International Urogynecological Association (IUGA) and the International Continence Society (ICS) and the Joint IUGA/ICS Working Group on Complications Terminology formulated a standardized terminology and classification of complications related to the use of prosthesis in female pelvic floor surgeries. It was mainly purposed to globally standardize the complications and related definitions in order to obtain factual rates and to enable comparisons and surgical audits. Although this unique classification has frequently been cited in the literature, some concerns have been raised against its complexity of use and inter- and intraobserver variability. This review aimed to discuss the rationale behind the IUGA/ICS complication classification system, underline the opposing views, and provide the Turkish version of an online calculator facilitating the universal coding to increase the utility. (J Turk Ger Gynecol Assoc 2020; 21: 57-61)

Keywords: Calculator, complications terminology, female pelvic floor surgeries, graft, prosthesis

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Introduction

The International Urogynecological Association (IUGA) and the International Continence Society (ICS) and the Joint IUGA/ICS Working Group on Complications Terminology formulated a standardized terminology and classification of complications related to the use of prosthesis in female pelvic floor surgeries (1). This classification system is the first attempt to systematically classify the related complications. It was mainly purposed to globally standardize the complications and related definitions in order to obtain factual rates and to enable comparisons and surgical audits. Although this unique classification currently has over 150 citations (https://citations.springer.com/item?doi=10.1007/s00192-010-1324-9, data received at 11/02/2019), some concerns has been raised against its complexity of use and inter- and intraobserver variability (2,3). This non-systematic review aimed to discuss the rationale behind the IUGA/ICS complication classification system, underline the opposing views, and provide the Turkish version of an online calculator facilitating the universal coding to increase the utility (Supplement).

Rationale

Mid-urethral sling is the gold standard and the most common surgical procedure to treat stress urinary incontinence (SUI) with a proven superiority over other surgical procedures (4). Although mid-urethral slings exhibit a good safety and effectivity profile, a safety concern has been raised globally against the vaginal use of mesh, particularly to treat pelvic organ prolapse. The use of synthetic mesh has statistically decreased between 2011 and 2013 after the second United States Food and Drug

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Administration Public Health Notification; however, the number of mesh revision surgeries increased by almost three-fold from 2007 to 2013 (5).

A recent meta-analysis consisting of 28 randomized controlled trials (RCTs) and 15,855 patients showed that patients who received mid-urethral sling had higher overall and objective cure rates than those who underwent Burch colposuspension (4). The latest Cochrane systematic review assessing mid-urethral slings for SUI determined that major complications such as nerve, bowel or major vascular injuries, pelvic haematoma, necrotizing fasciitis, ischiorectal abscess, and death were found to be uncommon in mid-urethral slings (6). Bladder perforation, reoperation, urinary retention, pelvic haematoma, infection, vaginal tape erosion/extrusion and groin pain occurred in 3.9%, 2.4%, 1.6%, 1.9%, 0.7%, 1.5% and 0.4% of women underwent to retropubic tape procedure, respectively. Those rates were 0.4%, 2.2%, 0.5%, 0.5%, 0.6%, 0.4%, and 1.6% for transobturator tapes (6). Another large population-based retrospective series consisting of 95,057 women was recently published (7). Women who had their first mid-urethral sling procedure to treat SUI were included and followed for 5.5 (interquartile range, 3.2-7.5) years. They found that the rate of mesh sling removal was 1.4% at 1 year, 2.7% at 5 years, and 3.3% at 9 years. The rate of all reoperations was found as 2.6%, 5.5%, and 6.9%, at 1, 5, and 9 years, respectively. By contrast, the recent largest study of vaginal mesh in the treatment of SUI including 92,246 women, revealed that almost one out of every ten patients experienced a complication within 5 years of the initial mesh surgery (8). Among those, rate of complications have risen during the surgery and in the first month were found as 2.4% and 1.7%, respectively.

It has been argued that RCTs designed for long-term follow-up possess limited information about whether there was a hidden cache of serious adverse effects that might have been set against the benefits of curing incontinence (6). Many reporting systems belonging to the major registries were characterized by passive surveillance systems limited by the inclusion of the potential submission of incomplete or inaccurate data, under-reporting of events, lack of denominator data, and the lack of report timeliness) (6).

Due to the inconsistent and increasing reports of complication rates, the IUGA and ICS proposed a well-detailed but inclusive classification system of complications related to the use of all types of prostheses including meshes, implants, tapes, and grafts in female pelvic floor surgery (1).

Classification system and coding

The IUGA/ICS system was developed to cover all possible physical complications, including trocar-related insertion complications and healing abnormalities. The classification system depends on three main factors: Category (numeric) and division (letter), Time (numeric + letter), and Site (numeric + letter), respectively, and all together, this is called the cheque truncation system (CTS). “Category” refers to the general description of the complication such as the degree or extent of erosion (according to former usage), affected site or the condition of the patient. “Division” refers to four common major complication types: A-Asymptomatic, B-Symptomatic, C-Infection, D-Abscess. “Time” describes the duration between the surgery and clinically diagnosed complication. “Site” describes the localization of the complication. One can obtain a code of 3 letters and 3 numerals after classification (e.g. 2B/T3/S1) (Figure 1). The only sub-group reflects “pain” according to the vaginal examination and/or anamnesis. Pain adds a lower case next to the division (e.g. 2Bc/T3/S1, if a patient expresses pain during sexual intercourse).

One of the main prominent features in the newly proposed joint terminology is that the term erosion is not favoured. Mesh inherently interacts with adjacent tissue. Therefore, it is replaced by terms of vaginal epithelium separation, exposure, extrusion, contraction, prominence, and sinus tract formation. Additional new terms include compromise, perforation, and dehiscence (1). Although exposure can simply be described as visible or palpable mesh through separated epithelium (mainly the vaginal wall) in the early period, extrusion represents a subsequent delayed process by which mesh protrudes gradually out of a body structure or adjacent tissue such as the vagina, bladder, and urethra. Perforation frequently refers to perioperative events. In addition, the classification system has dynamic characteristics. Naturally, multiple complications may occur in the same patient at the same time or over a period of time and all should be reported separately (1).

The boundaries of the CTS system include not covering the urinary tract infections, functional issues (e.g. voiding dysfunction), intraperitoneal adhesions and prion or viral infection of a xenograft. Secondly, recurrence is not situated in the CTS system because recurrence is not counted as a complication. Those exclusions are probably postulated to be not directly related to the insertion of prosthesis. Lastly, complications linked to the bulking agents are also not included.

Literature and opposing views

Petri and Ashok assessed the applicability of the IUGA-ICS classification by retrospectively analysing 359 patients who underwent surgical management due to a complication directly related to insertion of a synthetic sling and classified each complication according to the new IUGA-ICS classification using an online calculator (https://www.ics.org/complication). Although they found that the new classification

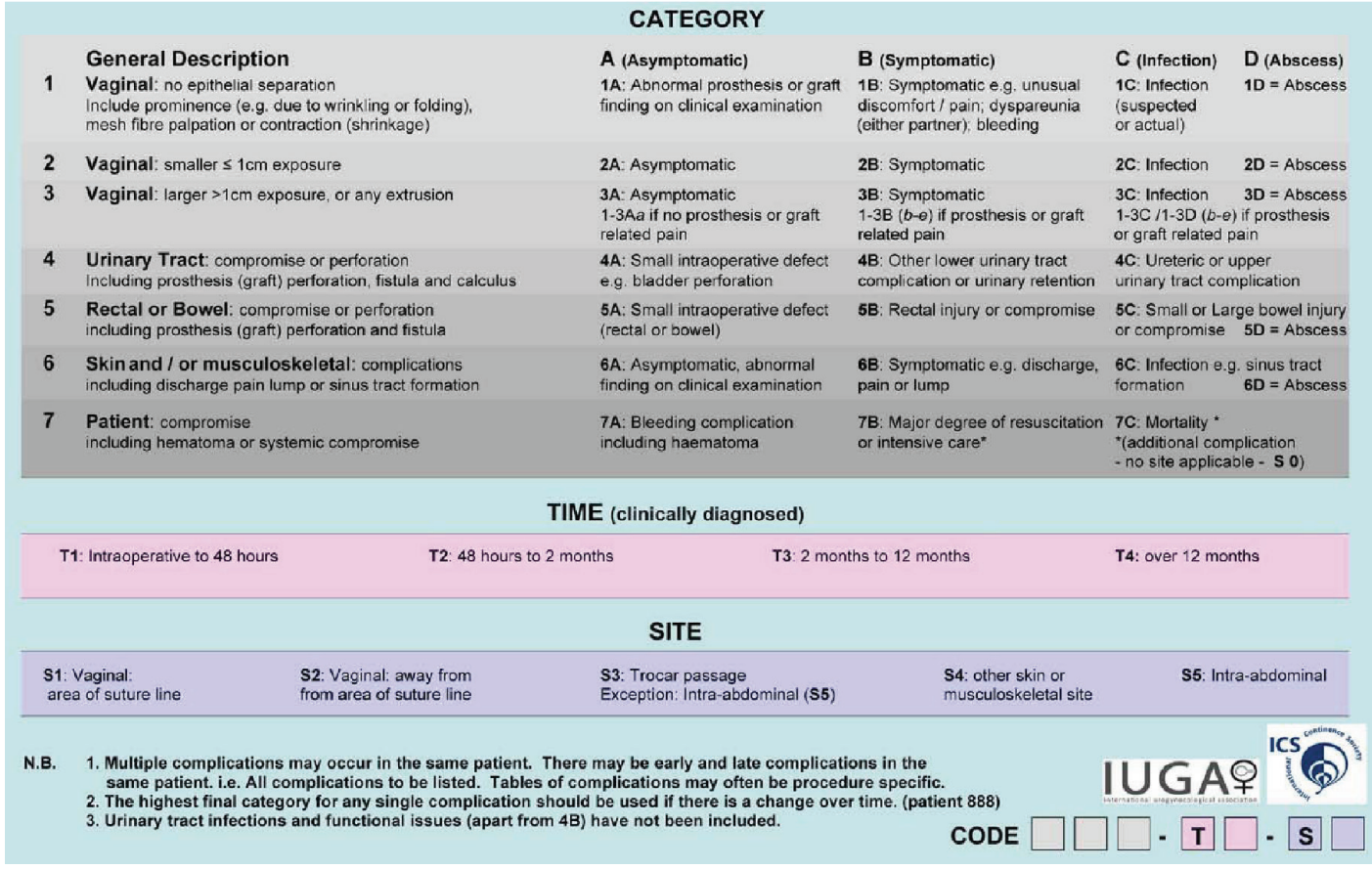

Figure 1. The IUGA/ICS classification system of complications of prosthesis and graft insertion[1]

IUGA: International Urogynecological Association, ICS: International Continence Society

system had good general applicability, it was inadequate to classify overactive bladder (OAB), which was accounted as the most common complication with a rate of 54% (n=193). Lower urinary tract obstruction requiring resection or cutting the sling was the second most common complication at 48% (n=174). This complication was classified as 4B; however, the authors could not state the "Site". Except those two, the CTS system was beneficial in classifying most of the rare and common complications. Along with including OAB and sub-classifying 4B, Petri and Ashok also recommended some other rare complications to be labelled as miscellaneous such as dyspareunia of the partner, urine loss during intercourse, and foreign body sensation in the vagina.

In 2015, Miklos et al. (9) analyzed mesh complications among women who had undergone pelvic floor reconstructive surgery with mesh including sub-urethral mesh slings, transvaginal synthetic mesh, and sacrocolpopexy in their multi-centre retrospective study. A total of 445 patients were included from three tertiary urogynecological referral centers. Unlike Petri and Ashok, all of the complications that mainly consisted of complicated and often recurrent cases were possible to be classified using the IUGA-ICS classification system in their study.

Tunitsky et al. (2) retrospectively analyzed 1236 patients and identified 133 eligible patients presenting after pelvic organ prolapse or incontinence surgery with 195 mesh-related complications in their study to assess the interrater reliability of the IUGA-ICS classification. The complications were classified by 2 independent reviewers using the ICS/IUGA classification system. They observed low agreement at 44.09% on vaginal complications (categories of 1A-3D), high agreement on urologic (96.1%, categories of 4A-4C) and bowel complications (100%, categories of 5A-5C). The authors claimed that 2.2% of the complications could not be classified into any organ/severity categories, and the "Site" of the complications could not be located in 38% due to the lack of clarity of the IUGA-ICS classification. Interestingly, they also observed low agreement on "complication time" and "complication site" between the two independent reviewers with 47.6% and 29.7%, respectively. Tunitsky et al. (2) suggested that complications might be classified by symptom and intervention rather than the physical findings. For example, they argued that Category 5, which was

designated for bowel complications, did not cover defecatory dysfunction. Although that proposal would probably increase the complexity of the classification system, we believe that Tunitsky et al. (2) might have a point, particularly in pelvic organ prolapse surgeries, but not necessarily in anti-incontinence procedures (10,11). We were able to explain all complications using the CTS system after insertion of old- and new-generation mid-urethral slings to treat USI.

The feasibility and the difference of the complication system between prolapse and anti-incontinence surgeries was assessed in a single-centre retrospective study that used a wide range of surgical kits (12). The most frequent complications varied with the type of the surgery, which were found to be bladder outlet obstruction for vaginal sling-plasty, and pain for prolapse surgery. The affected site also differed between them, but the time remained statistically similar. The authors commented that using the CTS code might provide a quick overview of patients' major findings in a more general way; however, the complication classification system needed to evolve in a such way that it covered functional disorders (e.g. urgency, constipation, and dyschezia) given that 17.32% (n=31/179) of the patients presented with only functional problems in their study.

Following the assertion of poor interrater reliability of the IUGA-ICS classification, Gowda et al. (3) had similar results in their study that stratified interobserver reliability by stage of training. It should be noted that the authors stated their study was underpowered and had sampling bias. As a response to studies showing poor interrater and interobserver reliability, the original authors ran the hypothesis that the poor reproducibility was because of imperfect study designs and that the reliability could be strengthened through optimized training prior to use of the CTS IGAU/ICS complication classification system. Haylen et al. (13) achieved excellent interobserver reliability (93%) with no significant differences among 39 respondents after giving structured instructions supported by photos and quizzes, even though the participants were under time pressure and had no access to the online calculator.

Batalden et al. (14) assessed the retrospective applicability of the IUGA/ICS classification system. The authors only included complications with mesh erosion and the newly expanded definitions consisting of contraction, prominence, separation, exposure, extrusion, perforation, dehiscence, and sinus tract formation. They observed that the classification did not predict the treatment or outcome of the complication, and 30% of the mesh erosions could not be retrospectively coded with the CTS system. However, it was mainly due to missing information that did not exist in the clinical documentation or operative reports.

Bontje et al. (15) specifically assessed the complications of patients who consecutively underwent vaginal prolapse repair using mesh. The authors were able to code 43 complication from 39 patients out of 107 (36.45%). They stated that the classification system was found to be generally successful, but only needed to expand the coverage such as the need of reoperation, the duration of the impact of the complication, and severity of bleeding. In a small scaled retrospective study with 57 patients, Hammett et al. (16) drew attention to the rate of the resolution of symptoms after mesh removal. They showed that the complete resolution or improvement rate was 57.3% with the use of the IUGA/ICS classification system.

Conclusion

The IUGA/ICS complication classification system is one of a kind and the first universal classification coding system facilitating the standardized data accumulation and surgical audit specifically for vaginal prostheses. The system can be enriched and strengthened by covering urinary functional problems. Although gaining a prompt and deep insight into the CTS system seems difficult, the online calculator can accurately simplify classification. We believe that the complications' classification system should be increasingly used to achieve an objective and international agreement. This may allow to standardize documentation, leading to a more accurate assessment of complications and their severity.

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Supplement

ICS/IUGA Protez-Greft Komplikasyon Sınıflandırılması*
https://www.ics.org/complication

KATEGORİ

1. Vajinal: Epitelyal ayrılma yok,
- Vajinal çıkıntılar (buruşma veya katlanma gibi), meş lifinin palpasyonu veya kontraksiyonu (büzüşmesi) dahil.
2. Vajinal: ≤1 cm dışarı çıkma,
3. Vajinal: >1 cm dışarı çıkma (veya herhangi ekstrüzyon olması).
4. Üriner trakt:
- Herhangi bir kötüleşme veya perforasyon. Perforasyon, fistül ve taş (kalkül) dahil.
5. Rektum veya barsak:
- Herhangi bir kötüleşme veya perforasyon. Greft perforasyonu ve fistül dahil.
6. Deri ve/veya kas-iskelet:
- Akıntı, ağrı, şişkinlik (topaklaşma) veya sinüs traktı oluşumu.
7. Hastada kötüye gidiş:
- Hematom veya sistemik kötüleşme dahil.

1. BÖLÜM (kategori 1)

A. Anormal protez (meş veya greft),
- Klinik muayenede meşe dair herhangi bir anormallik.
B. Semptomatik,
- Örneğin; alışılmadık rahatsızlık hissi/ağrı; disparoni (partnerde de olabilir); kanama.
C. Enfeksiyon varlığı veya şüphesi,
D. Apse.

2. BÖLÜM (kategori 2, 3)

A. Asemptomatik,
B. Semptomatik,
C. Enfeksiyon,
D. Apse.

3. BÖLÜM (kategori 4)

A. Küçük intraoperatif defekt,
- Örneğin; mesane perforasyonu.
B. Alt üriner trakt,
- Diğer alt üriner trakt komplikasyonu veya üriner retansiyon.
C. Üretere veya üst üriner trakta ait.

4. BÖLÜM (kategori 5)

A. Küçük intraoperatif defekt,
- (Rektal veya bağırsak).
B. Rektal hasar veya kötüleşme,
C. Küçük veya büyük bağırsak hasarı veya kötüleşme,
D. Apse.

5. BÖLÜM (kategori 6)

A. Asemptomatik,
- Klinik muayenede anormal bulgu.
B. Semptomatik,
- Örneğin; akıntı, ağrı veya şişkinlik (topaklaşma).
C. Enfeksiyon,
- Örneğin; Sinüs traktı oluşumu.
D. Apse.

6. BÖLÜM (kategori 7)

A. Kanama,
- Hematom dahil.
B. Majör resüsitasyon veya yoğun bakım ihtiyacı,
C. Mortalite.

AĞRI

Sınıflandırılamayan;
A. Asemptomatik veya ağrı yok,
B. Uyarılma ile ağrı,
- (Vajinal muayene esnasında).
C. Cinsel aktivite sırasında ağrı,
D. Fiziksel aktivite sırasında ağrı,
E. Spontan ağrı.

SÜRE

T1: İntraoperatif-48 saat,
T2: 48 saat-2 ay,
T3: 2-12 ay,
T4: >12 ay.

YER

S1- Vajinal: Sütur hattı boyunca,
S2- Vajinal: Sütur hattı alanından farklı bölgede,
S3- Trokar geçiş hattında (batın içi hariç),
S4- Diğer deri veya kas-iskelet alanları,
S5- Batın içi.

NOTLAR

1. Aynı hastada birden fazla farklı komplikasyonlar görülebilir. Aynı hastada erken ve geç komplikasyonlar görülebilir. Bütün komplikasyonlar belirtilmelidir. Komplikasyonlar tablosu uygulanan prosedüre spesifik olmalıdır.
2. Bir kçomplikasyona ait zaman içinde bir değişiklik görülürse en büyük final kategorisi not edilmelidir.
3. Üriner trakt enfeksiyonları ve fonksiyonel problemler (4B haricindeki) dahil edilmemiştir.

TANIMLAR

Çıkıntı: Yüzeyden dışarı uzanma (örneğin; epitelyal ayrılma olmadan buruşma veya katlanma sebebiyle).

Kontraksiyon: Büzüşme veya boyutta küçülme.

Eksposure: Açığa çıkması, görülebilir veya ulaşılabilir hale gelmesi (örneğin; meş ekstrüzyonu).

Ekstrusion: Bir vücut parçası veya doku boyunca parça halinde dışarı çıkması, yürümesi.

Reference

Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. Neurourol Urodyn 2011; 30: 2-12.

What is your diagnosis?

A para 4, 35-year-old woman with 3 living issues and farmer by occupation presented to our hospital with symptoms of acute urinary retention for which an indwelling urinary catheter was inserted. There were no associated symptoms of hematuria, frequency, urgency or burning micturition. She also had a history of progressively increasing lump abdomen for past 6 months with dull aching pain. The patient gave a history of having undergone laparotomies twice during her childhood for a liver pathology, but she was unaware of the actual diagnosis. No records were available.

A physical examination revealed a 10x8 cm cystic abdominal mass in the left lumbar region. The mass was freely mobile and non-tender. There was another large abdomino-pelvic lump corresponding to 18-20 weeks' gestation, cystic, mobile from side to side, non-tender, and the lower border could not be discerned. A per vaginal examination revealed a normal-sized uterus with a large 10x15 cm cystic mass felt through the right and posterior fornix.

Ultrasound revealed two large multi-septated cystic lesions on the right and left side reaching up to the epigastrium with multiple small cysts seen in both masses with no increase in vascularity, no solid areas, and no free fluid in the abdomen (Figure 1).

Contrast-enhanced magnetic resonance imaging (MRI) showed non-enhancing peritoneal and omental-based clusters of non-loculated cystic lesions in the mid abdomen (14x11x11 cm), in the left iliac fossa (6x7x7 cm), and in the pelvis (13x10x10 cm) with multiple small cysts within (Figure 2).

The patient was planned for a laparotomy. Intra-operatively, the uterus was normal size. A 10x15 cm clear cyst was seen arising from the left ovary with multiple small cysts with viscous pale, yellow fluid inside them. A similar 2x2 cm cyst was seen arising from the right ovary, and a 20x10 cm cyst and a 5x6 cm cyst were seen arising from the greater omentum (Figure 3). Total abdominal hysterectomy with bilateral salpingo-oophorectomy with omental cyst excision was performed.

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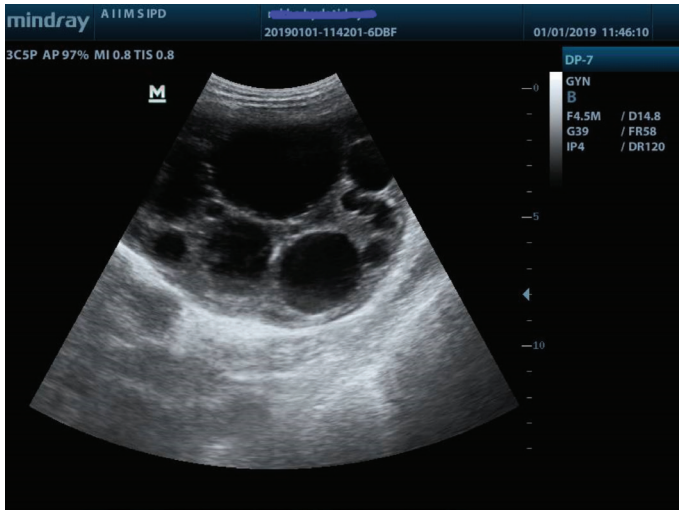

Figure 1. Ultrasonography pelvis showing multiseptated cystic lesion with multiple small cysts within both adnexae

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Table 1. World Health Organization classification of cystic echinococcosis and treatment stratified by cyst stage

WHO stage	Description	Stage	Size	Preferred treatment	Alternate treatment
CE1	Unilocular unechoic cystic lesion with double line sign	Active	<5 cm	Albendazole alone	PAIR
			>5 cm	Albendazole + PAIR	PAIR
CE2	Multiseptated, "rosette-like" "honeycomb" cyst	Active	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE3a	Cyst with detached membranes (water-lily sign)	Transitional	<5 cm	Albendazole alone	PAIR
			>5 cm	Albendazole + PAIR	PAIR
CE3b	Cyst with daughter cysts in solid matrix	Transitional	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE4	Cyst with heterogeneous hypoechoic/ hyperechoic contents; no daughter cysts	Inactive	Any	Observation	-
CE5	Solid plus calcified wall	Inactive	Any	Observation	-

Albendazole is dosed 10 to 15 mg/kg per day in two divided doses; the usual dose for adults is 400 mg twice daily. Duration of therapy is discussed in the text.
WHO: World Health Organization; CE: Cystic echinococcosis; PAIR: Puncture, aspiration, injection, reaspiration

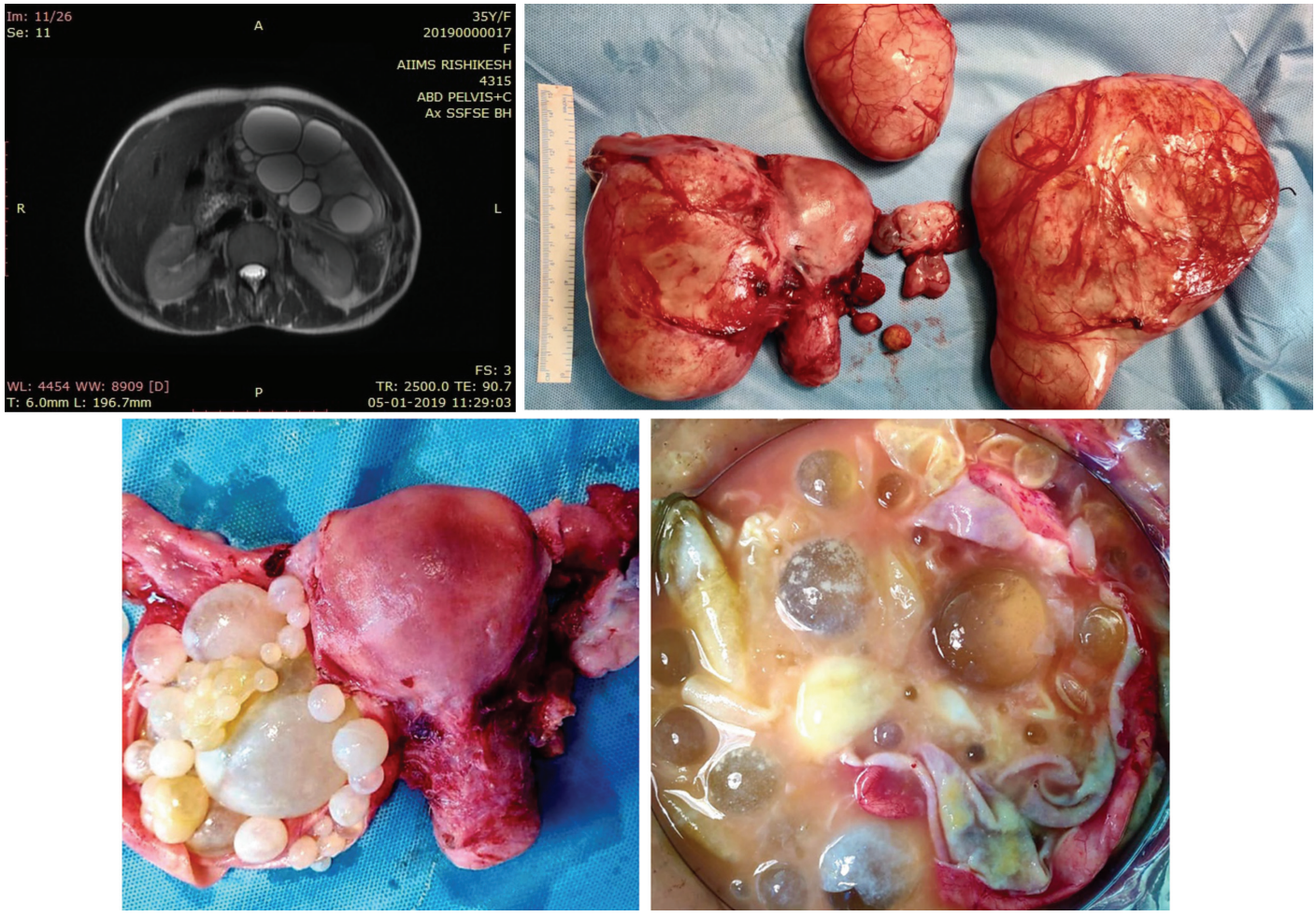

Figure 2. T2-weighted magnetic resonance imaging image showing smooth walled clusters of fluid signal cystic lesion in the pelvis with clusters of multiple tiny fluid signal cysts. Intra-operative finding showing multiple fluid filled cysts in the ovary and omentum

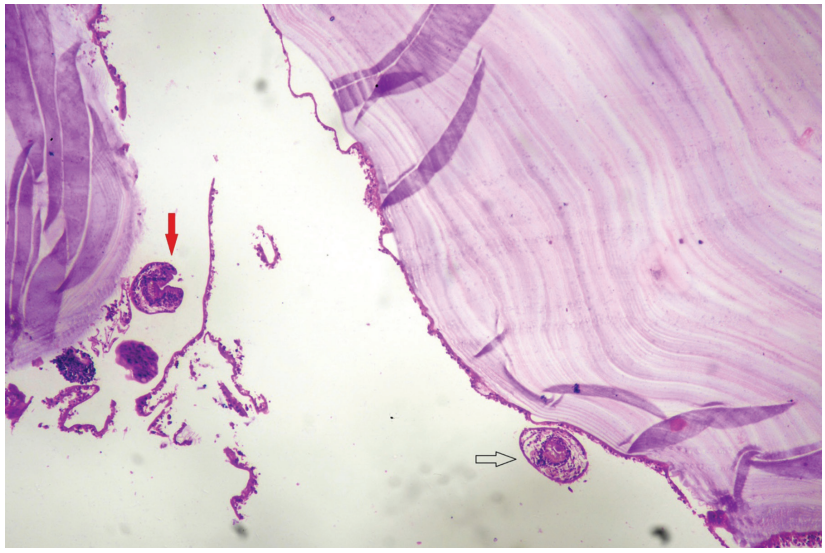

Figure 3. Hematoxylin and eosin (100x), section shows lamellated membranes of Echinococcus granulosus. Also seen are brooding daughter cysts (black arrow) and the scolex of the parasite (red arrow)

Answer

A histopathologic examination revealed hydatid cysts lined by an innermost germinal layer with attached brood capsule and daughter cysts. An avascular, eosinophilic, and refractile laminated membrane was seen. The outer layer was fibrovascular with chronic inflammatory cells and giant cell reaction. To our surprise, even the myometrium had evidence of hydatid cysts (Figure 3).

The patient was a farmer and livestock handler by occupation. Ultrasound and MRI findings along with the history of two previous surgeries in the past raised a high index of suspicion for hydatid cyst. Pre-operative echinococcal serology was positive. CA-125 was normal. With a provisional diagnosis of suspected peritoneal and ovarian hydatid cyst, the patient was given a course of albendazole 400 mg twice daily for 6 weeks, following which she was taken for surgery.

Echinococcosis or hydatidosis is caused by larvae of tapeworm Echinococcus granulosus, belonging to the family Taeniidae. With dogs being the dominant carriers, Echinococcus often infects humans via echinococcus eggs in contaminated food, water or contact with infected animals (1). We present a case of a 35-year-old woman with co-existing ovarian, myometrial, and omental hydatid cysts.

Hydatid disease is an endemic parasitosis in regions such as China, Russia, South America, the Mediterranean Region, Eastern Europe, and Central Asia (2). Prevalence of hydatid disease in liver or lung is 80% (3). Very rarely, the disease has pelvic or omental involvement (4). The prevalence of pelvic hydatid cysts requiring surgery was reported as <1% (5). Due to the non-specific symptoms such as abnormal uterine bleeding, sterility and urinary retention, diagnosis and treatment of pelvic hydatid cyst poses a challenge. Cysts with unusual location such as the ovary and uterus tend to grow slowly, leaving the patient asymptomatic for a long time (6).

The World Health Organization (WHO) Informal Working Group Classification of cystic echinococcosis (CE) is shown in Table 1 (3). Diagnosis can be made by imaging, ultrasonography (USG) or computed tomography or MRI in conjunction with serology. USG lacks sensitivity for the determination of cyst viability. The sensitivity of USG for the evaluation of Echinococcus is 90% to 95% (7). Amongst the serologic tests, specific immunoglobulin G ELISA is the most sensitive measure. However, there is no consistent correlation between the number or size of cysts and serologic results (8). Serologic tests are more reliable for the diagnosis of echinococcus multilocularis infection than echinococcus granulosus infection. Antibody detection is more sensitive than antigen detection for the diagnosis of echinococcus granulosus (9). Cyst aspiration-fluid polymerase chain reaction may also be useful for diagnosis.

Treatment modalities include puncture aspiration injection reaspiration, which is reserved for uncomplicated cysts that do not have daughter cysts (e.g. WHO stage CE1 and CE3a) (3). Percutaneous treatment is associated with a risk of anaphylaxis. Modified catheterization techniques are used to remove the entire endocyst and daughter cysts from the cyst cavity using large bore catheters and cutting devices together with an aspiration apparatus. Drug therapy may be used for definitive or adjunctive therapy. Albendazole is the primary antiparasitic agent for the treatment of Echinococcus granulosus. Surgery is the treatment of choice for complicated cysts or for cysts with

many daughter vesicles (e.g. WHO stage CE2 and CE3b). Due to its high antigenic nature, the toxic fluid of hydatid cyst cause anaphylaxis and recurrence. Hence, cysts should be removed intact and if spillage occurs, 15 to 20% hypertonic saline wash may be used. The WHO recommends postoperative chemotherapy with albendazole for 1 month or mebendazole for 3 months if spillage occurs (3). A high index of suspicion must be kept for this disease because the incidence of pelvic hydatid cyst is very low and it mimics ovarian malignancy or other ovarian tumors.

Our patient presented with cysts belonging to stages C2 and C3b for which the preferred treatment is albendazole followed by surgery, which was implemented for this patient (3). The patient was healthy at the time of writing this case report having completed a 3-month course of albendazole postoperatively.

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Pelvic lymphadenectomy: Step-by-step surgical education video

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Abstract

Pelvic lymph node dissection is one of the leading surgical procedures in gynecologic oncology practice. Learning the proper technique with anatomic landmarks will improve surgical skills and confidence. This video demonstrates a right-side systematic pelvic lymphadenectomy in a cadaveric model.

Keywords: Lymph node, anatomy, gynecologic oncology, lymphadenectomy, surgery

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Introduction

Pelvic lymphadenectomy is a supplementary part of staging and treatment in gynecologic oncology. Additionally, it influences the prognosis and guides the adjuvant treatment. The role of lymphadenectomy in ovarian cancer is controversial, in endometrial cancer high-risk patient groups deserve lymphadenectomy and in cervical cancer lymphadenectomy is a complementary part of the surgical treatment. Lymphadenectomy can be performed in a selective or systematic approach. This video demonstrates a right-side systematic pelvic lymphadenectomy in a cadaveric model.

Pelvic lymphatic drainage

Drainage from the lymphatics of the perineum, lower extremities, lower abdominal wall, and pelvic viscera (except the sigmoid colon) is to the pelvic wall lymph chain. The upper paracervical (supraureteral paracervical) and lower paracervical (infraureteral paracervical) pathways are the basic routes of pelvic lymphatic drainage (1). Additionally, a lymphatic branch from the ovary runs downward from the utero-ovarian ligament and follows ovarian-uterine artery branch, consequently draining via the upper paracervical pathway (2).

The pelvic lymph nodes mainly include the external iliac, internal iliac, and obturator lymph nodes, which are below the bifurcation of the common iliac artery. The lymphatic tissues lay on the external iliac vessels anteriorly and medially, over the internal iliac vessels, at the interiliac junction, and over the obturator nerve; these lymph nodes should be removed in order to achieve a complete (systematic) pelvic lymphadenectomy (3).

The borders of the pelvic lymph nodes are the genitofemoral nerve laterally, bifurcation of the common iliac artery cranially, the deep circumflex iliac vein caudally, the obturator nerve inferiorly, and the obliterated umbilical artery medially (4).

Sacral lymph nodes are generally not encountered in the pelvic lymph node group and its dissection is not a routine part of pelvic lymphadenectomy. Sentinel lymph node mapping studies also showed that sentinel lymph nodes are rarely

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detected in the presacral area (5); however, if there is a bulky lymph node it should be dissected.

Surgical technique

In order to achieve a successful pelvic lymphadenectomy, first, a good anatomic exposure should be maintained to visualize the entire surgical field (Figure 1), secondly, lymph nodes over the external and internal iliac vessels are dissected and then the obturator lymph nodes are removed.

After exploring the abdomino-pelvic cavity, the uterus is drawn over to the contralateral pelvic side wall, caudo-medially. The lateral parietal peritoneum is incised between the round ligament and the infundibulopelvic ligament, so the retroperitoneal space is accessed (transection of the round ligament to access the retroperitoneal area is optional). The incision is enlarged and the peritoneum is cut parallel to the infundibulopelvic ligament. The ureter is identified at the base of the posterior sheet of the broad ligament. The pararectal space is developed between the internal iliac artery (lateral) and ureter (medial). The paravesical space is developed between the bladder (medial) and pelvic side wall (lateral); the obliterated umbilical artery divides the paravesical space into two parts and the lateral part indicates the obturator fossa. The peritoneal tissue of the round ligament where it enters the inguinal canal under the inguinal ligament is pulled upward. The ureter is retracted medially, and the pelvic lymphadenectomy starts over the external iliac artery, below the bifurcation of common iliac artery.

The fibroadipose lymphatic tissue over the external iliac artery is gently elevated and mobilized medially, and a tiny dissection is performed to separate the lymphatic tissue from the fibrous sheath. While dissection is performed longitudinally over the external iliac artery, a cleavage is opened at the mid-level to clear the lymphatic tissue over the external iliac vein until the level of deep circumflex iliac vein, which is the caudal border. Therefore, internal iliac lymph nodes are also removed over the anterior part of internal iliac artery. Afterwards, lymph node dissection turns around the superior pubic ramus of the pubic bone, which forms a part of the obturator foramen, and the pubic vein, the connection between the external iliac and obturator vein (corona mortis), is identified. The dissection of obturator lymph nodes starts from this point after retraction of external iliac vessels laterally to the psoas muscle and maintaining a medial retraction on the paravesical space, which retracts the obliterated umbilical artery medially (Figure 2). All the lymphatic tissue over the obturator nerve lateral to the obliterated umbilical artery is stripped from the attachments and finally the lymphatic tissue is removed.

Additionally, if there is a bulky or huge lymph node over the external iliac vessels and extending to the psoas muscle, the external iliac vessels are separated from the psoas muscle by sharp and blunt dissection so the medial part of psoas muscle and obturator internus muscle can be exposed (Figure 3). This maneuver also provides a lateral access to the obturator fossa and the obturator nerve can easily be

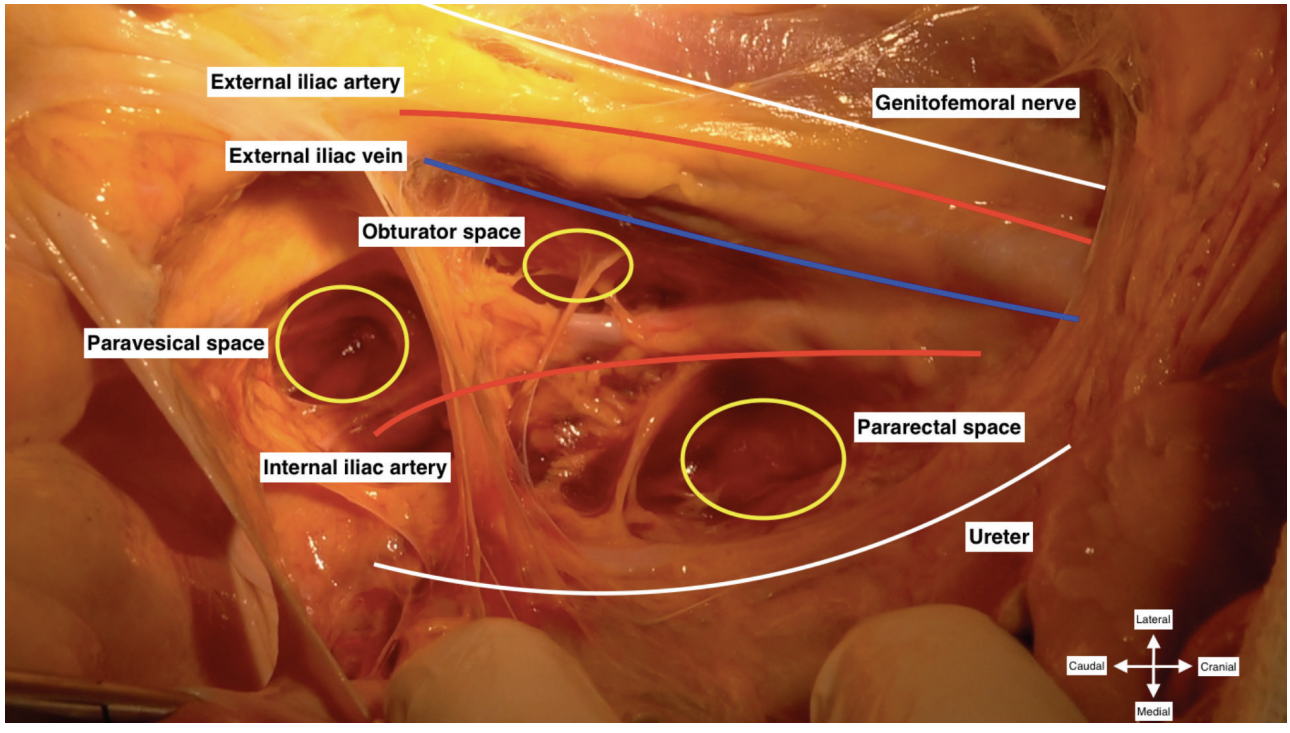

Figure 1. Pelvic anatomy for proper pelvic lymphadenectomy (right pelvic side wall)

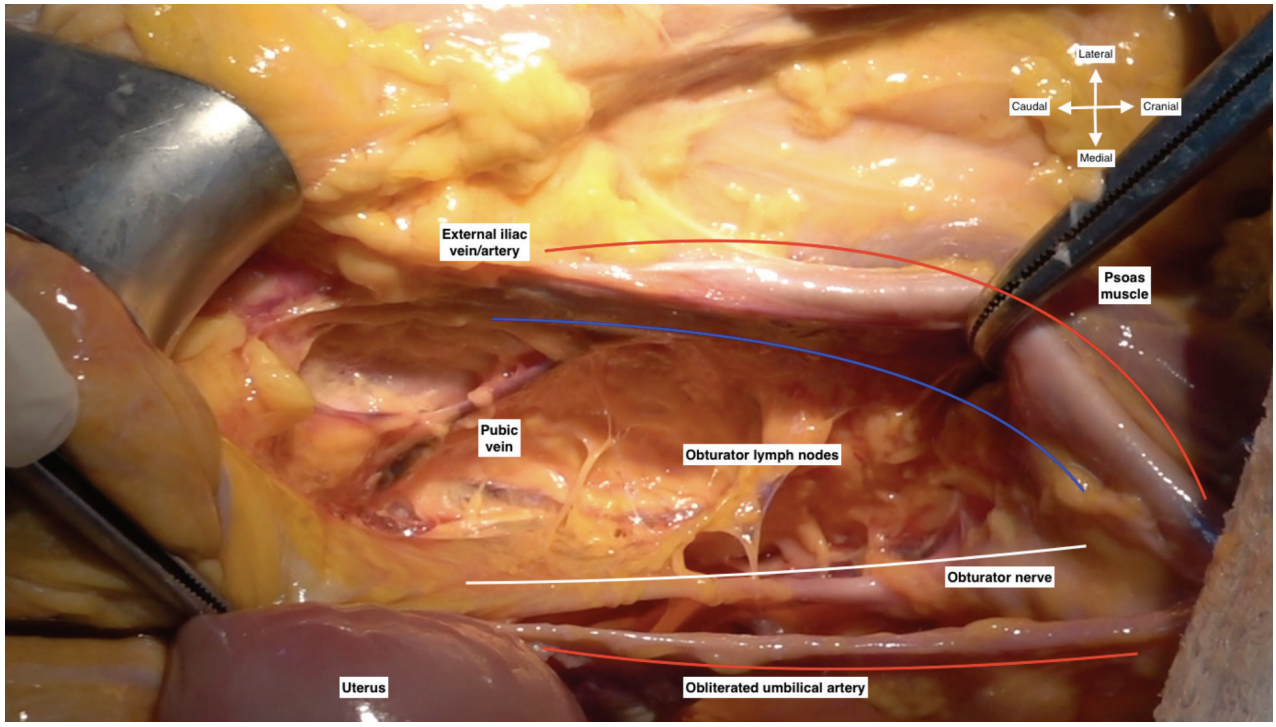

Figure 2. Pubic vein and obturator lymph nodes (right pelvic side wall)

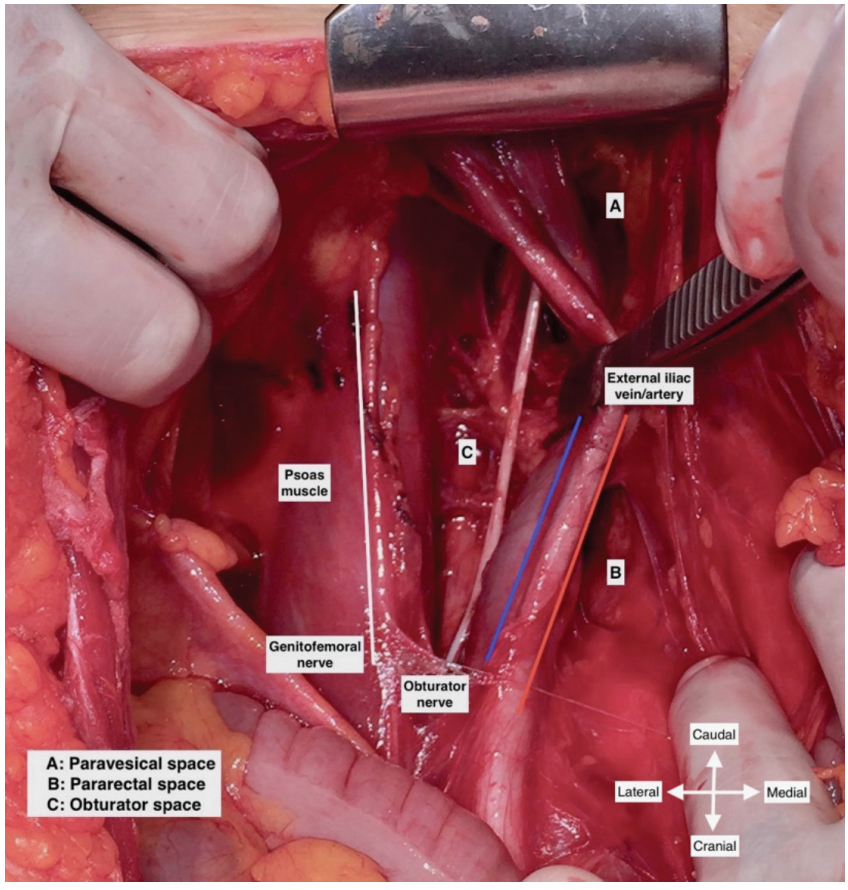

Figure 3. Exposure of obturator space after medial retraction of external iliac vessels (left pelvic side wall/live surgery-pelvic lymphadenectomy)

identified by applying gentle traction on the obturator lymph nodes (3,4,6).

Probable surgical complications

- Bleeding

External iliac vessels, internal iliac vessels, obturator vessels, or pubic vein or artery (corona mortis);

- Nerve injury

Genitofemoral nerve, obturator nerve;

- Ureter injury
- Lymphorrhea
- Lymphedema

Tips and tricks for pelvic lymphadenectomy

- Starting lymph node dissection over the anterior surface of external iliac artery is a safe method in creating the right cleavage.
- If there is a bulky lymph node at the obturator fossa and lying under the obturator nerve, care should be taken during stripping the attachments under the obturator nerve. There is an extensive venous vascular bed and collateral circulation of internal iliac vein, which makes the control of bleeding difficult (7).
- If corona mortis is formed by a pubic vein (most frequent type), the bleeding can easily be controlled (8).
- Obturator nerve injuries are rare; however, end-to-end anastomosis can be performed or nerve grafts may be applied (9).
- Ureter injuries are managed according to the region of injury; double-J-stents or end-to-end anastomosis are the options.
- The distal part of the external iliac or obturator lymph nodes over the deep circumflex iliac and pubic vein can be clipped or sutured to prevent lymphorrhea (4).
- Any self-retaining retractor may provide adequate gross exposure; however, caudomedial retraction from the paravesical space using a Deaver retractor and lateral retraction of external iliac vessels by a vessel retractor are critical points.
- Monopolar or bipolar cautery or a Metzenbaum scissor are used in dissection. Additionally, any other vessel sealing device can be used according to the preferences of the surgeon.

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Video 1. *10.4274/jtgga.galenos.2019.2018.0167.video1*

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

March 4-7, 2020	**International Society of Gynecological Endocrinology 19th World Congress, Florence, Italy**
March 28-31, 2020	**Society of Gynecologic Oncology (SGO) Annual Meeting, Toronto, Canada**
April 3-5, 2020	**16th ISUOG International Symposium, Cairo, Egypt**
April 30-May 3, 2020	**17th World Congress on Menopause, Melbourne, Australia**
June 10-13, 2020	**XXVII European Congress of Perinatal Medicine (ECPM), Lisbon, Portugal**
July 5-8, 2020	**European Society of Human Reproduction and Embryology (ESHRE) 36th Annual Meeting, Copenhag, Denmark**
September 11-13, 2020	**International Gynecologic Cancer Society (IGCS) 2020 Meeting, Rome, Italy**
October 1-4, 2020	**IFCPC – 2020 – 17th World Congress for Cervical Pathology and Colposcopy, Hyderabad, India**
October 11-14, 2020	**ESGE 29th Annual Congress, Lisbon, Portugal**
October 17-21, 2020	**American Society for Reproductive Medicine (ASRM) 76th Annual Meeting, Portland, United States**
October 17-21, 2020	**30th World Congress on Ultrasound in Obstetrics and Gynecology, Glasgow, United Kingdom**
November 15-19, 2020	**49th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Colorado, United States**
November 19-21, 2020	**World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Berlin, Germany**

CONGRESS CALENDER

NATIONAL MEETINGS

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April 18-22, 2020	**18. Ulusal Jinekoloji ve Obstetrik Kongresi-TJOD, Antalya, Turkey**
May 29-31, 2020	**Türk-Alman Jinekoloji Derneği Geleneksel Pfingst Alman Kongresi, İzmir, Turkey**
June 10-13, 2020	**9. Ulusal Jinekolojik Endoskopi Kongresi, İstanbul, Turkey**
November 4-8, 2020	**9. Üreme Sağlığı ve İnfertilite Kongresi – TSRM, Antalya, Turkey**

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