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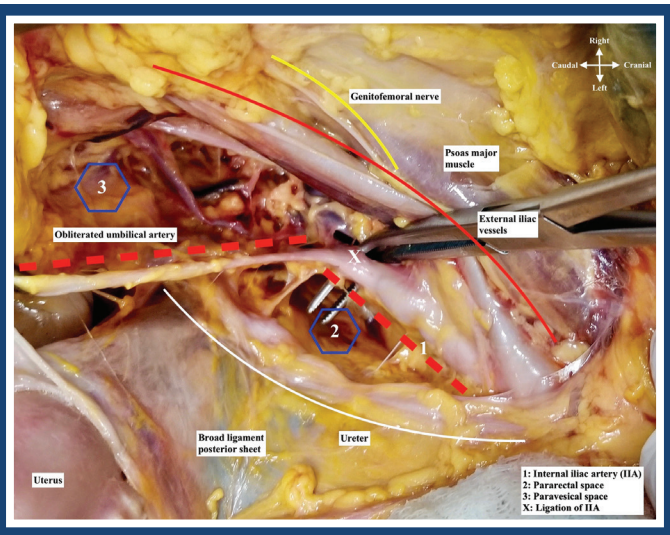

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Cover Picture: Selçuk et al. Ligation of the internal iliac artery

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AŞIRI UTERİN KANAMA'NIN TEDAVİSİNDE*:

FARKLI KADINLAR, FARKLI YAŞAMLAR, FARKLI GEREKSİNİMLER

Oral tedaviyi tercih eden anormal uterin kanamalı kadınlarda[1]

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

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

Mirena®
Levonorgestrel

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

*Organik patoloji saptanmayan vakalarda

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

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

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

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Book;

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

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

Journal and Society Web sites:

www.dtgg.de
(Deutsch-Türkische Gynäkologengeselleschaft)

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

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

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

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

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Contents

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

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MOST CITED AND MOST VIEWED ARTICLES

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

Website

Prognostic effect of isolated paraaortic nodal spread in endometrial cancer by Osman Türkmen, Derman Başaran, Alper Karalok, Günsu Cömert Kimyon, Tolga Taşçı, Işın Üreyen, Gökhan Tulunay, Taner Turan

Web of Science

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

Scopus

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

PubMed

Placental location and pregnancy outcome by Shumaila Zia

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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Journal of the
Turkish-German
Gynecological Association

Editorial

Dear Colleagues,

It is my great pleasure to present you the second issue of Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc) in the publishing year of 2019. J Turk Ger Gynecol Assoc is the official, scientific, open Access publication of the Turkish-German Gynecological Education and Research Foundation that publishes original studies on all aspects of gynecology since 2000. Now we are publishing 20th volumes. It was an enormous journey during this 20 years. We learned many things from you and we contribute huge data and experience to you and to our gynecology community. It was a great pleasure for us to have this prestigious journal, and thanks God we have still the same enthusiasms for publishing and growing our young journal.

Dear Reviewers,

Reviewers play a key role in our journal. They pick up best articles. They corrected the manuscripts. With their contribution, editors maintain the quality of the published research, enhance a journal's impact, and contribute to the advancement of the broader scientific community. If any of you are interested for this position, please feel free to contact me directly. Reviewing requires the investment of time and a certain skill set. Before you decide if you want to become a reviewer, we recommend that you read more about the peer review process (www.jtgga.org/instructions-to-authors).

Dear Authors,

If you're just starting out as a reviewer, don't be deterred. We are often looking to expand our pool of reviewers, which means there will be a demand for your particular area of expertise. Who Can Become a Reviewer? In short, anyone who is an expert in the article's research field. If you're new to peer review and feeling unsure of yourself, don't worry. Confidence will come with experience. Gaining the support of an experienced mentor and familiarizing yourself with the process of peer review should help you build your confidence and track record.

Dear Researchers, Dear Colleagues,

My advise for anyone wanting to become a better researcher is to never stop learning. To be a good researcher, you must be intelligent enough to express your ideas, be enthusiastic about new information, and hardworking to improve your skills. Be positive and do not be afraid of failure. Curiosity, persistence and an open mind are some of the key features of researchers. A good researcher must be open-minded and must also adopt a critical way of thinking. Besides, he/she should be hard working, diligent, focused and devoted to his/her specific field of interest. Updating his/her knowledge is of utmost importance and can be accomplished in several ways, such as following the current literature, attending conferences or exchanging ideas with colleagues working in a relevant field. Furthermore, a modern researcher must be resourceful and inventive in order to transform his/her scientific queries and hypotheses into a realisable protocol.

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Editorial

I would also like to inform you about the seventh Social Responsibility Project of Turkish German Gynecological Education and Research Foundation (TGGF), which will be held on September 6-7, 2019, in Ordu - Turkey. Ordu is a port city on the Black Sea coast of Turkey. Ordu was the place of ancient Cotyora, founded by Greek colonists in the 5th century. Ordu is now a centre for hazelnut processing and exporting, fishing, and timber exporting. The project held in this beautiful city is traditionally organized from four steps; public awareness meeting with participation of the locals, the scientific meeting with participation of health professionals, performing of the advanced operations and medical examination/screening to local women, and finally a medical device donation to a local hospital. We believe our project could be considered a success if only one maternal or neonatal death is prevented. Since it is these small steps which may one day make the difference. We would be excited to have our colleagues join us in this intense scientific activity.

You will read many interested articles in this particular issue. You will enjoy to read the papers from the authors all around the world. Next time you could be the one who will be read by the others. We are looking forward to receiving your valuable submissions.

Have a nice spring and summer!

Best regards,

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

Altuzan ile anti-anjiyogenez

Anjiyogenezi durdurun. Yaşamı sürdürün.[1,2]

Reküran, persistan veya metastatik servikal kanserde Altuzan'ın kombinasyon kemoterapisine eklenmesi sağkalımı artırır.[3]

Referanslar: 1. Pinedo ve ark. The Oncologist 2000; 5(suppl.1):1-2. **2.** Hurwitz ve ark. N. Engl. J .Med. 2004; 350;2335-42. **3.** Tewari SK et al. N Engl J Med 2014; 370:734-743.

ALTUZAN® 100 mg / 4 ml ve 400 mg /16 ml Konsantre infüzyon çözeltisi içeren şakon - Kısa Ürün Bilgisi (KÜB) Özeti

Formülü: Her bir şakon 16 ml'lik çözelti içinde 400 mg bevasizumab veya 4 ml'lik çözelti içinde 100 mg bevasizumab içerir. Bevasizumab, Çin Hamsteri over hücresinde rekombinant DNA teknolojisi ile üretilen bir rekombinant hümanize monoklonal antikordur. Yardımcı madde olarak Sodyum dihidrojen fosfat monohidrat ve Susuz disodyum fosfat içerir; her bir şakon 1 mmol (23 mg)'dan daha az sodyum içerir. **Endikasyonları: Metastatik Kolorektal Kanser (mKRK):** ALTUZAN (bevasizumab), 5-şorourasil/folinik asit veya 5-şorourasil/folinik asit/irinotekan ile kombine olarak metastatik kolon ve metastatik rektum kanserinin birinci basamak tedavisinde kullanılır. Daha önceki basamaklarda bevasizumabın kullanılmadığı durumlarda 5-şorourasil/folinik asit veya 5- şorourasil/folinik asit/irinotekan ile kombine olarak ikinci ve sonraki basamaklarda kullanılır. ALTUZAN, daha önce adjuvant amaçlı kemoterapi almamış olan metastatik kolon veya rektum kanserli hastalarda, birinci basamak tedavi olarak oksaliplatin ile kapesitabin veya 5- şuorourasil/folinik asit ile kombine olarak kullanılır. **Malign Glioma (DSÖ Evre IV) – Glioblastoma:** ALTUZAN, histolojik olarak Glioblastoma Multiforme (GBM) tanısı almış ve birinci seri temozolomid sonrası nüks gelişmiş veya progresyon göstermiş hastalarda kemoterapi ile beraber progresyona kadar kullanımında endikedir. Progresyon sonrası kullanılamaz. **Serviks kanseri:** ALTUZAN'ın, lokal tedavilere uygun olmayan persistan, rekürren veya metastatik serviks kanseri olan erişkin hastaların birinci basamak tedavisinde paklitaksel ve cisplatin veya paklitaksel ve topotekan ile kombinasyon halinde progresyona kadar kullanımı endikedir. ALTUZAN, rekürren/persistan ya da metastatik serviks kanser tedavisinde daha önce radyo duyarlaştırıcı haricinde sistemik kemoterapi tedavisi almış ve progresyon göstermiş hastalarda endike değildir. **Özellikleri:** ALTUZAN, insan vasküler endotelyal büyüme faktörüne (VEGF) spesiŞk olarak bağlanan ve biyolojik aktivitesini nötralize eden bir rekombinant hümanize monoklonal antikordur. ALTUZAN, VEGF'nin, endotelyal hücreleri yüzeyindeki Flt-1 ve KDR reseptörlerine bağlanmasını inhibe eder. VEGF'nin biyolojik aktivitesini nötralize ederek tümörlerin damarlanmalarını ve dolayısı ile tümörlerin büyümelerini yavaşlatır. **Kontrendikasyonları:** ALTUZAN'ın içerdiği herhangi bir maddeye karşı aşırı duyarlılığı olan kişilerde, Çin hamster over hücresi ürünlerine veya diğer rekombinant insan veya hümanize edilmiş antikorlara aşırı duyarlılığı olan kişilerde ve gebelerde kontrendikedir. **Özel kullanım uyarıları ve önlemleri:** ALTUZAN'dan bevasizumab içeren biyobenzer ürünlere, bevasizumab içeren biyobenzer bir üründen ALTUZAN'a, bevasizumab içeren biyobenzer bir üründen bevasizumab içeren diğer biyobenzer ürünlere geçiş yapmanın güvenliliği ve etkililiğini gösteren çalışmalar mevcut değildir. Bu tür dönüşümlü kullanma veya geçiş yapma işlemleri dikkatli bir şekilde ve yalnızca hekim gözetimi altında gerçekleştirilmelidir.Gastrointestinal perforasyon gelişen hastalarda ALTUZAN kalıcı olarak kesilmelidir. Hastalar, ALTUZAN ile tedavi edildiklerinde artan Şstül gelişme riski altında olabilirler. ALTUZAN tedavisi sırasında Derece 3 veya 4 kanama görülen hastalarda ALTUZAN kalıcı olarak kesilmelidir. ALTUZAN intravitreal kullanım için uygun değildir. ALTUZAN ile tedavi edilen küçük hücreli dışı akciğer kanseri hastaları, ciddi ve bazı vakalarda ölümcül olabilen pulmoner kanama/kan tükürme riski altında bulunabilirler. ALTUZAN ile tedavi edilen hastalarda hipertansiyon insidansında bir artış gözlenmiştir. Tıbbi olarak anlamlı hipertansiyon yeterli biçimde kontrol edilemediği veya hasta hipertansif kriz ya da hipertansif ensefalopati geliştirdiği takdirde ALTUZAN'ın tamamen kesilmesi gerekir. Geri dönüşümlü posterior lökoensefalopati sendromu (PRES) gelişen hastalarda, ALTUZAN tedavisinin kesilmesi ve hipertansiyonun kontrolü de dahil olmak üzere spesiŞk semptomların tedavi edilmesi tavsiye edilmektedir. Arteriyel tromboembolik reaksiyonlar gelişen hastalarda ALTUZAN kalıcı olarak kesilmelidir. Hastalar, ALTUZAN tedavisindeyken pulmoner embolizm gibi venöz tromboembolik reaksiyonlar geliştirme riski altında olabilir. Önceden var olan koroner arter hastalığı veya konjestif kalp yetmezliği gibi klinik olarak anlamlı kardiyovasküler hastalığı olan hastaları ALTUZAN ile tedavi ederken dikkatli olunmalıdır. Bazı miyelotoksik kemoterapi rejimleri ile ALTUZAN tedavisi gören hastalarda tek başına kemoterapiye göre daha yüksek oranda şiddetli nötropeni, febril nötropeni veya şiddetli nötropeniyle veya şiddetli nötropeni olmaksızın enfeksiyon (bazı fataliteler de dahil) gözlenmiştir. ALTUZAN yara iyileşme sürecini olumsuz etkileyebilir. ALTUZAN kullanan hastaların %1.4'ünde Derece 4 proteinüri (nefrotik sendrom) görülmüştür. Nefrotik sendrom gelişen hastalarda, ALTUZAN tedavisi tamamen kesilmelidir. Hastalar, infüzyon/aşırı duyarlılık reaksiyonları gelişimi açısından risk altında olabilir. ALTUZAN ile tedavi edilen kanser hastalarında çene osteonekrozu vakaları bildirilmiş olduğundan, ALTUZAN ve i.v. bifosfonatlar aynı anda ve art arda kullanıldığında dikkatli olunmalıdır. ALTUZAN kadın fertilitesini azaltabilir. Bu sebeple, ALTUZAN tedavisine başlamadan önce çocuk doğurma potansiyeli olan kadınlar ile fertilite koruma stratejileri görüşülmelidir. **İstenmeyen etkiler:** ALTUZAN'ın en ciddi advers ilaç reaksiyonları şunlar olmuştur: Gastrointestinal perforasyonlar, küçük hücreli dışı akciğer kanseri hastalarında daha yaygın olarak karşılaşılan pulmoner hemoraj/hemoptizi de dahil olmak üzere hemoraj, arteriyel tromboembolizm. ALTUZAN uygulanan hastalar üzerinde sürdürülen klinik deneyler sırasında en yaygın olarak karşılaşılan advers reaksiyonlar hipertansiyon, yorgunluk veya halsizlik, ishal ve karın ağrısı olarak tespit edilmiştir. **Diğer tıbbi ürünler ile etkileşimler ve diğer etkileşim şekilleri:** Bir popülasyon farmakokinetiği analizi sonuçlarına göre, birlikte uygulanan kemoterapinin ALTUZAN farmakokinetiği üzerine klinik olarak anlamlı farmakokinetik etkileşimi gözlenmemiştir. Radyoterapi ile eş zamanlı olarak ALTUZAN uygulamasının güvenliliği ve etkililiği belirlenmemiştir. **Pozoloji ve uygulama Şekli:** Önerilen ALTUZAN dozu, **Metastatik Kolorektal Kanser (mKRK) için:** Birinci basamak tedavi: 2 haftada bir verilen 5 mg/kg vücut ağırlığı veya 3 haftada bir verilen 7.5 mg/kg vücut ağırlığı İkinci basamak tedavi: 2 haftada bir verilen 10 mg/kg vücut ağırlığı veya 3 haftada bir verilen 15 mg/kg vücut ağırlığı şeklindedir. ALTUZAN tedavisine altta yatan hastalığın ilerlemesine kadar devam edilmesi önerilir. **Malign Glioma (DSÖ Evre IV) – Glioblastoma:** Önerilen ALTUZAN dozu intravenöz infüzyon halinde 2 haftada bir verilmek üzere 10 mg/kg veya intravenöz infüzyon halinde 3 haftada bir verilmek üzere 15 mg/kg'dır. ALTUZAN tedavisine altta yatan hastalığın ilerlemesine kadar devam edilmesi önerilir. **Serviks Kanseri:** ALTUZAN, aşağıdaki kemoterapi rejimlerinden biriyle kombinasyon halinde uygulanır: paklitaksel ve sisplatin veya paklitaksel ve topotekan. ALTUZAN için önerilen doz, 3 haftada bir intravenöz infüzyon şeklinde uygulanan 15 mg/kg vücut ağırlığıdır. Altta yatan hastalığın progresyonuna kadar veya kabul edilemez toksisite oluşana kadar tedaviye devam edilmesi önerilir. **Saklamaya yönelik özel tedbirler:** Flakonları 2- 8°C'de buzdolabında saklayınız. Flakonları ışıktan korumak için dış ambalajında saklayınız. DONDURMAYINIZ. ÇALKALAMAYINIZ. Hazırlandıktan hemen sonra kullanılmalıdır. Hazırlandıktan sonra hemen kullanılamadığı durumda, hazırlanan ilaç 2-8°C'de saklanmalı ve 24 saat içinde kullanılmalıdır. **Ruhsat Sahibi:** Roche Müstahzarları Sanayi Anonim Şirketi, Uniq İstanbul, Ayazağa Cad. No.4 D/101 Maslak 34396 Sarıyer-İstanbul Tel: (0212) 366 90 00 Faks: (0 212) 285 22 00 "Daha geniş bilgi için Şrmamıza başvurunuz" **Üretim Yeri:** Roche Diagnostics GmbH, Mannheim, Almanya. **Ticari Şekli:** ALTUZAN 400 mg/16 ml konsantre infüzyon çözeltisi, 1 şakon ve ALTUZAN 100 mg/4 ml konsantre infüzyon çözeltisi, 1 şakon **Ruhsat Tarihi ve Numarası:** ALTUZAN 400 mg/16 ml konsantre infüzyon çözeltisi: 22.12.2005 - 118/94, 100 mg/4 ml konsantre infüzyon çözeltisi: 22.12.2005 - 118/92 **KÜB Onay Tarihi:** 11.10.2018 **KÜB Özeti Tarihi:** 23.10.2018 **ALTUZAN 400 mg /16 ml konsantre infüzyon çözeltisi %8 KDV Dahil Perakende Fiyatı ve Onay Tarihi:** 3.706,88 TL / 19.02.2019 **ALTUZAN 100 mg /4 ml konsantre infüzyon çözeltisi %8 KDV Dahil Perakende Fiyatı ve Onay Tarihi:** 1.012,68 TL / 19.02.2019

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Vajinite Hızlı, Etkili ve Güvenli Çözüm![1-3]

Referanslar: 1. Lefler E, Stevens DA. Antimicrob Agents Chemother. 1984; 25(4):450-454. **2.** Sobel JD, et al. Clin Infect Dis. 2001;33(8):1341-6. **3.** Sobel J, et al. Infect Dis Obstet Gynecol 2001;9:9-15. **4.** Gynomax-XL KÜB.

Gynomax® XL KÜB ÖZETİ: ÜRÜN ADI: Gynomax® XL 200 mg/ 300 mg/ 100 mg Vajinal Ovül. **FORMÜL:** 1 vajinal ovül 200 mg tiokonazol, 300 mg tinidazol, 100 mg lidokaine eşdeğer lidokain HCl içerir. **ENDİKASYONLAR:** Kandidal vulvovajinit; bakteriyel vajinoz ve trikomonal vajinit ile karma vajinal enfeksiyonların tedavisinde kullanılır. **KULLANIM ŞEKLİ VE DOZU:** Hekim tarafından başka şekilde tavsiye edilmediği takdirde, gece yatmadan önce bir ovül 3 gün süreyle uygulanır. **UYGULAMA ŞEKLİ:** Vajinal. **KONTRENDİKASYONLAR:** 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 kullanılmamalıdır. **ÖZEL KULLANIM UYARILARI ve ÖNLEMLERİ:** Disülfiram benzeri reaksiyon görülebileceğinden tedavi süresince ve tedavi bittikten 3 gün sonrasına kadar alkol alınmamalıdır. Lastikte hasar yapabileceğinden ovüller kontraseptif diyafram ve prezervatifle temas etmemelidir. Spermisidler, vajinal duşlar veya vajinal yoldan uygulanan diğer ürünlerle birlikte kullanılmamalıdır. Trikomonal vajinit vakalarında eş tedavisi de gereklidir. Çift doz kullanılmamalıdır. Menstruasyon döneminde kullanıldığında etkisi azalabileceğinden veya kullanım zorluğu meydana gelebileceğinden, bu dönemde kullanılmaması önerilmektedir. Ovüller yutulmamalı veya başka bir yoldan uygulanmamalıdır. Cinsel olgunluğa erişmemiş kız çocuklarında ve bakirelerde kullanılmamalıdır. **İLAÇ ETKİLEŞİMLERİ VE GEÇİMSİZLİKLER:** Asenokumarol, anisindion, dikumarol, fenindion, fenprokumon, varfarin, kolestiramin, simetidin, siklosporin, disülfiram, fluorourasil, fosfenitoin, ketokonazol, lityum, fenobarbital, fenitoin, rifampin, takrolimus ve CYP3A4 indükleyicileri/inhibitörleri ile tinidazolün emilimine bağlı etkileşim görülebilir. Oksikodon ile tiokonazolün emilimine bağlı etkileşim görülebilir. Propranolol, simetidin, antiaritmik ürünler, fenitoin ve barbitüratlar ile lidokainin emilimine bağlı etkileşim görülebilir. **GEBELİK ve EMZİRME:** Gebelik kategorisi: C. Tinidazol anne sütüne geçtiğinden emzirme döneminde tedavi sırasında bebek sütten kesilmelidir, tedavi bittikten 72 saat sonra emzirmeye devam edilmelidir. **ARAÇ ve MAKİNE KULLANIMI:** Herhangi bir etkisi bulunmamaktadır. **İSTENMEYEN ETKİLER:** İntravajinal uygulamada, tinidazol, tiokonazol ve lidokainin kan düzeyleri sistemik kullanıma kıyasla daha düşük olacağından yan etkiler çok daha seyrek görülür. Yaygın: 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. Bilinmiyor: Lökopeni (geçici), nötropeni (geçici), alerjik reaksiyonlar (ağır vakalarda anafilaktik şok görülebilir), ataksi, koma (nadir), konfüzyon (nadir), depresyon (nadir), uyuşukluk, sersemlik hali, insomnia, uyku bozuklukları, anksiyete, psikoz, nöbet, konuşmanın bozulması, ajitasyon, kaygı, vertigo, periferal nöropati, konvülsiyon, kramp, aşırı heyecan, dezoryantasyon, öfori, halüsinasyonlar, hiperestezi, hipoestezi, letarji, aritmi, bradikardi, arterial spazm, kardiyovasküler kollaps, defibrilatör eşiğinde artma, ödem, yüz kızarması, kalp bloğu, hipotansiyon, sinüs düğümünde süpresyon, karın ağrısı, diyare, paslı dil (nadir), stomatit, dil renginde değişiklik, ağız kuruluğu, psödomembranöz kolit, kaşıntı, ürtiker, anjionörotik ödem, kutanöz erüpsiyon, lokal yanma, üriner yanma, ödem, lokal iritasyon, kaşıntı, vajinal akıntı, disparoni, nokturi, vajinal ağrı. **DOZ AŞIMI VE TEDAVİSİ:** Doz aşımında içerdiği etkin maddelere bağlı sistemik etkiler görülebilir; tinidazolün doz aşımına bağlı yan etkileri bilinmemektedir, tiokonazolün lokal uygulama ile doz aşımı mümkün değildir. Lidokain topikal olarak çok yüksek dozda uygulandığında kalp ritim bozuklukları, nefes alma zorluğu, koma ve hatta ölüme yol açabilmektedir. **RAF ÖMRÜ VE SAKLAMA KOŞULLARI:** 36 ay-25°C'nin altındaki oda sıcaklığında saklayınız. **TİCARİ TAKDİM ŞEKLİ:** PVC/LDPE çift katlı folyo ovül ambalajı, 3 ovül. **FİYATI:** 41,16 TL (Şubat 2019 itibariyle). **ÜRETİM YERİ:** Exeltis İlaç San. ve Tic. A.Ş./Çerkezköy-TEKİRDAĞ **RUHSAT SAHİBİ:** Exeltis İlaç San. ve Tic. A.Ş. Kültür Mah. Nisbetiye Cad. No: 56 Akmerkez B Blok Kat:6 D:574 Etiler Beşiktaş / İSTANBUL. **RUHSAT TARİH/NO:** 04.02.2013–248/3. **KÜB Güncellenme Tarihi:** 07.09.2018 **REÇETE İLE SATILIR. GERİ ÖDENİR. Kısaltılmış KÜB güncellenme tarihi:** 26.02.2019 Daha geniş bilgi için firmamıza başvurunuz. Tel: 0 212 365 93 30, infoTR@exeltis.com. Herhangi bir şüpheli advers reaksiyon ile karşılaşılması halinde TÜFAM'a bildiriniz. (www.titck.gov.tr; e-posta: tufam@titck.gov.tr) Tel:0 800 314 00 08; Faks: 0 312 218 35 99.

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Detrimental effect of Hypericum perforatum on ovarian functions

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Abstract

Objective: *Hypericum perforatum* is widely used for depression and distress treatment as an over-the-counter plant at any age. This study investigated the safety of *H. perforatum* on ovarian function and infertility.

Material and Methods: *H. perforatum* was given to rats in two different dosages (100 and 300 mg/kg/day) with drinking water for four weeks. Half of the treatment groups were sacrificed at the end of the four-week intervention, the remainder was sacrificed after an additional four-week waiting period to see if there was reversibility. At the end of the experiment, blood samples and both ovarian tissues were obtained under anesthesia with ketamine and xylazine (50 mg/kg and 5 mg/kg, respectively).

Results: Although primordial follicle numbers were not affected with a dose of 100 mg/kg, they were significantly decreased (28.6%) when the dose was tripled. Primary follicle numbers stayed the same, but secondary and tertiary follicles numbers were significantly dose-dependently decreased, and remained significantly low four weeks after the intervention. Anti-mullerian hormone (AMH) levels were not significantly different between the groups.

Conclusion: *H. perforatum* treatment did not change serum levels of AMH because the primary follicle number did not decrease. However, the other follicle counts decreased in a dose-dependent manner and full recovery was not regained after four weeks. The detrimental effect of *H. perforatum* on primordial follicles should be taken into consideration because any woman using *H. perforatum* could also experience ovarian failure. (J Turk Ger Gynecol Assoc 2019; 20: 65-9)

Keywords: Anti-mullerian hormone, ovarian capacity, rational drug treatment, rat, St. John's wort

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Introduction

Although psychological distress by itself can cause psychosomatic infertility or decrease treatment success (1), the treatments of distress and depression with medicines and plants may also have a negative impact on ovarian function. There is a growing interest in plants and their derivatives, with an assumption that they are a safe method of treatment. Patients with infertility are increasingly using complementary and alternative medicines to support or replace medical fertility treatments (2). Extracts from the plant *Hypericum perforatum* (St John's wort) have become an appealing alternative therapy to prescription serotonin-modulating drugs and are widely available to women of childbearing age (3,4).

There is little research on *H. perforatum* and its use in pregnancy, and its effect on fertility has not been established, even in European Medicines Agency guidelines (EMA) (5). Therefore, we evaluated impact of *H. perforatum* on ovarian tissue by counting follicles and assessing anti-mullerian hormone (AMH) levels.

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Material and Methods

Chemicals and animals

H. perforatum (St. John's Wort Herb Extract/SOLGAR, İstanbul, Turkey) was obtained from a local pharmacy store. Thirty-five 16-20–week-old female Wistar rats were obtained from the university and all experiments were performed according to the principles and guidelines of the University Animal Ethical Committee's approval (HADYEK 64583101/2016/3). The "Principles of laboratory animal care" (NIH publication no. 86-23, revised 1985) and specific national laws were followed throughout the study. On the study day, the rats were randomly assigned to five groups of seven animals each.

Experimental design

Control group: The rats in this group were allowed free access to tap water.

Low-*H. perforatum* group: The rats in this group were administered 100 mg/kg *H. perforatum* with drinking water for four weeks.

Low-*H. perforatum* waiting group: The rats in this group were administered 100 mg/kg *H. perforatum* with drinking water for four weeks, and then the rats received no medication and were sacrificed 4 weeks later.

High-*H. perforatum* group: The rats in this group were administered 300 mg/kg *H. perforatum* with drinking water for four weeks.

High-*H. perforatum* group: The rats in this group were administered 300 mg/kg *H. perforatum* with drinking water for four weeks, and then the rats received no medication and were sacrificed 4 weeks later.

The rats were weighed every monday and the doses of *H. perforatum* were adjusted for every cage. At the end of the experiment, under the anesthesia with ketamine and xylazine (50 mg/kg and 5 mg/kg, respectively), blood samples were obtained by cardiac puncture, centrifuged at 3000 rpm/4 °C, and sera were stored at -80 °C for AMH measurement. In addition, both ovaries were harvested and kept in 10% formalin.

The suggested daily dosage of *H. perforatum* for humans is 900 mg (or 15 mg/kg per day for a 60 kg human being); Rayburn et al. (3), calculated the rodent dosage as 180 mg/kg per day in their study. Considering that study, we wanted to apply two different doses of *H. perforatum* treatment to have a better understanding of dose effect and determined doses of 100 mg and 300 mg/kg (low and high). Additionally, we sacrificed some rats after a waiting period to determine if there was any reversibility of effect.

Follicle counting

After routine tissue processing, the obtained samples were sliced in 5-micrometer thickness and evaluated under an optical microscope (Zeiss Primo star, Ankara, Turkey) with hematoxylin-eosin (H-E) staining. Oocyte classification was based on previous studies (6,7).

Primordial follicle; follicles comprising a central oocyte and surrounding monolayer of flat squamous granulosa cells (Figure 1a-c).

Primary follicles; a central oocyte and surrounding monolayer of cubic granulosa cells or at least 3 cubic epithelial cells in monolayer granulosa cells (Figure 1d-g).

Secondary follicle (pre-antral follicle); follicles containing two or more layers of granulosa cells, without formed antrum follicles (Figure 1h, i).

Tertiary follicle (antral follicle, graff follicle); follicles containing two or more layers granulosa cells, with formed antrum follicles (Figure 1j-m).

Measurement of serum rat AMH

The serum level of rat AMH was determined using a commercial enzyme-linked immunosorbent assay (ELISA) kits (rat ELISA kit, Sunred, Baoshan District, Shanghai, China). The rat AMH ELISA kit sensitivity was 0.101 ng/mL with a coefficient of variation of <5%. Procedures were performed according to manufacturer's instructions.

Data presentation and statistics

AMH levels and ovarian count evaluation was performed using the Mann-Whitney U test. Data are presented as mean ± standard error mean, p values below 0.05 were considered significant. Follicle counts are also represented as percent changes.

Results

The control groups' number of primordial follicles number was 41.86±0.96, primary follicles: 12.29±0.42, secondary follicles: 9.00±0.66, and tertiary follicles: 23.29±0.81 (Table 1, Figure 1).

At the end of four weeks of low-dose *H. perforatum* treatment (100 mg/kg), the primordial follicles number increased by 2.03% (42.71±1.11), but decreased by 11.63% (10.86±0.55), 31.7% (6.14±0.40) ($p<0.01$), and 62.6% (8.71±0.61) ($p<0.01$) for primary, secondary, and tertiary follicles, respectively. Four weeks after ceasing *H. perforatum* treatment, the primordial follicle number (44.86±1.28) was still 7.1%, slightly higher than the control (41.86±0.96), the primary follicle number was nearly equal to the control value (12.43±0.37), the secondary follicle number was 65.1%, which was higher than the control (14.86±0.60) ($p<0.01$), and tertiary follicles had recovered

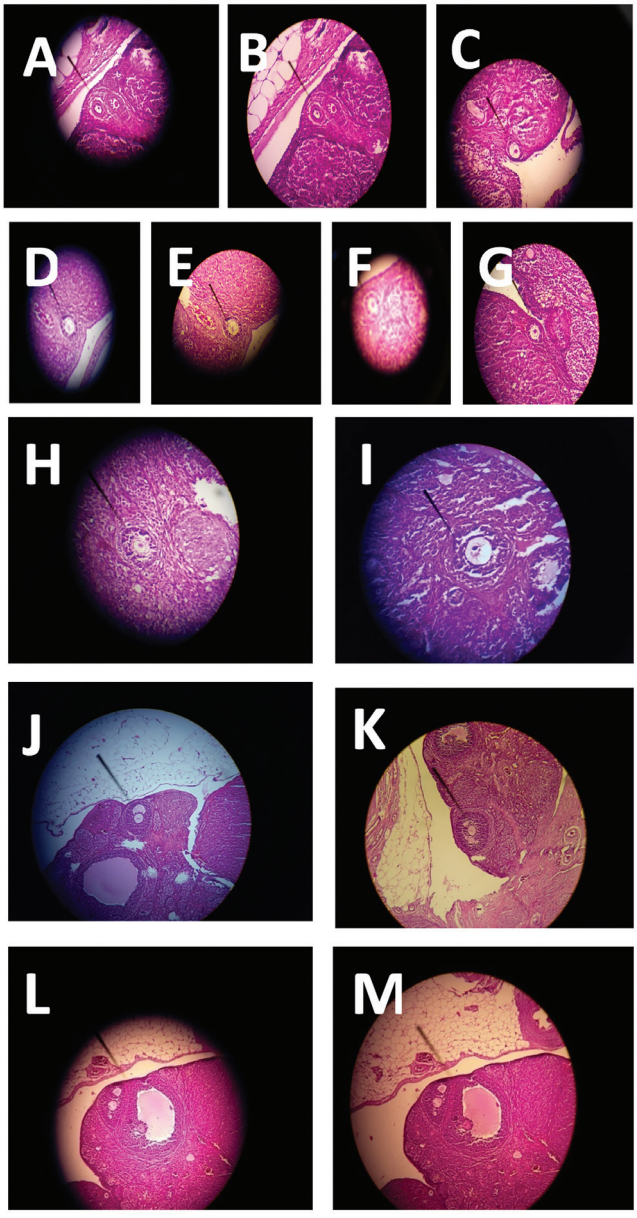

Figure 1a-m. Pictures of primordial (a, b, c magnification ×10) and primer follicles (d, e, f ×10 magnification; g Magnification ×40), pictures of secondary (h, i magnification ×10) and tertiary follicles (j, k ×10 magnification; l, m magnification ×40)

mostly, but still remained 10.4% (20.86±0.96) ($p<0.05$) lower than the control value.

In the high-dose *H. perforatum* treatment group (300 mg/kg), the primordial follicle count dropped 29.0% (29.71±1.15) ($p<0.01$), and after the waiting period of four weeks the number was even lower 43.6% (23.57±0.84) ($p<0.01$). Although the primary follicle number did not change in both situations (11.57±0.65, 11.71±0.92), the number of secondary follicles did not change at the end of treatment (8.86±0.51), but declined 65.1% (3.14±0.60) ($p<0.01$) four weeks later. At the end of treatment, the decline of tertiary follicles was 87.7% (2.86±0.74) ($p<0.01$), and recovered to 9.29±0.68 but remained 60.1% ($p<0.01$) lower than control.

Serum AMH level of the three groups were not significantly different from each other ($p>0.05$); the control group's AMH level was found as 4.39±0.47 ng/mL, the low-dose *H. perforatum* group was 4.63±0.63 ng/mL, and the high-dose *H. perforatum* group was 5.02±0.29 ng/mL.

Discussion

Many researchers have focused on the beneficial anti-depressive effects of *H. perforatum*, and despite there being few reports about its harmful effects, unfortunately, this does not signify the plant's safety, it shows a lack of rigorous research. This over-the-counter plant is available in many countries as an alternative treatment modality to anti-depressive medicines (5). The EMA determined in its guidelines the adult dosage is a total 900 mg/day (three-times 300 mg/day) for the treatment of depression (5). Unfortunately, it has been reported that it can be abused among adolescents who believe it can make them feel good (8), in this case, its limited upper dose has not been established due to its non-prescription use. Depression can affect people of any age and disturb fertility, and any woman could be exposed to *H. perforatum*, assuming that it is safe, either before being pregnant and even while pregnant. Therefore, this study has investigated harmful effects of *H. perforatum* on ovarian tissue in two different doses and evaluated reversibility and if there was any alteration on ovarian reserve.

In this study, 100 mg/kg doses of *H. perforatum* did not inhibit the primordial stage, but when the dose was tripled, these parts

Table 1. Ovarian follicles counting of all experimental groups

	Primordial follicles	Primary follicles	Secondary follicles	Tertiary follicles
Control	41.86±0.96	12.29±0.42	9.00±0.66	23.29±0.81
100 mg/kg *H. perforatum*	42.71±1.11	10.86±0.55	6.14±0.40#	8.71±0.61#
100 mg/kg *H. perforatum* + waiting period	44.86±1.28	12.43±0.37	14.86±0.60#	20.86±0.96*
300 mg/kg *H. perforatum*	29.71±1.15#	11.57±0.65	8.86±0.51	2.86±0.74#
300 mg/kg *H. perforatum* + waiting period	23.57±0.84#	11.71±0.92	3.14±0.60#	9.29±0.68#
n=7; *p<0.05; #p<0.01				

of the follicles were also affected. The primary follicle number remained the same in both doses; secondary and tertiary follicles numbers decreased in a dose-dependent manner and the ovarian cell count waiting did not recover after a four-week treatment cessation period. An earlier study showed that one-hour pretreatment of *H. perforatum* (0.6 mg/mL) resulted in zero penetration of hamster zona-free oocytes and significant denaturation of sperm DNA to decrease the sperm viability, leading to concerns that its use may lead to decreased fertility (9). When *H. perforatum* was given as 180 mg/kg to mice two weeks before mating, the authors found no specific concerns about the pregnancy rates of the treated and non-treated groups; however, the study was focused on pup development and the number of live pups per litter were not found different between the groups (3).

There are no toxicity reports with regard to exposure to *H. perforatum* on direct ovarian tissues in the literature, but it is possible to find some deleterious effects on other organs. Gregoretti et al. (10) gavaged rats during gestation and for 21 days during lactation at doses 100 or 1000 mg/kg and renal and hepatic damage was identified in the pups at both doses. We did not want to use 1000 mg/kg doses of *H. perforatum*, which seem very high, our aim was just to mimic real life and worked with lower-moderate doses as 100 mg/kg and 300 mg/kg, following Rayburn et al. (3) study.

We also searched reports of HP on hormonal status in the literature. One study evaluated *H. perforatum* (900 mg/kg) interaction with oral contraceptive therapy in sixteen healthy women. As the CPY3A4 enzyme was induced, which is well-known aspect of *H. perforatum*, the metabolism of these hormonal components was increased by approximately 25% and resulted in breakthrough bleeding, pre-ovulatory follicles and follicle exceeding (11). Thirty-six women aged 18-45 years with regular menstrual cycles who were diagnosed as having mild premenstrual syndrome were given *H. perforatum* (900 mg/day); in the follow-up, there were no differences in plasma follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, prolactin, and testosterone found compared with the non-treated group (4). Contrarily, hypo-prolactinemic activity has been reported in healthy male volunteers and plasma growth hormone levels increased due to dopaminergic action of *H. perforatum* (12). Plasma cortisol levels were significantly elevated in only four male volunteers out of twelve (12). Similarly, Di Carlo et al. (13) showed an inhibitory activity of *H. perforatum* (100 mg/kg) on prolactin production in male rats with 15 days' treatment and suggested its clinical reflection might be luteal inadequacy, probably observed due to following pharmacologically-induced low prolactin secretion. An animal study on the hypothalamic-pituitary-adrenal axis (HPA) determined that two weeks' treatment with hypericin (0.2 mg/kg) significantly down-regulated circulating plasma levels of ACTH and corticosterone; the authors suggested that this flavonoid of *H. perforatum* played an important role in the modulation of HPA axis function (14). Considering that stress and anxiety activate the HPA, and this activation can disturb the hormones of fertility (1), *H. perforatum* treatment sounds beneficial, but this approach requires detailed analysis. These previously published reports show that *H. perforatum* has the capability to interact with endocrine pathways; at some point, this might be helpful to explain the detrimental effect of *H. perforatum* on follicle growth. Interestingly, it was not possible to find a current study about *H. perforatum* and hormone profiles.

AMH is produced by the granulosa cells of early developing follicles and inhibits the transition from primordial follicles to the primary follicular stage. AMH can be measured in serum and has been shown to be proportional to the number of small antral follicles (15). It has been suggested that there is a strong positive correlation between serum AMH levels and antral follicle count; the use of AMH combined with antral follicle counts may improve ovarian reserve evaluation (16). In our study, we found no significant changes in AMH levels and also the primary follicle reserve remained stable with both doses of *H. perforatum*.

It has been clearly shown that *H. perforatum* treatment decreased follicle counts in a dose-dependent manner, especially primordial and tertiary pools. This study should help navigate future research on the hormonal aspect of the effect of *H. perforatum*, which has to be investigated in detail. Any woman who takes *H. perforatum* could experience ovarian failure.

Ethics Committee Approval: *Adnan Menderes University Animal Ethical Committee's Approval, HADYEK 64583101/2016/3.*

Informed Consent: *It was taken.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - B.D., T.A.; Design - B.D.; Supervision - B.D., T.A., Y.Ö.; Materials: F.K., M.Y., Y.Ö.; Writer - B.D.*

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

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Using an innovative stacked ensemble algorithm for the accurate prediction of preterm birth

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Abstract

Objective: A birth before the normal term of 38 weeks of gestation is called a preterm birth (PTB). It is one of the major reasons for neonatal death. The objective of this article was to predict PTB well in advance so that it was converted to a term birth.

Material and Methods: This study uses the historical data of expectant mothers and an innovative stacked ensemble (SE) algorithm to predict PTB. The proposed algorithm stacks classifiers in multiple tiers. The accuracy of the classiffication is improved in every tier.

Results: The experimental results from this study show that PTB can be predicted with more than 96% accuracy using innovative SE learning.

Conclusion: The proposed approach helps physicians in Gynecology and Obstetrics departments to decide whether the expectant mother needs treatment. Treatment can be given to delay the birth only in patients for whom PTB is predicted, or in many cases to convert the PTB to a normal birth. This, in turn, can reduce the mortality of babies due to PTB. (J Turk Ger Gynecol Assoc 2019; 20: 70-8)

Keywords: Preterm birth, neonatal death, risk factors of preterm birth, stacked ensemble, stacked generalization, meta-learning

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Introduction

Births that happen after 37 weeks of gestation and before 39 weeks are termed as normal birth (TB). Babies born before 37 weeks of gestation are considered as premature babies and such births are termed as preterm birth (PTB) (1,2). Premature babies typically have many severe complications such as breathing/respiratory problems (apnea), chronic lung disease, jaundice, anemia, infections, bleeding in the brain (intraventricular hemorrhage). In the worst cases, premature babies die in the early days of life. Such deaths are termed as neonatal death (3). The United Nations International Children's Emergency Fund report published in 2015 stated that PTB was a major cause of the neonatal death (4-6). Due to PTB, some women also have poor mental health, and in some extreme cases have mental disorders (7). The long-term consequences of PTB for the babies are cognitive problems (intellectual disability and learning disability), asthma, intestinal problems, vision problems, hearing loss problems, dental problems, poor growth, and increased risk of sudden infant death syndrome.

When the expectant mother undergoes prenatal checkups, the clinical pathologic status may indicate the possibility of a PTB. In the Obstetrics and Gynecology (O&G) world, these indicators are called risk factors of PTB (8-11). The physician analyzes these risk factors and diagnoses the birth as either TB or PTB. While diagnosing PTB, the physician also takes into consideration the behavioral and social characteristics of the expectant mother (12). Hence, they are also considered as risk factors of PTB. All risk factors are not critical in nature and they do not contribute equally to PTB. Hence, risk factors are categorized as primary risk factors and secondary risk factors based on their criticality. The primary and secondary risk factors associated with PTB are listed in Table 1.

Obtaining evidence for PTB in clinical pathology is a challenging task. More than that, some clinical tests are too expensive to for patients from developing countries. Accordingly, predictive

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analytics is the way forward. Predicting a PTB as a TB can lead to fatal consequences, thus learning algorithms with high accuracy are very much needed. Ensemble learning gives better accuracy than individual learning algorithms and hence is suitable for predicting PTB (15,16). Ensembles perform effectively, especially if the base learners are diverse and are moderately performing (17). Using a trainable combiner to learn from the predictions of base learners generalizes better than traditional ensembles (18). Such learning systems are termed as stacked ensemble (SE) systems (19,20). They use base classifiers to train level-0 models and a generalizer to learn from the predictions of level-0 models. Thus, the predictions of base classifiers form the input space for the generalizer. These predictions are termed as meta-features and the generalizer is said to perform meta-learning (21-23).

This study uses an innovative SE algorithm for the accurate prediction of PTB. It differs from traditional SEs in producing the meta-features. Rather than using the predictions of level-0 models as meta-features, it combines them using multiple combination schemes to produce meta-features. The meta-features along with the critical features are used to train the generalizer. The combination schemes produce the joint distributions of the level-0 predictions. The predictions from level-0 models are the abstraction of the mapping between the input space and the actual labels. Hence, these joint distributions map the level-0 predictions to the actual label and indirectly map the input space with the actual label. This in turn produces meta-features that better abstracts the relationship between the input space and the actual labels. In doing so, the proposed algorithm performs better than traditional SE algorithms. The performance of the algorithm is measured using its accuracy and recall.

The following are the contributions of this study: (i) the introduction of an innovative SE algorithm to improve prediction accuracy, (ii) the algorithm enables accurate predictions of PTB, and (iii) motivation for the research community to use this algorithm for classification problems. Organization of the remaining sections: Section II describes the work conducted in predicting PTB. Section III depicts the proposed algorithm in detail. Experimental results along with the inferences are reported in section IV. Section V is the conclusion and the scope for future work.

Table 1. Risk factors associated with PTB (13,14)

Primary risk factors	Premature rupture of membranes
	Presence of fetal fibronectin in vaginal discharge
	Cervix shortens earlier than third trimester
	Excessive amount of amniotic fluid
	Conceived with assisted reproductive technologies
	Prior history of PTB
	Prior history of abortion
	Multiple gestation
	Vaginal or urinary tract infections
	Short inter-pregnancy interval
Secondary risk factors	Under weight (<45 kg)
	Short stature (height <145 cm)
	Stress/hypertension
	Heavy work
	Family history
	Prior history of pregnancy loss
	Lack of antenatal check-up
	Low economic status
	Smoking
	Diabetes

PTB: Preterm birth

Related work

Using machine learning or statistical analysis for predicting PTB based on historical data is gaining momentum in O&G. Bittar et al. (24) used statistical analysis to predict spontaneous PTB for a high-risk group of expectant mothers who had prior PTB. They used the cervical length and the level of protein-1 (phIGFBP-1) in cervical secretions as the input for their statistical analysis. In the first step, they used phIGFBP-1 and cervical length to perform the logistic regression analysis to predict PTB. For examining the contributions of these two factors on PTB, they performed multiple logistic regression analysis. A dataset with 105 expectant singleton mothers were used for their analysis. They found that phIGFBP-1 level measured during the 30th week of gestation helped in predicting PTB accurately. In combination with this, measuring the cervical length between the 22nd and 24th weeks and using it for the statistical analysis improved the prediction rate of PTB. They achieved a prediction rate of 92% before the 34th week and a prediction rate of 80% before the 37th week. Though their study resulted in high prediction rate, the number of PTB instances in the dataset was only 12. Hence generalizing their result involves an element of risk.

A similar kind of study was conducted by Care et al. (25) to predict PTB in women with prior PTB and normal cervical length (>25 mm) between 22-24 weeks. They used a dataset with 196 instances out of which 134 patients had a normal cervical length and 62 patients had shorter cervical length. Out of the 134 patients with normal cervical length, 28 patients had a PTB and 12 of these had a prior PTB. Of the 62 patients with shorter cervical length, 25 patients had a PTB. All these patients were from the White British population demographic.

They used SPSS to conduct analyses, which revealed that a normal cervix or long cervix did not provide any assurance on recurrence of PTB. They concluded that that normal cervical length and the demographic information of the patients were not good features to predict PTB. They also suggested using other factors such as amniotic fluid, vaginal discharge, genetic, and social and environmental factors to predict PTB.

Predicting PTB outside of the clinical pathology is a better approach for the early prediction of PTB. Catley et al. (26) used back propagation feed forward Artificial Neural Network (ANN) for predicting PTB. They used Perinatal Partnership Program of Eastern and Southeastern Ontario databases for conducting the experiments. The dataset was skewed towards TB and hence they removed the TB instances to balance the dataset. While dividing the dataset into a training set and a test set, they ensured that the distribution of TB and PTB was not skewed. They used a logarithmic sensitivity index for measuring the performance of the prediction. They used MatLab with the Neural Network Toolkit to conduct the experiment. The authors used the weight-elimination cost function to improve the classification performance, and one hidden layer with three hidden nodes. When the skewed dataset was used, the sensitivity reached a peak at 20.4%. The sensitivity of the prediction reached a peak at 33.4% with a more balanced dataset. They observed that the number of fetuses in the womb in the current pregnancy and previous pregnancies, number of children, and smoking after 20 weeks of gestation were the factors with the highest connection weights in the ANN. Hence, these were major contributors for PTB.

Analyzing electrohysterography (EHG) signals for predicting PTB is another popular approach. This approach uses the signals generated by the contractions and expansions of the uterus. Ren et al. (27) used EHG signals to classify births as TB or PTB. They used the EHG signals of 300 patients available in the PhysioBank. Though the signal had a wide frequency spectrum, they filtered the frequency range of 0.3 Hz to 3 Hz. The signal was decomposed into intrinsic mode functions using empirical mode decomposition. The first ten functions were selected for prediction. They used the Gabriel Rilling EMD toolbox for this purpose. The dataset had 262 patients with TB and 38 patients with PTB. The dataset was balanced using SMOTE. They used principal component analysis to select the components such that it could improve area under the curve (AUC) values. They used multiple classifiers to classify PTB. On average, they achieved a maximum AUC value of 86.2%. They analyzed the impact of using the features from 3 channels of EHG against using only the features from channel 3. When the features from only channel 3 were used, the AUC reached a maximum of 89%. Among the classifiers, AdaBoost reached the highest accuracy of 98.6%. The limitation of this approach is the availability of EHG signals of patients in developing countries.

There are three types of features that can be extracted from uterine EHG signals. They are linear analysis; non-linear analysis and Discrete Cosine Transform analysis. Naeem et al. (28) extracted three types of features and analyzed them using ANN. They used three different forms of ANNs such as cascade-forward back propagation network, feed-forward network, and Kohonen network. The authors trained the networks with linear features, non-linear features, DCT features, and a combination of these features. They used PCA to select 10 components and used them for prediction. They compared the results obtained for all the types of features with three different forms of ANNs and concluded that the accuracy reached a peak value of 90% when feed-forward network with the linear and DCT features of uterine EHG signals were used. After analyzing the consequences of false positives, the accuracy of 90% is not enough for PTB.

The use of SE has found mention in many studies. Wang et al. (29) applied SE on a dataset constructed by Chou and Elrod (30) to predict membrane protein types based on pseudo-amino acid composition. Support Vector Machine (SVM) and Instance-Based Learning were used as level-0 classifiers. A combination of these two classifiers provided more information about the input space and its relationship with the class label. To achieve faster training, a Sequential Minimal Optimization (SMO) algorithm was used to train SVM. These classifiers were cross-validated using k-fold cross-validation. The cross-validated predictions from level-0 SVMs were used as input level-1 generalization. A Decision Tree was used as level-1 generalizer. Re-substitution test, jack-knife test and the independent dataset test were used to examine the quality of prediction through bias and variance estimation. Among the three tests, a high success rate of 85.4% was achieved in the jack-knife test. SE has achieved remarkably good performance and thus helped in providing the direction for functionally characterizing gene products using gene sequences.

Material and Methods

When the traditional SE is used, the level-1 generalizer inherits some level of bias and variance from level-0 models. Hence the problem of overfitting or underfitting is not eliminated to the maximum possible extent. To address this issue, this study proposes an innovative SE algorithm by stacking classifiers in multiple tiers (31). The proposed algorithm stacks the classifiers in three tiers namely (i) base tier, (ii) ensemble tier, and (iii) generalization tier (32). The base tier focuses on training a set of suitable learners to achieve moderate accuracy. The second tier uses a set of combinations schemes to combine the predictions from the base learners. The outputs from the combination schemes form the input space for the next tier.

The third tier does the meta-learning using the newly formed input space. The performance of this algorithm is optimized using a suitable number of base learners and a suitable number of combination schemes. The choice of meta-learner in the third tier also plays a vital role in improving the accuracy of this algorithm. The base tier ensures a reduction of bias, the ensemble tier and the generalization tier ensure the reduction of variance. As a result, the bias is perfectly balanced with the variance. Due to this, the proposed algorithm improves the classification accuracy. Hence this algorithm is suitable for classifying PTB based on the historical data of expectant mothers.

In general, for any classifier, cross-validation helps in reducing bias (33,34). In the proposed algorithm, a 10-fold cross validation is also used to train the base learners. The dataset is partitioned into 10 disjoint sets. Each of these 10 sets is used one after the other as a test set. Each fold is used nine times as a training set. As a result, the base learners produce the cross-validated predictions. Figure 1 depicts the cross-validation of the base learners. The output of the base tier is multiple sets of cross-validated predictions because this process is repeated for each base learner. This serves as the input for the next tier.

As depicted in Figure 2, the set of cross-validated predictions from each base learner are used as input in the second tier. The goal of the second tier is to combine the predictions from the base tier and to map them with one of the class labels. Hence, it creates a joint distribution of the base learners' predictions. The output from each combination scheme provides a meta-feature. The quality of the meta-features depends on the choice of the combination schemes used in this tier. The better the combination schemes, the better the meta-features capture the inherent relationship between the input space and the actual labels. Therefore, the meta-features play an important role in the accuracy of this innovative SE algorithm. The combination schemes to be used in this tier are decided depending upon the problem on hand. Popular combination schemes such as averaging and majority voting work well for most of problems.

As depicted in Figure 3, the meta-features and the top three critical features selected from the original input space form the

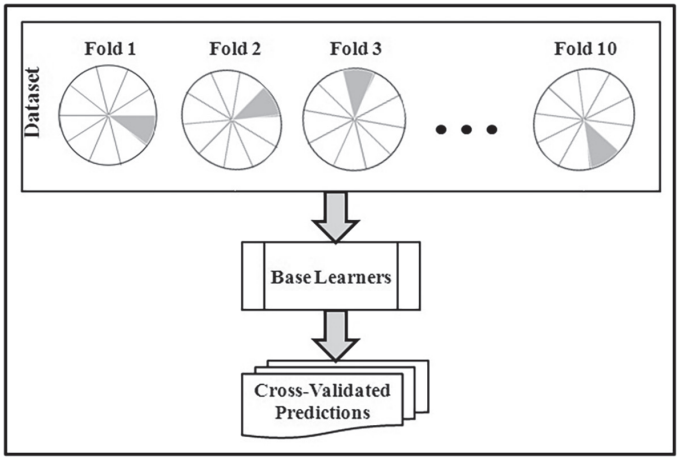

Figure 1. Training the base learners – base tier

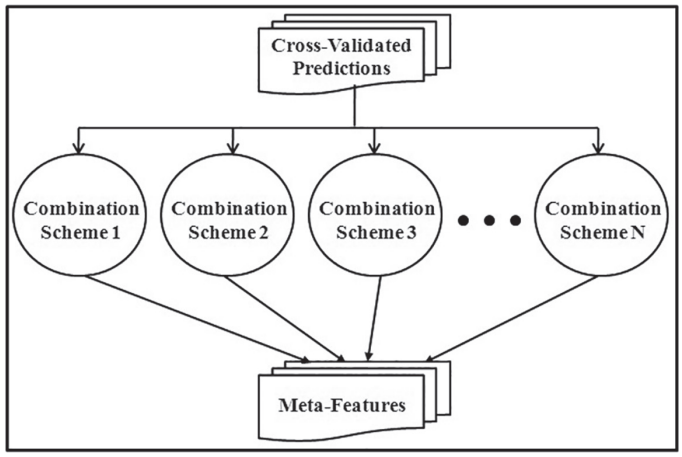

Figure 2. Combining the predictions from the base learners – ensemble tier

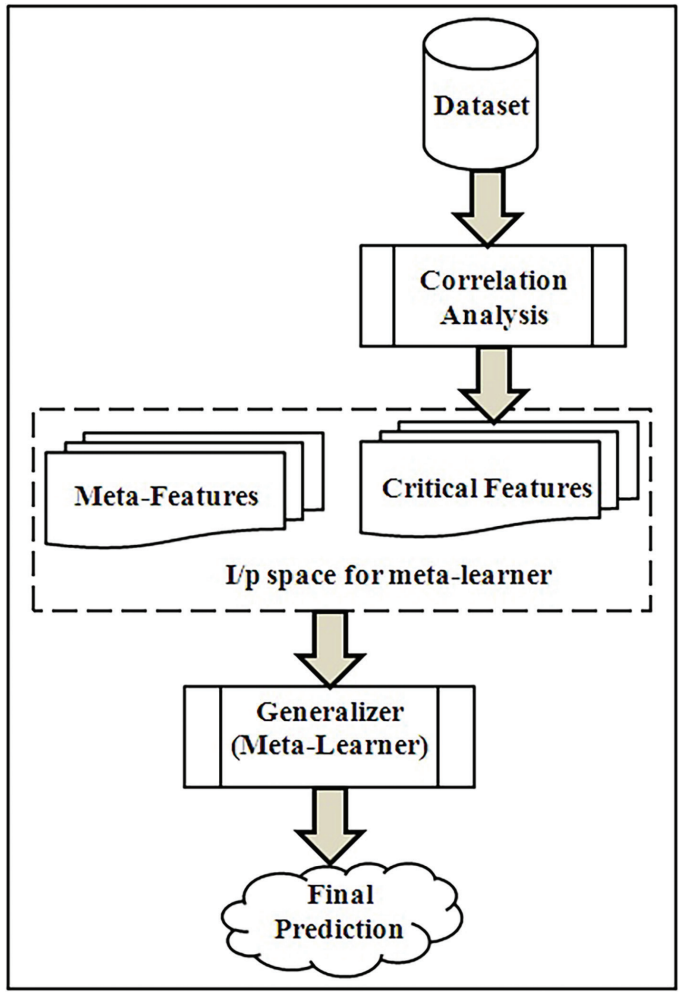

Figure 3. Training the meta-learner – generalization tier

input space for the meta-learner. The top three features are selected by analyzing the correlation of each feature with the class labels. The features that have high correlation with the class label are selected.

After analyzing the historical data of the patients, we decided to use the following list of base learners, the combination schemes, and the meta-learner in this study. This is shown in Table 2.

The experiment was implemented using the Python and Scikit-learn library (35). A dataset consisting of the historical data of 2600 patients was used to carry out this study. The dataset was a masked dataset without any reference to the personal details of the patients. Accordingly, the need to obtain informed consent and ethics committee approval did not arise. The details about the data set are given in Table 3. The data were thoroughly reviewed to check if the dataset had a good mix of all the possible cases: (i) mother with risk factors and had a PTB, (ii) mother without risk factors and had a PTB, (iii) mother with risk factors but had a TB, and (iv) mother without risk factors and had a TB. This mix of all the possible cases was also ensured in the training and testing data.

The distribution analysis of the class labels in the dataset reveals that the dataset was asymmetric one and skewed towards TB. PTB was the minority class and TB was the majority class. Hence, the SMOTE (Synthetic Minority Over-sampling Technique) algorithm was used to balance the dataset. Balancing the dataset increases the number of minor instances to match with the number of major instances. This in turn increases the total number of instances. The count of TB and PTB in the dataset before and after SMOTE is shown in Figure 4.

The dataset was thoroughly analyzed for missing data or null values because missing data plays a large role in pulling down the accuracy of models. If missing data or null values were found in any of the features, the criticality of the feature in which it is found was analyzed. For all critical features, mean values were used to replace missing data. For all non-critical features, the default values were used. A scatter plot of the historical data was plotted to reveal the outliers. The top 5 critical features were selected and concatenated because most of the features were binary in nature. The concatenated feature is taken along the x-axis and the class label is taken along the y-axis. The central mass of the plot was identified and the points that were further away from this central mass were analyzed to identify the outliers. The identified outliers were removed from the dataset. Normalizing the dataset also helps in improving the performance of the learning algorithm. Accordingly, different normalization methods were analyzed to select a suitable one for the problem on hand. In this study, the dataset was normalized by performing mean cancellation.

To assess the impact of primary and secondary factors on the classification accuracy, multiple experiments were conducted with different subsets of features in the dataset. The list of experiments conducted is depicted in Table 4. These experiments help to understand the contributions of primary

Table 2. Classifiers used in different tiers

Base learners	Support vector machines Decision trees Logistic regression K-Nearest neighbors Gaussian Naïve Bayes Stochastic gradient descent Passive aggressive classifier Perceptron
Combination schemes	Aggregation (Averaging and rounding off) Majority voting Weighted majority voting Confidence based voting
Generalizer	Decision trees

Table 3. Description of the dataset

#Instances	2600
#Attributes	26
#Classes	2
#Major instances	1936
#Minor instances	664
Imbalance ratio	2.92

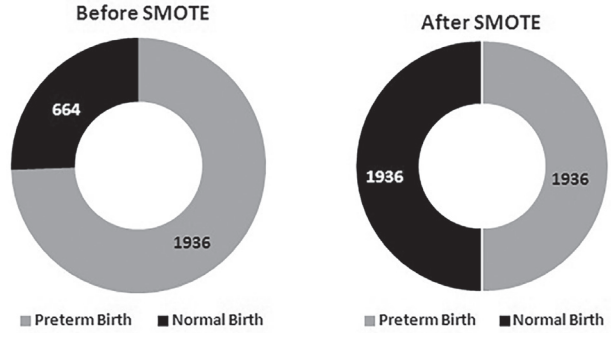

Figure 4. Count of NB and preterm birth in the dataset

Table 4. List of experiments

No.	Experiment	Description
1	Top 5 secondary	Top 5 features from the secondary risk factors
2	Only secondary	All features from the secondary risk factors
3	Top 5 primary	Top 5 features from the primary risk factors
4	Only primary	All features from the primary risk factors
5	All factors	All risk factors

and secondary risk factors for PTB. Each experiment was repeated 10 times to ensure the consistency of the results. The average values of the accuracy, precision, recall, and the F-1 score across the trials are reported in this study. Receiver operating characteristic (ROC) curves were also drawn for each experiment and these are also reported in this study.

Results

A comparative analysis of different performance metrics for SE and the proposed algorithm was conducted. In addition, analysis of how the feature subsets improved or degraded the performance metrics was also performed. This analysis helps in understanding the factors that make a major contribution to PTB. The results reveal that the performance metrics reached the maximum when all the features in the dataset were used for training the algorithms. Irrespective of the number of risk factors used for training, the performance of the proposed algorithm is better than the performance of SE. The results of the experiments in which all the risk factors are used for training is summarized in Table 5.

The analysis of accuracy for SE and the proposed algorithm is depicted in Figure 5. Among the five experiments conducted, the accuracy was at the minimum for the experiment conducted with only the top five secondary risk factors. There was a big jump in accuracy when other secondary risk factors were also used for training the algorithms. The improvement in accuracy of the proposed algorithm reached the maximum of 12% when only the secondary risk factors were used for training. This implies that, when only trivial features are available, the proposed algorithm can still perform much better than SE. This is mainly due to the reason that the proposed algorithm is not affected much by overfitting or underfitting. When all the factors are used for training, there is an improvement of more than 3% in accuracy over SE. When only the primary risk factors were used for training, the accuracy of the proposed algorithm was just 1.3% below the accuracy of the proposed algorithm when all the risk factors were used. Hence the contribution of the secondary risk factors in PTB is not significant. Even the maximum accuracy of 93.8% achieved by SE when all the factors are used for training is 1.8% less than the accuracy achieved by the proposed algorithm with only primary factors. Hence, for high-dimension datasets also, the proposed algorithm can use minimal features and achieve better accuracy than SE.

The analysis of precision for SE and the proposed algorithm is depicted in Figure 6. The observed values of precision are also in similar lines of accuracy. The precision of the proposed algorithm reached the peak value of 98.56% when all the risk factors were used for training. The high value of precision for the proposed algorithm implies that the number of false

Table 5. Summary of the results

Performance metrics	SE	Proposed algorithm	Performance improvement
Accuracy	93.80%	96.90%	3.10%
Precision	94.83%	98.56%	3.73%
Sensitivity/recall	93.16%	94.44%	1.28%
F1 score	92.95%	95.01%	2.06%
AUC	92.67%	94.92%	2.25%
SE: Stacked ensemble; AUC: Area under the curve			

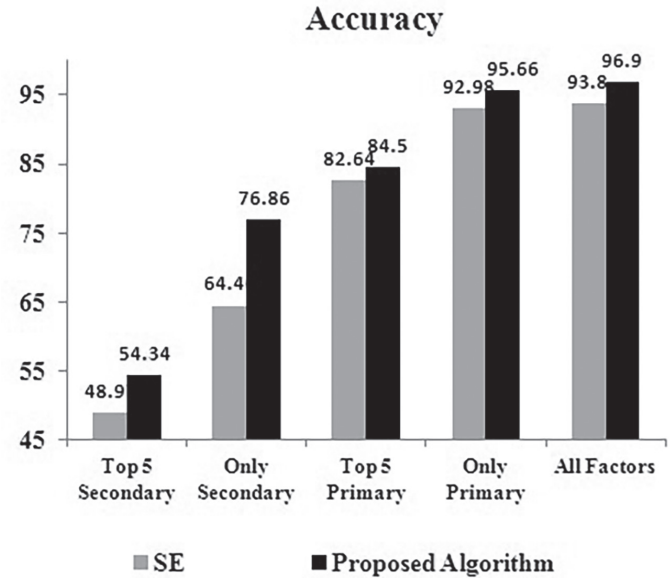

Figure 5. Accuracy of the classifiers – stacked ensemble vs proposed algorithm

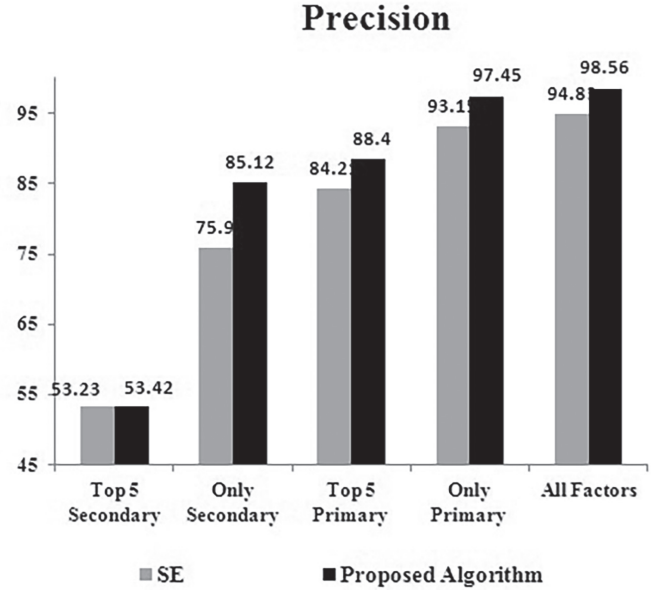

Figure 6. Precision of the classifiers – stacked ensemble vs proposed algorithm

positives was less. The high precision implies that most of the TB cases were predicted as NBs. This avoids unnecessary treatment being given to expectant mothers who would otherwise have undergone treatment. The improvement in precision reached a maximum of 10% when only secondary risk factors were used for training. Even with trivial factors, the proposed algorithm performed better than SE.

The analysis of sensitivity for SE and the proposed algorithm is depicted in Figure 7. The high value of sensitivity for the proposed algorithm implies that the number of false negatives was less. The high sensitivity implies that most of the PTB cases were predicted as PTBs. This indicates that the patients who need immediate medication are not ill-affected by the predictions of the proposed algorithm. The improvement in sensitivity reached the maximum of 8.5% when only primary risk factors were used for training. When the top five secondary risk factors were used for training, there was no improvement in sensitivity.

The analysis of F1 scores for SE and the proposed algorithm is depicted in Figure 8. The F1 score is the harmonic mean of precision and sensitivity. As the proposed algorithm achieved improvement in both precision and sensitivity, its F1 score was also better than that of SE for all five experiments. The F1 score reached the minimum when only the top 5 secondary risk factors were used to train the algorithms. The difference in the F1 score of SE and the proposed algorithm was as high as 13% when only the secondary risk factors were used for training. The F1 score reached the maximum when all the risk factors were used for training.

ROC curves were drawn to analyze the AUC. The ROC for SE and the proposed algorithm for the five experiments are depicted in Figure 9. The set of graphs in the first row correspond to SE and the set of graphs in the second row correspond to the proposed algorithm. In the below graphs, the middle way mark of 50% is represented as dotted lines. As expected, the AUC reached the minimum when only the top five secondary risk factors were used to train the algorithms. The AUC increased with the number of critical factors used for training. The greater the number of critical factors used for training, the greater is the AUC. It reached a peak for both SE and the proposed algorithm when all risk factors were used for training. The minimum values of AUC for the top 5 secondary risk factors imply that the true positive rate did not reach the peak even if the false positive rate reached the minimum. This means that false negatives were high in the prediction. From the perspective of PTB, this is alarming. High values of false negatives imply that a patient who needs immediate attention and treatment may not receive treatment.

The application of the innovative SE algorithm for predicting PTB achieved better performance than SE for all the experiments conducted in this study. For all the performance

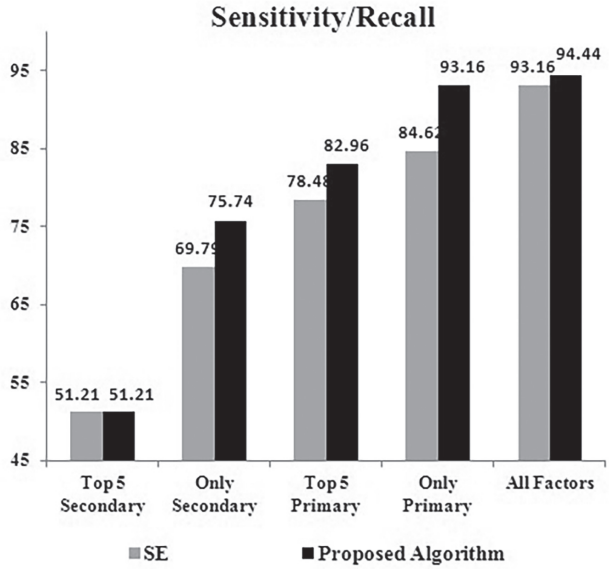

Figure 7. Sensitivity of the classifiers – stacked ensemble vs proposed algorithm

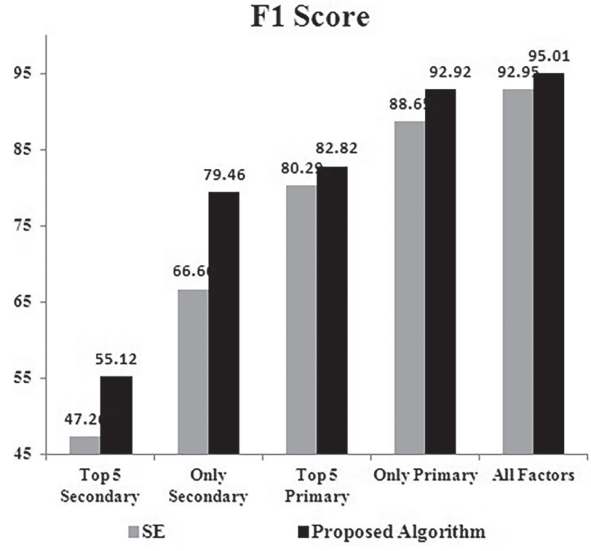

Figure 8. F1 score of the classifiers – stacked ensemble vs proposed algorithm

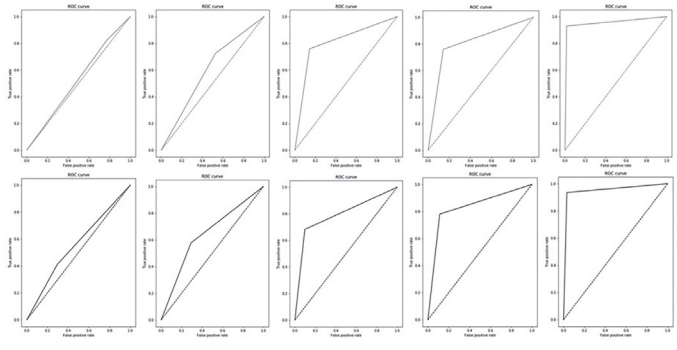

Figure 9. ROC curves for stacked ensemble (first row) and the proposed algorithm (second row)

metrics considered in this study, the innovative SE algorithm is way ahead when compared with the traditional SE algorithm. Primary risk factors play a major role in predicting PTB. When secondary factors were used along with primary risk factors, the performance metrics improved marginally (little more than 1%). Hence, using only primary risk factors with the proposed algorithm is the efficient method for PTB prediction. The time complexity of the proposed algorithm with different sets of factors can be considered for future work. The accuracy can be further improved by using a large number of base learners and combination schemes because the proposed algorithm is scalable in these terms. Finding the optimal number of base learners and combination schemes is also an interesting area to explore further. In order to increase the clinical use of this algorithm, we are considering the possibility of designing a mobile app with a wrapper around the algorithm. The mobile app allows physicians to enter the results of clinical tests of expectant mothers using an interface and provides the corresponding prediction. This mobile app hides the complexities of the statistical methods from the end user and thus greater numbers of physicians can benefit from this algorithm. We are also exploring if this algorithm can be enhanced and extended to analyze other maternal complications.

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Informed Consent: *It isn't taken.*

Peer-review: *Externally peer-reviewed.*

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Selective fetal reduction in monochorionic twins: Preliminary experience

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Abstract

Objective: In complicated mono-chorionic twin pregnancies, vaso-occlusive techniques like bipolar cord coagulation (BPCC), radiofrequency ablation (RFA), interstitial laser ablation (ILA) of cord and fetoscopy guided cord coagulation with lasers are the methods proposed for selective fetal reduction. This study brings forth preliminary data of selective fetal reduction procedures at a tertiary care center in India.

Material and Methods: This was a prospective observational study of 31 patients with complicated mono-chorionic twin pregnancies. Methods used were ILA, RFA and BPCC. Outcome measures included overall co-twin survival after selective feticide, survival rates with each method, miscarriage (defined as all fetal loss before 24 weeks), early fetal death (<24 hours after procedure) and late fetal death (>24 hours after the procedure) of co-twin.

Results: Technical success was achieved in 30/31 (96.8%) of pregnancies. Over all take home baby rate was 63.3%. Live birth rates were 50%, 71.4% and 75% with ILA, RFA and BPCC respectively.

Conclusion: Data from initial cases of selective fetal reduction in complicated mono-chorionic twins suggests that these procedures are feasible but are associated with high adverse perinatal outcome. (J Turk Ger Gynecol Assoc 2019; 20: 79-83)

Keywords: Monochorionic, selective fetal reduction, bipolar cord coagulation, interstitial laser, radiofrequency ablation

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Introduction

It is a well-accepted fact that multiple pregnancies have more maternal complications (abortion, preterm labor, preterm pre-labor rupture of membranes, hypertension in pregnancy, anemia, ante and post-partum hemorrhage, malpresentation, cesarean section) and fetal complications (malformations, intrauterine fetal growth restriction, and complications of prematurity) (1). Therefore, with triplet and higher order gestation, fetal reduction to achieve a total number of two live fetuses is offered to couples with an aim of minimizing these complications. Fetal reduction from twin to singleton in dichorionic twins is debatable, but selective termination in twin gestation discordant for malformations or genetic abnormality is acceptable (2).

In monochorionic twins, fetal reduction may be performed for indications other than twins discordant for anomalies. Monochorionic twins have a unique set of complications such as twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction, and twin reversed arterial perfusion sequence (TRAP). These complications are due to the presence of inter-fetal vascular anastomoses, which may put one twin at risk of death and adversely affect the health of the other twin. In the event of one twin dying, the transfer of a significant amount of blood from the normal to the dying fetus, through these placental vascular anastomoses, may occur leading to hypotension, hypo-perfusion of the brain leading to cerebral injury (20-30%) and fetal demise (up to 10%) (3-5). In a situation where death in one twin is imminent but pregnancy is very preterm, resorting to fetal reduction can optimize outcomes in the surviving twin. Unlike dichorionic pregnancies, fetal reduction using potassium chloride (KCl) instillation in fetal thorax/heart is not an option in mono-chorionic twins due to the presence of placental vascular anastomosis; KCl

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might transfer to the other fetus and thus inadvertently cause demise of both twins. Vaso-occlusive techniques such as bipolar cord coagulation (BPCC), radiofrequency ablation (RFA), interstitial laser ablation (ILA) of cord, and fetoscopy-guided cord coagulation with laser are the methods proposed for selective fetal reduction in complicated monochorionic twins (6).

We describe our experience of selective fetal reduction in complicated monochorionic twin pregnancies at a Maternal Fetal Medicine unit in a tertiary care center in India.

Material and Methods

This is a prospective study that included 31 patients with complicated mono-chorionic twin pregnancies who underwent selective fetal reduction from June 2013 to June 2017, in our unit. The pregnancies were very preterm and at risk of demise of one fetus, which could have adversely affected the other fetus. Informed written consent was obtained from each patient prior to the procedure. The analysis and publication of these data was approved by the institutional ethics committee.

Methods used for cord coagulation were ILA, BPCC, and RFA. ILA was used for fetal reduction in the first half of the study period, whereas in the second half BPCC and RFA was used. The choice of method also depended on the period of gestation and the indication for reduction.

All procedures were performed under ultrasound (US) guidance, using aseptic precautions. Patients received intravenous (i.v.) sedation, injection cefazolin (1 g i.v.) after a sensitivity test, and one dose of 100 mg micronized progesterone intramuscularly (i.m.) prior to the procedure as per the unit protocol. Trocar/needle insertion site was infiltrated with 10 mL of 1% solution of xylocaine.

Bipolar occlusion of cord

The procedure was performed in pregnancies between 18-26 weeks' gestation and only if the maximum diameter of the fetal cord was 15 mm or less. Using US guidance, a 3 mm port was inserted into a pocket of amniotic fluid of the affected fetus, preferably at a place away from the placenta. The cord was approached at the abdominal insertion, grasped with the prongs of the bipolar insert, and then pulled to ensure that it was held in its entire width and complete occlusion was confirmed by the absence of flow on color Doppler. Coagulation of the cord was then performed using 20-40 W energy in bursts of 10-15 sec. Echogenic bubbles could be seen and the area of the cord appeared echogenic following the procedure. Two areas of cord were coagulated. The procedure was considered successful if cardiac asystole and absence of flow in the umbilical cord was observed.

Interstitial laser ablation of cord

The procedure was conducted in pregnancies between 18-26 weeks' gestation. A 400-micron diode laser was delivered through an 18-G spinal needle under US guidance, targeting intraabdominal fetal umbilical vascular confluence. The laser was fired in short (6-10 sec) pulses at 20-40 W bursts till blood flow ceased.

Radiofrequency ablation of cord

RFA was performed in pregnancies between 16-27 weeks' gestation. Under continuous US guidance, a 16-G RFA needle was inserted into the fetal abdomen, alongside the umbilical cord insertion. The prongs of the RFA needle were then deployed in the fetal abdomen and 40 W of energy was delivered to build up the temperature to 100 °C for 2-3 minute till cardiac asystole and cessation of blood flow in umbilical cord was observed; the procedure was repeated in the absence of which.

In cases with cervical length less than 25 mm, cerclage was performed in the same sitting.

An US examination was performed after 24 hrs to re-document absent cardiac activity in the reduced twin and to check the cardiac activity in the other twin. Middle cerebral artery (MCA) peak systolic velocity (PSV) was measured in the surviving twin to detect fetal anemia, following which the patients were discharged and kept on 2-weekly follow-up. Fetal magnetic resonance imaging (MRI) was performed for some patients after 28 weeks (or 3-4 weeks after procedure) to look for intracranial hemorrhage and cerebral injury.

Outcome measures included overall co-twin survival after selective feticide, survival rates with each method, miscarriage (defined as all fetal loss before 24 weeks), early fetal death (<24 hours after procedure), and late fetal death (>24 hours after the procedure) of the co-twin.

Results

Of 31 patients undergoing the procedure, technical success was obtained in 30/31 (96.77%), one patient with a failed procedure was excluded from the analysis. This patient was at 26 weeks with TTTS stage III and gross polyhydramnios, BPCC was unsuccessful. The indications for selective fetal reduction and methods used in the other 30 patients are shown in Table 1.

The mean gestational week at fetal reduction was 23 weeks and 2 days (range, 16-26+4 weeks). Early intrauterine fetal death (IUFD) occurred in 5/30 (16.67%) patients and late IUFD occurred in 1/30 (3.33%); there were 2 spontaneous abortions (6.66%). Both early and late fetal deaths happened in fetuses less than 24 weeks' gestation. Thus, there were 8 (26.67%) miscarriages (defined as pregnancy loss at or less than 24 weeks gestation).

The mean gestational week at delivery was 35 (range, 26-39)

weeks: 13/30 (43.33%) women delivered at or beyond 36 weeks' gestation, 2/30 (6.67%) delivered between ≥32-36 weeks, 3/30 (10%) delivered at ≥28-32 weeks' gestation. Of the 4 patients who delivered between 24 and 28 weeks, 3 had stillbirths.

The overall live birth rate was 19/30 (63.3%). There were 3 stillbirths (10%). These three patients delivered between 26-28 weeks' gestation.

Vaginal birth was achieved in 18/30 (60%) patients. Four babies (21%) required care in the neonatal intensive care unit. The perinatal outcomes of the three procedures are shown in Table 2.

Follow-up after the procedure

We detected raised MCA PSV after the procedure in 3 cases, one of which aborted subsequently. The other two pregnancies had a normal fetal MRI, the values decreased on follow-up and they delivered a healthy baby at term.

Fetal brain MRI was performed in 14 cases and was found to be normal.

Patients were followed up bi-weekly for growth scans, and monitored for fetal wellbeing. There was no evidence of infection (clinical) in the patients following the procedures.

Table 1. Indications and methods used for fetal reduction

Total number of patients	31
Successful procedures	30/31 (96.8%)
Indications for selective fetal reduction	TRAP 4/30 (13.33%) TTTS 9/30 (30%) sFGR 3/30 (10%) Discordancy for malformations/NIH 14/30 (46.67%)
Methods used for selective fetal reduction in the 30 patients included in analysis	IL 12/30 (40%) BPCC 4/30 (13.33%) RFA 14/30 (46.67%)

TRAP: Twin reversed arterial perfusion, TTTS: Twin-to-twin transfusion syndrome, sFGR: Selective fetal growth restriction, NIH: Non immune hydrops, IL: Interstitial laser, BPCC: Bipolar cord coagulation, RFA: Radio frequency ablation

Discussion

We evaluated perinatal outcomes after selective feticide in complicated monochorionic twins. The overall survival rate of the co-twin was 63.3%. The survival rate was lower with ILA (50%), whereas survival after RFA and BPCC was similar (71.4 and 75%). A systematic review of selective fetal reduction in 345 complicated mono-chorionic twin pregnancies had an overall fetal survival rate of 79% (65-90%) (2). The authors (2) observed that fetal survival rates were highest with RFA (86%), followed by BPCC (82%), laser cord coagulation (72%), and lowest with cord ligation (70%). The overall survival of the co-twin in our cohort was lower than that reported in this systematic review, though comparable to the study published by Van Den Bos et al. (6) (67.2%). In their series of 131 cases, the survival was lowest with ILA at 46.7%. In our series, the mean gestational age at procedure was higher, this is because of late referrals. Also, TTTS was the indication for reduction in 30% of cases, with most associated with polyhydramnios and short cervix and higher risk of preterm delivery. Procedures with advanced gestation and larger-diameter cords may require more time and multiple cycles of coagulation leading to inter twin transfusion during the procedure, and increasing the risk of demise of the normal twin.

Studies have shown that fetal loss is higher when the procedure is performed before 18 weeks' gestation (6). As also shown in the systematic review (2), survival rates were better if the procedures were performed after 18 weeks (89% vs 69%). Yinon et al. (7) compared RFA and BPCC and found similar overall survival rates (88.9% vs 76.5%). Selective intrauterine growth restriction as a primary indication for feticide, compared with TTTS, showed a trend towards higher gestational age at delivery and longer procedure to delivery interval. Though the overall survival was similar, the interval between the procedure and delivery was shorter in >24 weeks' gestation group at the time of the procedure compared with that at <24 weeks. Bebbington et al. (8) compared RFA with BPCC and reported similar success rates. They also reported lower survival if

Table 2. Perinatal outcome according to technique for selective fetal reduction

	IL n=12	BPCC n=4	RFA n=14	Total n=30
Mean gestational week at procedure (weeks) Range (weeks)	23^{+4} (18-26^{+4})	22^{+5} (20-26)	24^{+3} (16-26^{+4})	23^{+2} (16-26^{+4})
Early IUFD	3	1	1	5 (16.67%)
Late IUFD	0	0	1	1 (3.33%)
Spontaneous abortion	1	0	1	2 (6.67%)
Still birth	2	0	1	3 (10%)
Mean gestational week atdelivery (in weeks) Range (in weeks)	34 26-39	36 28-37	36 28-38	35 26-39
Live birth rate	6/12=50%	3/4=75%	10/14=71.4%	19/30 (63.3%)

the indication for reduction was TTTS compared with other indications. Sun et al. (9) reported a fetal death rate of 23% after RFA. Variables associated with fetal death were indications for RFA, gestation age >20 weeks, >2 cycles of RFA coagulation, and maximal power setting. In multivariate analysis >2 cycles of RFA coagulation was the only factor independently associated with fetal death (odds ratio: 3.46) (10).

Preterm birth and preterm premature rupture of membranes (PPROM) has also been reported as an important cause of perinatal morbidity and mortality in other series (6,8). Van Den Bos et al. (6) reported an overall PPROM rate of 19.8% with 43.5% babies born between 28 and 37 weeks' gestation. Bebbington et al. (8) reported an overall PPROM rate of 21.9% after RFA and BCC with preterm delivery (<34 weeks) in 59% of RFA and 44% of BCC procedures (11). In our series, 30% women delivered before 32 weeks.

The procedure is performed to avoid neurologic sequelae in the co-twin when one twin is at risk of death and too premature to deliver. However, we need to understand that survivors after selective feticide in monochorionic twins are at increased risk of neurodevelopmental delay. Van Klink et al. (10) reported neurodevelopmental impairment in 6.8% of surviving twins at a minimum follow-up of 2 years. This is very important and should be part of pre-procedure counseling. We performed antenatal MRI after the procedure in a small number of cases.

Fetal reduction procedures in monochorionic twins are considered to be considerably complex and challenging. They require expertise with hand-eye-needle coordination and a great deal of patience, as needed for most fetal medicine procedures performed under US guidance. Anterior placenta poses technical difficulty because introducing the trocar/needle might result in hemorrhage into the amniotic cavity, which could limit visibility and may also compromise the fetuses. The position of the fetus is also crucial to the success of the procedure. With the fetal spine up towards the maternal abdomen, gaining access to the umbilical cord insertion during ILA/RFA might be difficult. During BPCC, the cord may slip from between the prongs resulting in exsanguination from an incompletely coagulated cord. The presence of polyhydramnios and short cervical length may contribute to an increased incidence of PPROM and preterm delivery/abortion.

This is probably one of the few studies from developing countries to deal with selective fetal reduction in complicated monochorionic twin pregnancies. The only other studies from our country include a retrospective series of 15 cases of complicated monochorionic twin pregnancies managed by RFA (11) and a single case of complicated TRAP sequence managed by interstitial laser (12).

Even though we performed the procedure in a small number of patients, this study highlights the feasibility of selective fetal reduction in complicated monochorionic twins in a low-resource setting. The drawbacks are that we could not retrieve the number of women having PPROM from our data, and also the follow-up of babies after discharge was not available. We did not record the cervical length and time/number of cycles required for successful reduction factors known to be risk factors for perinatal outcome. The number of cases of BPCC is small.

Data from initial cases of selective fetal reduction in complicated monochorionic twins suggests that these procedures are feasible but are associated with high adverse perinatal outcomes.

Ethics Committee Approval: *The analysis and publication of these data was approved by the institutional ethics committee.*

Informed Consent: *It was taken.*

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Effects of mature cystic teratoma on reproductive health and malignant transformation: A retrospective analysis of 80 cases

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Abstract

Objective: To examine cases of mature cystic teratoma (MCT) that were diagnosed and treated in our clinic regarding their association with fertility, and to detect the rate of malignant degeneration and the types of malignancies.

Material and Methods: Patients who underwent surgery due to adnexal mass between April 2012 and August 2017 and were diagnosed as having MCT were retrospectively examined. The mean age of the 80 patients who met the inclusion criteria was 30.60±10.5 years. Nine had infertility according to hospital records. Sixty-seven percent of these (n=6) had accompanying endometriosis and MCT was bilateral in 55.5% (n=5). Malignant degeneration was present in 6.25% (n=5), all were monodermal tumors. Malignant degeneration was more common among patients with larger diameter adnexal masses (9.1±2.9 cm) and in those of postmenopausal age. Tumor markers were within the normal range for patients who developed malignancy. Malignant degeneration was not present among infertile patients with endometriosis.

Results: Although MCTs do not seem to negatively affect the ovarian reserve, infertility is prominent in patients with concurrent endometriosis. During assessment, concurrent endometriosis should be considered. Imaging findings, large adnexal masses, and postmenopausal period are important for the assessment of MCT concerning malignant degeneration. It should not be overlooked because tumor markers may be normal.

Conclusion: MCTs can be present concurrent with endometriomas. In such cases, infertility is more distinct. In MCT malignant degeneration, mass diameter, complex mass internal structure, and postmenopausal status are important factors. (J Turk Ger Gynecol Assoc 2019; 20: 84-8)

Keywords: Mature cystic teratoma, malignant degeneration, infertility treatment

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Introduction

Mature cystic teratomas (MCTs) are the most common benign germ cell tumors during the adolescent and reproductive period. Histologically, they may include tissues differentiated from each of the three germ layers (ectoderm, mesoderm and endoderm). They are seen predominantly in the reproductive period; however, they are also seen in childhood and the postmenopausal period. MCTs account for 20-25% of all benign ovarian tumors and bilaterally rates are about 10-15% (1). The most common signs are abdominal pain and findings of a pelvic mass, but they can be detected incidentally as well.

Complications occur in 20% of patients with MCT (2). These complications include torsion, rupture, infection, and malignant transformation. Malignant transformation is quite rare and predominantly detected in the postmenopausal period, whereas other complications may cause undesirable reproductive outcomes concerning the age period when they occur.

Our purpose in this article was to examine the cases of MCT that were diagnosed and treated in our clinic regarding the effects on fertility, rates of malignant transformation, and clinicopathologic features.

Material and Methods

Files of patients who underwent surgery due to a prediagnosis of adnexal mass with a histopathologic diagnosis of MCT between April 2012 and August 2017 were retrospectively reviewed. Permission was obtained from the medical director

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of the hospital to access file information and computer records and from the ethics committee to use patient data. Patients who were diagnosed as having MCT after histopathologic evaluation and had sufficient demographic and medical information in their files were included in the study.

The inclusion criteria for our study were as follows: patients who were clinically evaluated, surgically treated, and diagnosed as having MCT in our hospital; patients who were not pregnant at the time of diagnosis; with a confirmed pathologic diagnosis of MCT; and adequate demographic and medical information in the case files. Diagnosis and treatment in another clinic, diagnosis during pregnancy, the presence of all other malignant and benign ovarian masses that received a different histopathologic diagnosis during the final evaluation, diagnosis such as tubo-ovarian abscess, and lack of sufficient information in the case file were set as criteria for exclusion.

Patient histories and file records were reviewed for patients with MCT, regarding the presence of any symptoms/reports of infertility before or during admission. In addition, the number of pregnancies and births were also taken into consideration. Imaging methods, tumor markers, and additional pathologies accompanying MCT were reviewed for all cases.

Concerning malignant transformation in MCT, the patient files were reviewed in terms of age, parity, family history, and malignancies of other organs.

Result

The records of 93 patients who underwent surgery due to an adnexal mass and were diagnosed as having MCT between April 2012 and August 2017 were accessed. Thirteen of which were excluded mostly due to a lack of sufficient medical history and different histopathologic diagnoses. Eighty patients formed our study group and the mean age was 30.60±10.50 (range, 14-65) years. Seven patents (8.75%) were of postmenopausal age (age >45 years), 91.25% (n=73) were of premenopausal age (age ≤45 years). The most common symptom before admission was pelvic pain accompanied by abdominal distention in 76.25% (n=61) of the patients. The remaining 23.75% (n=19) were detected incidentally.

The most commonly performed imaging technique was abdominopelvic ultrasonography (USG). After an initial evaluation of all patients with USG, 13 patients were evaluated using computed tomography (CT), 33 patients with magnetic resonance imaging (MRI), and 2 patients with both CT and MRI.

The most frequently requested tumor markers to evaluate the malignancy potential of the adnexal mass were as follows: CA125 (n=80), CA19-9 (n=63). The mean value of CA125 was 24.23±16.10 IU/mL (normal reference range: 0-35 IU/mL); the mean value of CA 19-9 was 32.43±89.10 IU/mL (normal reference range: 0-35 IU/mL). When the cut-off value of 35 U/mL was accepted for both tumor markers, CA125 and CA19-9 were detected as high in 17.50% (n=14) and in 19.04% (n=12) of the patients, respectively. Both tumor markers were high in only 4.76% (n=3) of patients.

Fifty of the 80 patients were multiparous, the mean gravida was 1.78, parity was 1.12. Thirty patients were nulliparous. When all patients were evaluated according to the initial symptom, 9 had infertility. Among these 9 patients who underwent surgical treatment, apart from a dermoid cyst, endometriosis was found in six and one had hydrosalpinx (Table 1). The mean CA125 and CA19-9 levels of these 6 patients, who had infertility and diagnosed as having both MCT and endometriosis, was 39.16±16.60 IU/mL and 19.33±14.40 IU/mL, respectively. The CA125 level was above the threshold value in 4 of these six patients (66.67%); the CA19-9 level was also above the threshold in one patient. In 5 of these six cases, bilateral teratomas were present and the mean diameter of tumor mass was 5.10±1.80 cm according to the USG measurement.

Malignant degeneration was observed in 6.25% (n=5) of the patients. All malignant degeneration was monodermal-specialized tumor. Malignant degeneration was observed in

Table 1. Accompanying pathologies in patients with MCT and infertility

Accompanying pathologies	Number of cases (n)	Rate (%)
Endometriosis	6	66.67%
Hydrosalpinx	1	11.11%
None	2	22.22%
Total	9	100%
MCT: Mature cystic teratoma		

Table 2. Histopathologic features and menopausal status of patients with MCT and malignant degeneration

Type of malignant degeneration	Premenopause	Postmenopause	Number of cases (n)	Rate (%)
Struma ovarii	1	1	2	40
Papillary microcarcinoma of thyroid	1	0	1	20
Oligodendroglioma	1	0	1	20
Strumal carcinoid tumor	0	1	1	20
Total	3	2	5	100
MCT: Mature cystic teratoma				

4.10% (3 of 73 patients) in the premenopausal period and in 28.57% (2 of 7 patients) in the postmenopausal period (Table 2). Among the patients with malignant degeneration, the mean mass diameter was 9.10±2.90 cm and no bilateral cases were observed. The mean values for tumor markers were 24.32±9.50 IU/mL for CA125, and 11.02±8.70 IU/mL for CA19-9, which were within normal reference values. Malignant degeneration was not observed in patients with infertility (Table 2).

Discussion

MCTs are the most common benign ovarian neoplasms in the reproductive period that can originate from all three germ layers (ectoderm, endoderm, mesoderm), as well as from a single germ leaf (1). The second and third decades are the peak ages and mean ages are reported as 30 years (2). In our case series, the mean age of onset was 30.60±10.5 and 91.25% (n=71) of the patients were in the reproductive period. The most common symptoms at admission were abdominal pain and distention. Although abdominal pain is more prominent with adnexal mass torsion, both findings are common during the adolescent period when the pelvic volume is limited (3). USG is the first and most frequently used imaging modality with clinical examination in all age groups (4). The initial evaluation of all our patients was performed using pelvic USG. MRI and CT are the most frequently requested imaging modalities for further evaluation. The size and contents of the cyst, ratio of solid components, presence of mural nodule, and vascular blood flow assessment with Doppler USG are radiologic findings that provide important information concerning the treatment plan (4).

Concerning the evaluation of MCT, which is observed during the reproductive period and in a wide spectrum ranging from a simple ovarian cyst to a complex adnexal mass, tumor markers are laboratory tests that are frequently used. MCTs do not have a specific tumor marker. Tumor markers are also insufficient in demonstrating malignant degeneration (2,5). The most frequently requested tumor markers in MCTs are CA125 and CA19-9. Neither CA19-9 nor CA125 is diagnostic for MCT, although they are frequently used in the evaluation of adnexal masses of the reproductive period. MCTs present as adnexal masses, and elevated tumor markers may be helpful concerning the evaluation of the malignant potential of the mass with further examinations (5-7).

Although MCT cases are seen in adolescence and in the postmenopausal period, the incidence increases in the reproductive period. The current literature is more focused on endometriotic cysts and infertility; however, the effects of MCT on reproductive health are unclear. As far as we know, there are no studies showing that infertility is directly related with MCTs, as it is in endometriotic cysts. The incidence of endometriosis among infertile women ranges from 9 to 50%; the incidence of teratomas in infertile women is unknown (8,9).

Unlike endometriomas, studies indicate that MCT does not reduce ovarian reserves (8-11). In our series, MCT was encountered in 9 patients during examinations for infertility, 6 of whom had accompanying endometriosis. In one patient, hydrosalpinx was also present. MCT was bilateral in 5 of these 9 patients. All patients with bilateral lesions (n=5) also had endometriosis. Endometriomas associated with MCTs are reported very rarely in the literature (12,13). Matalliotaki et al. (14) studied pathologies accompanying endometriosis in 1000 patients and reported that dermoid cysts were concurrently present in 1.2% of 295 cases of endometrioma.

Among the infertile patinets with MCT, the high incidence of accompanying endometriosis is the most characteristic feature of our case series. These results suggest that infertility is rather secondary to endometriosis. While evaluating patients with MCT who have infertility, bilaterality should be carefully investigated. Furthermore, foci of endometriosis should be thoroughly examined preoperatively with MRI or intraoperatively.

Given the inflammatory, infiltrative progression of endometriosis, growth in MCT is slow, expansive, non-invasive, and non-inflammatory. Unlike MCT, endometriosis causes destruction and fibrosis of the ovarian cortex, leading to a decrease in the number of follicles (8,10). MCTs are mostly unilateral, but even when they are bilateral, fertility is not adversely affected by proper surgical intervention in the presence of healthy ovarian tissue (15). In MCT, postoperative recurrence (4.2%) is extremely low compared with endometriomas (45-50%) (16). Due to these developmental features of MCT, ovarian reserve and fertility is not as adversely affected.

In the present study, no findings or problems related to fertility were found, according to the information collected from the patient records. In complicated large cysts (>8 cm), complications such as malignant degeneration, torsion, and rupture may develop; inappropriate surgical approach or spillage of cyst fluid may cause inflammation, irritation, and adhesions. In this case, if the preserved functional ovarian tissue is inadequate, subfertility and infertility may occur (8,10,17,18). If the cysts are small (<5 cm) and asymptomatic, they are unlikely to cause torsion and have a low potential for malignant transformation; we suggest that such special patient groups may be monitored until the completion of fertility. However, it is important to keep endometriosis in mind regarding patients with infertility.

Although dermoid cysts are slowly growing cysts, growth rates are increased by hormonal stimulation, especially by estrogen (19-21). Hormonal stimulation may be the reason for the high incidence of MCTs in reproductive age and also their tendency to become recognizable during pregnancy.

Complication (torsion, rupture, infection, malignant degeneration) rates were reported in the literature as up to 20% regarding MCTs, but no complications except malignant degeneration were observed in our series. Patients with adnexal masses and acute abdomen during pregnancy and emergency conditions were excluded in our study. Therefore, only patients who was selectively evaluated in a tertiary center were included in our case series.

Minimally invasive endoscopic approaches are important for the preservation of ovarian reserve and fertility in MCTs observed in the reproductive period and that are planned for surgical treatment because of the risk of complications (large mass diameter, rapid growth, pregnancy, risky imaging findings for malignant degeneration). Compared with endometriomas, MCT's expansive and noninfiltrative growth facilitates surgical dissection and causes less destruction in the ovary (8,10). For this reason, fertility is less adversely affected by surgery performed for MCTs.

Monitoring may be an alternative approach in MCTs with small mass diameters, that are stable in periodic controls, and not complicated by internal structures (19). The most important factors that affect the surgical decision in the reproductive period are mass size, bilaterality, the risk of emergency surgical intervention such as for torsion and rupture, the likelihood of malignant degeneration, a complicated internal structure of the image, increased tumor markers, and fertility status (20-22).

The incidence of malignant degeneration in MCT is reported as 0.2-2%. The most common malignant degeneration, squamous cell carcinoma (SCC), accounts for 80% of all malignant degeneration in MCT (22,23). In our series, the rate of malignant degeneration was 6.25% (n=5) and all malignancies were monodermal specialized tumors. The causes of malignant transformation of monodermal specialized tumors are unknown. These tumors may cause different clinical symptoms according to their originating germ layer and hormonal activations (e.g., carcinoid syndrome, thyrotoxicosis).

Although in our patients with malignant degeneration, the size of the mass (mean 9.1 cm) and the frequency of postmenopausal age were consistent with the literature, the high rate of malignant degeneration, the histologic type of malignancy, and normal tumor markers were differences that distinguish our series from the literature.

MCTs are common benign ovarian tumors in the reproductive period. Unless they grow rapidly or cause torsion, rupture and malignant degeneration, they do not seem to affect ovarian reserve harmfully. Teratomas develop expansively and in a non-inflammatory nature, while endometriotic cysts grow in an inflammatory nature and infiltrative way; this distinction is responsible for this outcome. In addition, the better response given to surgical treatment, having conservative approach as a valid option, and low rates of recurrence are among the important features of MCTs.

The most striking finding of our series is that regarding the patients in whom MCTs were concurrent with endometriomas, infertility was the initial symptom at admission.

An individualized conservative approach or delayed surgical treatment after completion of fertility may be appropriate and effective for patients with small and non-complex lesions in imaging studies, high expectation of fertility, and a high risk of losing significant ovarian reserve during surgery. However, if the mass is large, urgent surgical intervention should be considered because of the risk of torsion and rupture.

The outcome of ovarian protective treatment approaches is better than with endometriomas in terms of fertility when surgical excision is decided upon in MCT and appropriate surgical technique is selected. In the decision of exploratory surgical excision, patient age, clinical findings, possibility of emergency surgery, a complex internal structure in imaging modalities, elevated tumor markers, and reproductive expectations are determining factors.

Ethics Committee Approval: *Permission was obtained from the medical director of the hospital to access file information and computer records and from the ethics committee to use patient data.*

Informed Consent: *It was taken.*

Peer-review: *Externally peer-reviewed.*

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Association of decreased C1q/tumor necrosis factor-related protein-5 levels with metabolic and hormonal disturbance in polycystic ovary syndrome

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Abstract

Objective: C1q/tumor necrosis factor-related protein-5 (CTRP5) is a novel peptide hormone involved in the metabolism of energy regulation. Polycystic ovary syndrome (PCOS), which is a reproductive and metabolic disorder, is associated with insulin resistance. The aim of the current study was to compare circulating levels of CTRP5 in women with and without PCOS and to investigate possible associations between CTRP5 and metabolic-hormonal parameters.

Material and Methods: The present cross-sectional study contained 80 women with PCOS and 80 age and body mass index-matched women without PCOS. Circulating levels of CTRP5 were calculated using an enzyme-linked immunosorbent assay. We also measured hormonal and metabolic parameters.

Results: Patients with PCOS had lower levels of circulating CTRP5 compared with women without PCOS (6.90±2.64 vs 11.73±3.66 ng/mL, $p<0.001$). CTRP5 was negatively correlated with insulin resistance, free-androgen index, and body mass index in both the PCOS and control groups. Moreover, patients with PCOS who had insulin resistance showed lower circulating CTRP5 levels compared with those without insulin resistance. In both the control and PCOS groups, overweight subjects had lower circulating levels of CTRP5 compared with participants of normal weight. Logistic regression analyses indicated that subjects in the lowest tertile for CTRP5 level had higher risk for PCOS compared with those in the highest tertile of CTRP5.

Conclusion: Decreased circulating levels of CTRP5 were associated with higher risk of PCOS, as well as having metabolic disturbance among women with PCOS. (J Turk Ger Gynecol Assoc 2019; 20: 89-96)

Keywords: Polycystic ovary syndrome, C1q/tumor necrosis factor-related protein-5, insulin resistance, body mass index, free-androgen index

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Introduction

Polycystic ovary syndrome (PCOS) is known as a common metabolic and reproductive disease in women of reproductive age, which is characterized by ovulatory dysfunction, clinical and/or laboratory hyperandrogenism, and polycystic ovaries. Despite a lack of clear information about the pathophysiology of PCOS, genetic and environmental factors are believed to be influential in the development of the disease (1-3). Insulin resistance, glucose and lipid metabolism dysfunction, and

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obesity are frequently reported in women with PCOS. PCOS is also associated with low-grade chronic inflammation. Moreover, both insulin resistance and low-grade inflammation induce hormonal and metabolic abnormalities in women with PCOS (1,4). Changes in expression levels of various peptides in adipose tissue such as adiponectin in women with PCOS lead to hormonal and metabolic dysfunctions (5,6).

C1q/tumor necrosis factor-related protein-5 (CTRP5), a secreted peptide hormone and adiponectin paralog, is involved in energy metabolism, including glucose and lipid metabolism. CTRP5, which is expressed in many tissues such as adipose, myocyte, and liver (7-10), has the ability to induce phosphorylation of AMP-activated protein kinase (AMPK), thus stimulating glucose uptake and fatty acid oxidation (8,11). Hence, CTRP5 is highly expressed in obese and diabetic animal subjects (12). It has been illustrated that obesity level in humans is proportionate to enhanced expression in adipose tissue (13). On the other hand, genetically CTRP5-deficient mice showed improved insulin action (12). In accordance with these results, patients with type 2 diabetes (T2DM) were revealed to have lower CTRP5 levels, and CTRP5 was negatively correlated with both body mass index (BMI), as well as insulin resistance (14). It has also been reported that CTRP5 induces inflammation and proliferation in human aortic smooth muscle cells by activating a variety of pathways (15). In addition, a positive association was observed between CTRP5 and C-reactive protein (CRP) in subjects with chronic obstructive pulmonary disease (16).

In the current study, we compared CTRP5 levels in women with PCOS and control participants without PCOS and investigated relationships between CTRP5 and hormonal or metabolic parameters.

Material and Methods

Ethics

Ethical approval was issued by the ethics committee of İzmir Bozyaka Training and Research Hospital for the present study (no: 2. GOA/2016) and all participants provided written informed consent. The study was conducted and accomplished according to the Declaration of Helsinki (2008).

Study design and participants

This case-control study included two groups: 80 subjects with PCOS and a group of 80 age and BMI-matched women with normal menstruation. Participants aged 18-45 years were recruited. The study was conducted between June 2016 and January 2017 in the Endocrinology Department of the Bozyaka Training and Research Hospital in İzmir, Turkey. We consecutively recruited subjects who met all of the exclusion and inclusion criteria of the study to reach to the planned population. All participants had a BMI >18.5 kg/m^2 and ≤35 kg/m^2, and none had alcohol and tobacco addiction. The same researcher performed all examinations, and obtained detailed histories. All participants were subjected to 2-h 75-g oral glucose tolerance standard test (OGTT). All participants were drug naive.

PCOS group

The patients in the PCOS group were selected based on the Rotterdam Consensus Criteria (2003) and other possible causes of hyperandrogenism and ovulatory dysfunction were also excluded from the study (17). The presence of at least two of three criteria is needed to diagnose of PCOS, but we selected women who met all three criteria of Rotterdam Consensus Criteria to achieve homogeneity among the subjects. These criteria include 1- anovulation or oligoovulation; 2- either biochemical or clinical symptoms of hyperandrogenism, using Ferriman-Gallwey (FG) score to assess hirsutism (18); and 3- the existence of ≥12 follicles measuring from 2 to 9 mm in diameter or ovarian volume >10 mL (without a cyst or dominant follicle in one of the ovaries). Ultrasonographic signs consistent with PCOS in a single ovary were sufficient for diagnosis (M.A.).

Patients with FG score ≥8 were considered hirsute. Biochemical markers of hyperandrogenism were defined if serum levels of testosterone (normal range: 0.52 to 2.42 nmol/L), and/or dehydroepiandrosterone sulfate (DHEA-S) (normal range: 10-248 μg/dL), and/or free androgen index (FAI) ≥5% (19) were higher than the maximum limit of reference intervals.

Control group

The control group of comprised women who had visited the endocrinology and/or gynecology clinics for checkup and volunteer employees from the hospital. All controls had normal menstrual cycles. Disorders such as problems in concomitant health issue, acne, hyperandrogenism, or hirsutism symptoms were not detected in any patients in the control group.

Exclusion criteria

Participants who were pregnant/breastfeeding or had any other causes or signs of menstrual irregularity and/or androgen excess, such as adrenal, pituitary, or thyroid disorders (including congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, hyperprolactinemia and galactorrhea) were not included. Other exclusion criteria included reduced glucose tolerance, type 1/2 diabetes, or history of gestational diabetes; history of hypertension, hyperlipidemia, liver/renal disorders, coronary artery disease, congestive heart failure, malignancy or acute infection (in the past two weeks); and chronic inflammatory or autoimmune disorders. Furthermore, participants with hormonal contraception and/or anti-androgen

use in the past six months and those taking medications for treatment of hypertension, insulin resistance, hyperglycemia, dyslipidemia and obesity were excluded.

Anthropometric evaluation

Anthropometric measurements including age, waist circumference (cm), both weight (kg) and height (cm) were analyzed when the participants were wearing casual clothes and barefoot. The distance between the lower rib margin and the iliac crest at the end of a gentle expiration was used to find the waist circumference. Blood pressure was measured with the participants in a resting position after a 15 minute resting period. BMI was calculated considering the formula of weight (kg)/ height in meters squared (m^2).

Biochemical evaluation

Venous blood samples were obtained from all participants in the early follicular phase (day 3 to 5) of spontaneous or progesterone-induced menses, in the morning (between 08:00-09:00) after at least a 10 hour fast. The blood samples were held at room temperature for at least 30 minutes to allow coagulation. The samples were then centrifuged at 2000×g for 15 minutes and serum aliquots were maintained at -80 °C until analysis of CTRP5. Fasting blood glucose (FBG), glycated hemoglobin $A1_C$ ($HbA1_C$), serum insulin, high-density lipoprotein cholesterol (HDL-C), total amount of triglyceride, cholesterol and testosterone, DHEA-S, luteinizing hormone (LH), sex hormone of binding-globulin (SHBG), follicle-stimulating hormone (FSH), estradiol (E_2), 2-h plasma glucose following 75-g OGTT (2-h OGTT) and high-sensitivity of CRP levels were also measured. The levels of low-density lipoprotein cholesterol (LDL-C) were calculated considering the following formula: LDL-C=total cholesterol - (HDL-C + triglycerides/5). FBG, 2-h OGTT and hs-CRP of serum, serum, total cholesterol, triglycerides, and HDL-C were measured considering an auto-analyzer (Olympus AU 2700 Beckman Coulter Inc, CA, USA) with dedicated kits (Beckman Coulter Inc, CA, USA). The levels of insulin in serum were measured by means of chemiluminescent microparticle immunoassay (CMIA) with dedicated kits (Beckman Coulter Inc, CA, USA) along with auto-analyzer (UniCel DxI 800, Beckman Coulter Inc, CA, USA). High-performance liquid chromatography (Variant II Turbo, Bio-Rad, CA, USA) was used to measure $HbA1_C$ levels. LH, FSH, E_2, DHEA-S, the levels of total testosterone and SHBG were also measured using CMIA (UniCel DXI 800, Beckman Coulter Inc., CA, USA). We calculated FAI by the following formula as (total testosteron/SHBG)×100. We used the homeostasis model assessment of insulin resistance (HOMA-IR) for the calculation of insulin resistance: fasting insulin (μU/mL)×fasting glucose (mg/dL)/405 (20).

Measurement of circulating CTRP5 by ELISA

Commercially available human ELISA kits (E-EL-H4186, Elabscience-Biotech Co. Ltd, Wuhan, China) were used to measure serum CTRP5 levels (in duplicate) in accordance with the manufacturer's instructions. The intra-assay coefficient of variability (CV) showed a rate <6% and inter-assay CV showed a rate <8%. The detectable range for serum CTRP5 was 0.31 to 20 ng/mL.

Statistical analysis

Power analysis

The minimum number of participants required for a study power of 0.90 and α=0.05 was determined using G Power 3.0.10 G software for Windows (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) (21), based on the results of our pilot study on circulating CTRP5 levels. We evaluated 25 women with PCOS (CTRP5 levels: 5.38±3.13 ng/mL) and 25 women as controls (CTRP5 levels: 8.20±3.98 ng/mL). According to this analysis, a minimum of 68 subjects were needed in each group. The investigation of all data analyses was completed using the Statistical Package for the Social Sciences software version 18.0 (SPSS Inc. Chicago, IL, USA). Kolmogorov-Smirnov test showed that the numeric variables conformed to normal distribution. The data are stated as mean ± standard deviation. A t-test was considered for the comparison of laboratory and demographic characteristics between the two groups. The PCOS group was separated into two different subgroups: patients with insulin resistance (HOMA-IR >2.71) and those subjects without insulin resistance (HOMA-IR ≤2.71) (22). CTRP5 levels in the PCOS subgroups were also compared using the t-test. Relationships between CTRP5 and other variables were assessed using Pearson's correlation coefficient, and a linear regression model was formed to assess the presence of independent associations between CTRP5 and metabolic-hormonal parameters including FAI, BMI, and HOMA-IR. The variance inflation factor (VIF) of independent variables was calculated to determine multicollinearity. Variables with VIF >2.5, such as FBG and waist circumference, were not used in the model. We also adjusted the model for some parameters such as age, hs-CRP, and lipid parameters, as well as PCOS status. To estimate the possible association between CTRP5 levels (in tertiles) and PCOS risk, odds ratios (OR) were calculated using multivariate logistic regression analysis. Possible confounders such as BMI, age, HOMA-IR, FAI, and lipid parameters were included in the model for adjustment. The compatibility of the model was evaluated using the Hosmer-Lemeshow test (p>0.05). Confidence intervals (CI) were calculated at 95% and two-sided p values <0.05 were accepted as statistically significant.

Results

Laboratory and clinical characteristics of the population of the study

The comparison of the clinical and laboratory parameters of the enrolled groups are presented in Table 1.

CTRP5 levels were notably lower in women with PCOS than in those without PCOS (6.90±2.64 vs 11.73±3.66 ng/mL, p<0.001)

Table 1. Comparison of the demographic and laboratory characteristics of the study participants

Variables	PCOS n=80	Controls n=80	p[a]
Age, years	30.41±7.14	30.44±7.10	0.983
BMI, kg/m^2	26.34±4.47	26.76±4.59	0.554
Waist circumference, cm	93.42±12.34	92.2.66±14.40	0.721
SBP, mm Hg	108.04±12.70	107.63±11.51	0.832
DBP, mm Hg	74.50±6.52	73.33±5.75	0.228
Ferriman-Gallwey score	14.62±2.83	4.22±1.22	<0.001*
FBG, mg/dL	84.17±8.21	81.72±6.18	0.035*
2-h OGTT, mg/dL	123.38±12.94	120.29±11.73	0.116
HbA1c, %	5.29±0.18	5.29±0.19	0.301
Insulin, μIU/mL	17.59±6.47	11.09±4.61	<0.001*
HOMA-IR	3.68±1.45	2.22±0.91	<0.001*
Total cholesterol, mg/dL	208.39±33.85	203.87±45.10	0.475
LDL-C, mg/dL	137.91±28.66	132.54±28.38	0.235
HDL-C, mg/dL	41.65±9.53	49.21±11.13	<0.001*
Triglycerides, mg/dL	144.10±33.65	110.61±30.76	<0.001*
hs-CRP, mg/L	1.24±0.55	0.679±0.21	<0.001*
FSH, mIU/mL	6.95±1.80	7.38±1.87	0.139
LH, mIU/mL	13.86±4.36	8.72±2.85	<0.001*
Estradiol, pg/mL	51.14±12.29	49.33±8.23	0.276
Total-testosterone, nmol/L	2.91±0.42	1.70±0.35	<0.001*
SHBG, nmol/L	37.94±11.71	68.90±15.15	<0.001*
FAI, %	8.14±1.71	2.49±0.12	<0.001*
DHEA-SO$_4$, μg/dL	188.49±74.67	154.32±40.08	<0.001*

Results are given in mean ± standard deviation; [a]Independent samples t-test was used; A p value of <0.05 was considered significant (*); HbA1c: Glycosylated hemoglobin; BMI: Body mass index; DHEA-S: Dehydroepiandrosterone sulfate; DBP: Diastolic blood pressure; FAI: Free androgen index; FBG: Fasting blood glucose; FSH: Follicle-stimulating hormone; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; LH: Luteinizing hormone; PCOS: Polycystic ovary syndrome; SBP: Systolic blood pressure; SHBG: Sex hormone-binding globulin; 2-h OGTT: 2-hour oral glucose tolerance test

(Figure 1a). The levels of FBG, HOMA-IR and serum insulin were meaningfully higher in patients with PCOS as compared with controls. Moreover, patients with PCOS had markedly higher circulating levels of FAI, total testosterone, hs-CRP, and DHEA-SO$_4$ as compared with the controls. In the comparison of CTRP5 levels in the PCOS subgroups with insulin resistance (54 of 80 subjects with PCOS had insulin resistance) and without insulin resistance, CTRP5 level was remarkably lower in among the patients with PCOS with insulin resistance (6.43±2.67 vs 7.88±2.34 ng/mL, p=0.020*) (Figure 1b).

In addition, the study participants were also divided into four groups based on BMI (<25 kg/m^2 and ≥25 kg/m^2) and PCOS status. Circulating CTRP5 levels were compared between overweight and normal weight subgroups in both PCOS and control groups using t-tests. The subdivision of the PCOS and control groups based on their BMI showed that 40 participants in the PCOS group and 41 in the control group were overweight (p=0.999). In both groups, the mean values for circulating CTRP5 were meaningfully lower in overweight subjects compared with subjects with normal BMI (PCOS group: 6.17±2.50 vs 7.63±2.61 ng/mL, p=0.013*; control group: 10.89±4.10 vs 12.60±2.95 ng/mL, p=0.035*) (Figure 1c). Moreover, we compared circulating CTRP5 levels in the PCOS and control groups according to their BMI status (Figure 1d). CTRP5 levels were found to be decreased in PCOS group compared with the control group in both overweight and normal weight subjects (p<0.001*).

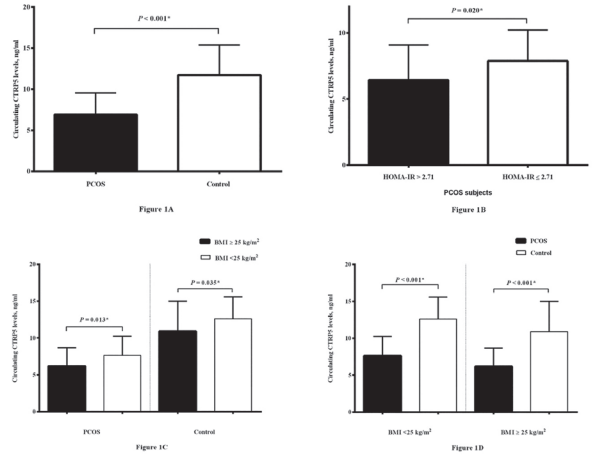

Figure 1. a) Circulating levels of CTRP5 in both control and PCOS subjects. b) Circulating levels of CTRP5 in PCOS patients having insulin resistance (HOMA-IR >2.71) and PCOS subjects with normal insulin levels (HOMA-IR ≤2.71). c) Circulating CTRP5 levels in both overweight/obese (in which BMI ≥25 kg/m^2) and normal weight (in which BMI <25 kg/m^2) participants. d) Circulating CTRP5 levels in PCOS and control groups based on BMI status

Statistically significant; CTRP5: C1q/tumor necrosis factor-related protein-5; PCOS: Polycystic ovary syndrome; HOMA-IR: Homeostasis model assessment of insulin resistance; BMI: Body mass index

Correlation of CTRP5 with other parameters

Pearson's correlation analysis was used to determine whether CTRP5 was associated with demographic or metabolic-hormonal parameters in the PCOS and control groups, as shown in Table 2.

We demonstrated that CTRP5 levels were in negatively correlated with waist circumference, BMI, HOMA-IR, FAI, and triglycerides, whereas HDL-C was positively correlated with CTRP5. CTRP5 showed no correlation with blood pressure, FSH, LH, and DHEA-S.

Multivariate regression analysis

Linear regression analysis was focused to assess the existence of independent relationships between CTRP5 and HOMA-IR, BMI, and FAI. PCOS status, age, hs-CRP, and lipid parameters were included in the regression model to adjust for their potentially confounding effects (Table 3). According to the results of the regression analysis, CTRP5 could show an independently negative association with HOMA-IR, FAI, and BMI.

Table 2. Correlation coefficient between CTRP5 levels and clinical parameters

	CTRP5			
	PCOS		Control	
	r	p	r	p
Age	0.103	0.275	0.114	0.167
BMI	-0.233	0.017*	-0.215	-0.021*
Waist circumference	-0.257	0.015*	-0.274	0.019*
Insulin	-0.378	0.007*	-0.203	0.014*
FBG	-0.221	0.029*	-0.132	0.033*
2-h OGTT	-0.135	0.256	-0.105	0.121
HOMA-IR	-0.291	0.019*	-0.153	0.041*
HbA1c	0.110	0.156	0.079	0.115
FSH	0.102	0.169	0.093	0.148
LH	0.115	0.257	0.153	0.261
FAI	-0.415	<0.001*	-0.107	0.041*
DHEA-S	-0.114	0.205	-0.092	0.113
hs-CRP	0.110	0.135	0.102	0.155
Total cholesterol	-0.053	0.076	-0.089	0.103
LDL-C	0.106	0.216	0.067	0.156
HDL-C	0.114	0.033*	0.215	0.017*
Triglycerides	-0.216	0.026*	-0.167	0.031*

Pearson's correlation analysis was used; r: Pearson's correlation coefficient; A p value of <0.05 was considered significant (*); HbA1c: Glycosylated hemoglobin; BMI: Body mass index; CTRP5: C1q/tumor necrosis factor-related protein-5; DHEA-S: Dehydroepiandrosterone sulfate; FAI: Free androgen index; FBG: Fasting blood glucose; FSH: Follicle-stimulating hormone; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin resistance; hs-CRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; LH: Luteinizing hormone; 2-h OGTT: 2-hour oral glucose tolerance test; INSL5: Insulin-like peptide 5; PCOS: Polycystic ovary syndrome

Multivariate binary logistic regression analysis

Binary logistic regression analysis was conducted to show the probable association between CTRP5 levels (tertile) and the risk of developing PCOS. Potential confounders such as age, HOMA-IR, BMI, FAI, and lipid parameters were included in the model for adjustment (Figure 2). The final results of the abovementioned analysis showed that the subjects in the lowest tertile for CTRP5 displayed meaningfully higher odds of having PCOS risk with respect to the subjects in the highest tertile for CTRP5 [OR=2.19, 95% CI: (1.79-2.67); p=0.021].

Table 3. Evaluation of BMI, HOMA-IR and FAI effects on circulating CTRP5 levels in all study population using the multiple linear regression analysis (R2=0.458)

	β	95% CI		p
Variables		Lower	Upper	
BMI	-0.315	-0.414	-0.216	0.019*
HOMA-IR	-0.371	-0.586	-0.156	0.011*
FAI	-0.563	-0.918	-0.208	0.007*

Multiple linear regression analysis was used; β: Unstandardized regression coefficient; CI: Confidence interval; A p value of <0.05 was considered significant (*); BMI: Body mass index; CTRP5: C1q/tumor necrosis factor-related protein-5; HOMA-IR: Homeostasis model assessment of insulin resistance; FAI: Free-androgen index

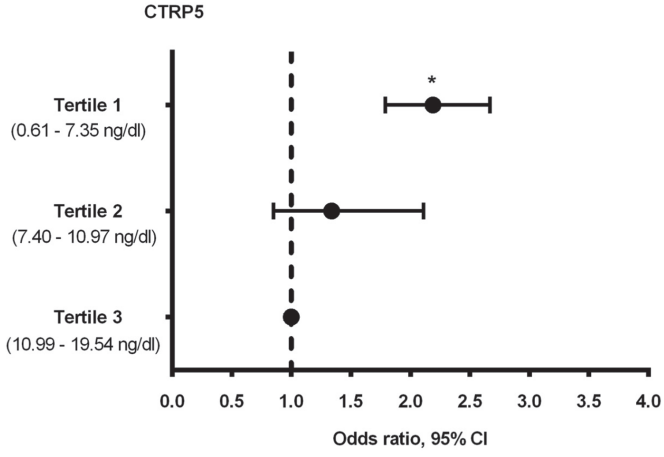

Figure 2. CTRP5 association with PCOS in previously adjusted models as multivariate adjusted OR for PCOS based on CTRP5 tertile (in reference to highest tertile). The model was basically adjusted for HOMA-IR, BMI, age, FAI, and lipid profiles

Statistically significant; CI: Confidence interval; OR: Odds ratio; CTRP5: C1q/tumor necrosis factor-related protein-5; PCOS: Polycystic ovary syndrome; HOMA-IR: Homeostasis model assessment of insulin resistance; BMI: Body mass index; FAI: Free androgen index

There was no remarkable difference in PCOS risk between participants in the second and highest CTRP5 tertiles [OR=1.34, 95% CI: (0.85-2.11); p=0.136].

Discussion

Patients with PCOS tend to have glucose and lipid metabolism disturbances. It is implicated that some adipokines also result in various metabolic abnormalities in women with PCOS. CTRP5 is a newly defined adipokine, which is involved in energy metabolism; therefore, we tried to evaluate CTRP5 levels in women with PCOS. We found that CTRP5 levels were significantly lower in subjects with PCOS than in controls. Decreased CTRP5 levels were also negatively associated with metabolic and hormonal disturbances.

Insulin resistance occurs in most patients with PCOS. It is implicated that insulin resistance has a critical role in the pathogenesis of PCOS although the its underlying molecular mechanism in women with PCOS is not fully understood. It is thought to be primarily related to defective insulin-dependent glucose transport into cells. Adipose tissue dysfunction may contribute to the development of insulin resistance in PCOS (1-4,23). Adipose tissue secretes numerous adipokines involved in regulating metabolic processes; therefore, altered adipose tissue secretion is implicated as one of the main causes of metabolic disorders in patients with PCOS (24,25). Adiponectin, a secreted adipokine, has an essential role in glucose metabolism. Decreased levels of adiponectin also contribute to the development of metabolic disturbance and insulin resistance (26). CTRP5 is a novel peptide hormone with similar structural properties to adiponectin, and it is also involved in energy metabolism (7-11). The structural similarities of CTRP5 to adiponectin revealed a way to clarify the relationship between CTRP5 and metabolic disorders for instance obesity as well as T2DM. The present study is the first to evaluate whether levels of CTRP are altered in women with PCOS compared with controls. We also investigated the link between metabolic/hormonal parameters and CTRP5 in women with PCOS. We found that CTRP5 levels were lower in subjects with PCOS than in controls. We also observed that CTRP5 showed a negative association with insulin resistance markers, BMI and FAI. Linear regression analysis confirmed the negatively independent associations with BMI, insulin resistance, and FAI. Furthermore, we determined that reduced levels of CTRP5 were associated with a high level in risk of having PCOS. Participants in the lowest tertile for CTRP5 had nearly 2.19 times higher risk of having PCOS as compared with those in the highest tertile for CTRP5.

CTRP5 is a member of the CTRP family of novel secreted hormones. Growing evidence supports the presence of a possible link between CTRP5 and metabolic disorders (7-11). Studies investigating the importance of CTRP5 in obesity and diabetes mellitus indicated that increased adipose tissue was associated with elevated CTRP5 secretion (12,13). Contrary to these findings, we detected a highly negative correlation between body weight and CTRP5 levels in the current study. Our findings are consistent with a clinical study in which CTRP5 levels were negatively correlated with BMI (14). There is no certain explanation for these discrepancies. Larger studies are needed to clarify this relationship.

There are also contradictory data in the literature concerning the effects of CTRP5 on insulin resistance. In one study, it was reported that CTRP5-deficient mice showed reduced hepatic steatosis and improvement of insulin resistance, and treatment with recombinant CTRP5 inhibited insulin-stimulated Akt phosphorylation. Therefore, the authors concluded that CTRP5 was a potential negative controller of the metabolisms of both glucose and insulin sensitivity (12). Interestingly, they reported that nutrition affected the expression of CTRP5, as refeeding resulted in a decrease of CTRP5 expression. In contrast to these findings, Yang and Lee (11) suggested that CTRP5 improved insulin resistance in myocytes. Their results corroborated those of a clinical study in which circulating CTRP5 levels were notably raised in healthy subjects compared with patients with T2DM and non-alcoholic fatty liver disease (NAFLD). In the same study, negative correlations were reported between CTRP5 and insulin, FBG, and insulin resistance, and lower circulating CTRP5 level was determined to be a statistically noteworthy risky factor for T2DM and NAFLD after adjustment for potential confounders (14). In the present study, CTRP5 levels showed a weak and negative correlation with insulin, FBG, and insulin resistance. We also determined that participants in the lowest CTRP5 tertile had higher PCOS risk compared with those in the highest CTRP5 tertile.

There are few reports regarding CTRP5 and lipid metabolism (8,14). CTRP5 was found to be increased in fatty acid oxidation via phosphorylation of AMPK (8). A negative correlation was reported between CTRP5 and triglycerides in a clinical study (14). In the current study, we also reported a weak and negative correlation between CTRP5 and triglycerides, whereas CTRP5 was positively correlated with HDL cholesterol.

PCOS is also known as an inflammatory-based metabolic disorder in which a variety of inflammatory markers are elevated. In our study, we explored why levels of hs-CRP were higher in women with PCOS. It has been suggested that CTRP induces inflammation in vascular smooth muscle cells (15). Moreover, CTRP5 was positively correlated with CRP in subjects with chronic obstructive pulmonary disease (16). However, we detected no notable correlation between CTRP5 and hs-CRP in the present study.

The current study has some limitations. The lack of assessment of other adipokines such as adiponectin is a restriction of this study. The cross-sectional design of the study is another limitation but we realized that cross-sectional studies cannot establish causality; however, they can advance our understanding of the connections between molecules and disorders.

To sum up, our results designate that decreased CTRP5 levels are linked both with PCOS and metabolic disturbances in this disorder. Reduced CTRP5 may be among the primary activators of PCOS or could simply be a result of the metabolic and hormonal changes that occur in PCOS. To clarify this point, more basic research is desired to explicate the role of CTRP5 in detail. Understanding the role of CTRP5 in hormonal and metabolic processes may lead to new treatments of metabolic abnormalities, as well as PCOS.

Ethics Committee Approval: *Ethical approval was issued by the ethics committee of İzmir Bozyaka Training and Research Hospital for the present study (no: 2. GOA/2016).*

Informed Consent: *All participants were provided both written and oral informed consent before being enrolled in the study. The study was followed strictly by the principles of the Declaration of Helsinki (2008).*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - M.Ç., M.A., A.G., A.M.I., B.A.; Design - M.Ç., M.A., P.A., G.Ü.K., A.G., G.B., Ö.F.; Data Collection and/or Processing - M.Ç., A.G., M.A., G.Ü.K., A.C.A.; Analysis and/or Interpretation - M.Ç., M.A., A.G., A.M.I., B.A., P.A.; Writer - M.Ç., M.A., A.G., A.M.I., B.A.*

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Spontaneous and in vitro fertilization pregnancies have comparable first trimester screening profiles for Down syndrome

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Abstract

Objective: We aimed to compare the first trimester screening profiles of spontaneous (n=972) and in in vitro fertilization (IVF) pregnancies (n=339) in a population of patients who had uncomplicated singleton pregnancies comparable for maternal age, gestation, body mass index, and ethnicity.

Material and Methods: A non-interventional analysis of retrospective cohort data and review of the literature.

Results: All IVF pregnancies were achieved via intracytoplasmic sperm injection using the same ovarian stimulation protocol with recombinant follicle-stimulating hormone and a gonadotropin-releasing hormone antagonist, cetrorelix acetate. The means of the multiple of median (MoM) of pregnancy-associated plasma protein-A (PAPP-A) were slightly lower in the fresh (1.19±0.6 vs 1.33±0.7, respectively; p=0.056) and frozen embryo transfer (1.03±0.5 vs 1.33±0.7, respectively; p=0.036) IVF pregnancies compared with natural conceptions. However, when the medians of the MoMs of PAPP-A and beta-human chorionic gonadotrophin (β-hCG), and their distributions were compared across the mode of conception, there were no differences between IVF pregnancies spontaneous pregnancies. Furthermore, the scatterplot diagram and curve fitting regression analyses revealed no difference in the temporal relations of β-hCG and PAPP-A with each other and gestational age between spontaneous and IVF pregnancies.

Conclusion: These results support the notion that uncomplicated singleton IVF pregnancies have similar first trimester screening profiles to spontaneous conceptions. (J Turk Ger Gynecol Assoc 2019; 20: 97-105)

Keywords: First trimester screening, pregnancy-associated plasma protein-A, beta-human chorionic gonadotrophin, nuchal translucency, pregnancy, in vitro fertilization, intracytoplasmic sperm injection

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Introduction

Prenatal screening for chromosomal abnormalities using maternal serum and sonographic markers has been integrated into routine antenatal care in many countries. First trimester screening test combines maternal age, nuchal translucency (NT), maternal serum pregnancy-associated plasma protein-A (PAPP-A), and free beta-human chorionic gonadotrophin (β-hCG) to generate a risk assessment for Down syndrome and other trisomies. This method has been reported to identify about 90% of cases of trisomy 21 with a 5% false-positive rate (1,2). An increasing number of pregnancies are achieved through assisted reproductive technologies (ART) every year. Several studies demonstrated that pregnancies conceived through ART are associated with altered maternal levels of the biomarkers of the first trimester screening, affecting the risk assessment for Down syndrome (3-10). A decrease in the maternal serum level of PAPP-A and normal or higher levels of β-hCG in in vitro fertilization (IVF) pregnancies appear to be the most consistent findings of these studies including the result of a recent meta-

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analysis (3-5,7,11,12). On the other hand, some other reports found no differences in the levels of these biomarkers between natural and IVF pregnancies (13-16).

Apparently, the inconsistent results among the studies are likely to be accounted for by several confounding factors such as heterogeneous patient populations, maternal age, and adverse obstetric outcomes. Notably, the levels of these biomarkers remained to be altered in some of these studies after adjusting for these variables and excluding cases with poor obstetric events (5,6). There are also limited data regarding the comparison of IVF pregnancies after fresh vs. frozen embryo transfer (ET) cycles in terms of their effect on the parameters of the first trimester test. Therefore, we conducted this retrospective cohort study in a homogeneous population of patients who were comparable for maternal age, gestation, body mass index (BMI) and ethnicity and had uncomplicated singleton pregnancies ending in the birth of full-term neonates. Our aims were to investigate whether (1) IVF pregnancies achieved after fresh and frozen ET IVF cycles were different from natural conceptions in terms of the first trimester test results in a patient cohort comprising uncomplicated singleton pregnancies; and (2) there were any differences in these parameters between fresh and frozen ET IVF pregnancies conceived using the same ovarian stimulation protocol with recombinant follicle-stimulating hormone (FSH) and a gonadotropin-releasing hormone (GnRH) antagonist.

Material and Methods

Patients

In this retrospective cohort study, the first trimester screening profiles of spontaneous (n=972) and IVF pregnancies (n=339) in a population of patients who had uncomplicated singleton pregnancies comparable for maternal age, gestation, BMI, and ethnicity were analyzed. All singleton pregnancies whose first trimester screening results were available were included. Of these, only 24 were excluded because of no information on pregnancy outcome (n=10), preeclampsia (n=4), gestational diabetes (n=2), which left 1331 for further evaluation. All pregnancies were singleton, uncomplicated and resulted in full term birth (37 completed weeks of gestation) of healthy neonates in a private hospital between January 2009 and July 2014. Nine hundred seventy-two of these were spontaneous pregnancies, whereas the remaining 339 were achieved through IVF-ICSI after the transfer of fresh (n=301) and frozen (n=38) embryos. The study was approved by the institutional review board of Koç University (IRB# 2015.207.IRB2.077, date: 10.09.2015). The study was performed in accordance with the ethical standards described in Declaration of Helsinki. For each patient, age at the time of the test, ethnicity, weight, smoking status, diabetes history, any previous pregnancy with trisomy, family history of trisomy, date of last menstrual period, crown-rump length (CRL), nuchal translucency, and serum PAPP-A and β-hCG levels and their multiple of median (MoM) values were recorded. All patients had Turkish ethnic background. A systematic literature search was performed using the key words provided to retrieve the relevant articles.

Fertility treatment

Fertility treatment records were reviewed to identify IVF-ICSI pregnancies after fresh and frozen ET. All embryos were generated via IVF-ICSI using ovarian stimulation with recombinant FSH (Gonal-F) and a GnRH antagonist, cetrorelix acetate. In fresh transfer cycles, 8% progesterone gel was started vaginally once a day on the day of the oocyte pick-up, and the frequency was increased to twice a day on the transfer day. No estrogen support was administered for fresh transfers. For frozen-thawed ET, endometrial preparation was provided with oral estrogen and vaginal progesterone gel. Patients were given a tablet of 2 mg estradiol/day in the first 4 days of the cycle, 2 tablets/day on the next 4 days, and 3 tablets/day thereafter. Eight percent progesterone gel was administered once daily 3-5 days before the transfer and twice a day starting on the day of the transfer. All medications were used until the 8th gestational week if pregnancy was achieved.

Risk assessment using the first trimester combined test

All patients underwent the first trimester screening test between 11+0 and 13+6 weeks of gestation. Gestational age was determined using CRL. NT was measured according to the Fetal Medicine Foundation protocol by the same physicians (17). For all cases, blood samples was obtained on the day of the NT scan for measurement of maternal PAPP-A and β-hCG levels and analyzed using a Delfia© Express 6000 Immunoanalyzer (PerkinElmer, Waltham, Massachusetts, USA). Down syndrome risk was calculated using the LifeCycle 2.2 Rev. 4 software (PerkinElmer, Waltham, Massachusetts, USA).

Statistical analysis

Demographic characteristics of the patients (maternal age, body weight, gestational age, BMI, and CRL) are expressed as mean ± standard deviation (SD) (Table 1). The MoM of the markers of the first trimester screening (NT, β-hCG and PAPP-A) are expressed as mean, median, SD, and percentile (25, 50, 75) (Table 2). The variables in the baseline demographic characteristics and the means of the MoMs between spontaneous and IVF (overall) pregnancies were compared using the t-test and Mann-Whitney U test, respectively. Additionally, spontaneous and IVF pregnancies conceived after fresh and frozen ET cycles were compared using the Kruskal-Wallis test and Dunn's multiple

comparison posthoc test. The variables were also tested as to whether they were distributed normally using the Kolmogorov Smirnov one-sample test. The medians of the MoMs and their distributions were compared using Wilcoxon's signed-rank test to explore if the mode of conception had any influence on these parameters. The two-tailed pearson correlation test and linear regression analysis were conducted to investigate the relationship among the variables in the first trimester screening test. P<0.05 was considered significant. Data analysis was performed using SPSS (version 21; SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the study population are shown in the Table 1. Control and IVF-ICSI patients were comparable in terms of mean age (31.5±3.7 vs 32.2±4.7 years, respectively; p>0.05), weight (64.5±10.1 vs 63.6±9.6 kg, respectively; p>0.05), BMI (20.8±2.5 vs 21.2±3.4 kg/m^2, respectively; p>0.05), gestational age (89.1±4.7 vs 89.1±5.6 days, respectively; p>0.05), and CRL (64.1±5.7 vs 64.2±6.1 mm, respectively; p>0.05).

Comparison of the mean MoM levels of the test biomarkers between spontaneous and IVF-ICSI pregnancies

Fetal NT and maternal blood levels of β-hCG and PAPP-A are expressed as MoMs. The mean ± SD, median, and percentiles (25, 50, 75) of the MoMs are shown in Table 2. First, we compared the means of the MoMs between spontaneous and IVF-ICSI (overall) pregnancies as two independent samples from a continuous field. There were no significant differences between these two different modes of conception in the mean MoM levels of β-hCG (1.24±0.8 vs 1.29±0.9, respectively; p>0.05), PAPP-A (1.33±0.9 vs 1.18±0.8, respectively; p>0.05), and NT (1.06±0.4 vs 1.11±0.4, respectively; p>0.05) (Table 1). Then, IVF pregnancies were subgrouped into fresh and frozen ET cycle IVF pregnancies and a multiple comparison was made among spontaneous, fresh, and frozen IVF pregnancies. The means of the MoM of PAPP-A were significantly lower in the fresh (1.19±0.6 vs 1.33±0.7, respectively; p=0.056) and frozen ET (1.03±0.5 vs 1.33±0.7, respectively; p=0.036) IVF pregnancies compared with spontaneous pregnancies. The MoMs of β-hCG (1.24±0.6 vs 1.26±0.8 vs 1.48±0.8, respectively; p>0.05) and NT (1.06±0.8 vs 1.13±0.8 vs 1.01±0.8, respectively; p>0.05) showed significant variations among spontaneous, fresh, and frozen ET IVF pregnancies. Furthermore, IVF pregnancies occurring after fresh ET cycles were not different from those after frozen ET cycles in terms of the mean MoM levels of these biomarkers (Table 2).

Comparison of the medians of the MoMs across the mode of conception and their distribution between spontaneous and IVF pregnancies

When the medians of the MoMs of β-hCG, PAPP-A and NT of IVF pregnancies were compared with the corresponding medians in the spontaneous pregnancies, no significant differences were found between spontaneous and IVF pregnancies regarding the distribution and median MoMs of the biomarkers (Table 2). The asymptotic significances were as follows: 0.544 for β-hCG, 0.89 for PAPP-A, and 0.53 for NT (Table 2). The MoMs of β-hCG, PAPP-A, and NT were not normally distributed in either spontaneous or IVF pregnancies on the Kolmogorov-Smirnov test.

Comparison of spontaneous and IVF pregnancies for the temporal relationship among β-hCG, PAPP-A, and gestational age

Both β-hCG and PAPP-A are produced by trophoblastic tissue during pregnancy (1). Thus, we investigated the temporal relationship between these biomarkers in spontaneous and IVF pregnancies using correlation analyses. Two-tailed pearson correlation analysis revealed that β-hCG was positively correlated with PAPP-A in both spontaneous (correlation co-efficient: 0.22, p<0.001) and IVF pregnancies (correlation co-efficient: 0.21, p<0.001). There was also a positive correlation between gestational age and β-hCG in spontaneous (correlation co-efficient: 0.12, p<0.001) and IVF pregnancies

Table 1. Comparison of the demographic characteristics of the spontaneous and IVF pregnancies

	Spontaneous pregnancies	IVF-ICSI pregnancies			p
		Overall (n)	Fresh ET (n)	Frozen ET (n)	
	n=972	339	301	38	
Age (years)	31.5±3.7	32.2±4.7	31.8±4.2	32.7±3.7	NS
Weight (kg)	64.5±10.1	63.6±9.6	64.5±9.4	61.5±9.7	NS
BMI (kg/m^2)	20.8±2.5	21.2±3.4	20.2±4.4	22.1±2.6	NS
Gestational age (days)	89.1±4.7	89.1±5.6	89.9±3.1	89.9±3.1	NS
CRL (mm)	64.1±5.7	64.2±6.1	64.3±5.4	64.2±6.5	NS

Demographic characteristics of the patients (maternal age, body weight, gestational age, BMI and CRL) were expressed as the mean ± standard deviation. There were no significant differences among spontaneous, fresh and frozen ET IVF pregnancies in terms of these variables. NS: Not significant, BMI: Body mass index, CRL: Crown-rump length, IVF: In vitro fertilization, ICSI: Intracytoplasmic sperm injection, ET: Embryo transfer

(correlation co-efficient: 0.14, p=0.014). Gestational age was inversely correlated with PAPP-A in spontaneous (correlation co-efficient: -0.13, p<0.001) and IVF pregnancies (correlation co-efficient: -0.11, p=0.013). In the linear regression analysis, β-hCG (R^2=0.10, p=0.002) and PAPP-A (R^2=-0.15, p<0.001) remained significantly associated with gestational age in spontaneous conceptions. Similar associations were found between β-hCG and gestational age (R^2=0.14, p=0.017), and between PAPP-A and gestational age (R^2=-0.12, p=0.013) in IVF pregnancies (Figure 1).

Discussion

We used different statistical models in this study to analyze and compare the first trimester screening test results of spontaneous and IVF pregnancies. Similar to some previous reports, we showed that IVF pregnancies had slightly lower

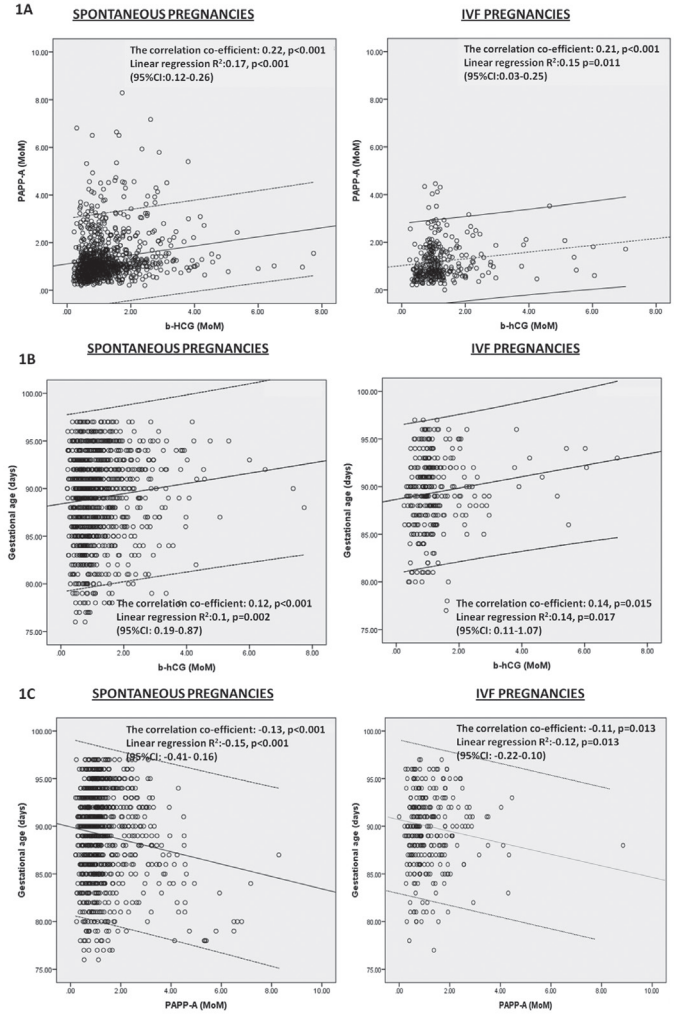

Figure 1. Temporal relationship between gestational age, β-hCG and PAPP-A in spontaneous and IVF pregnancies
β-hCG: β-human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein-A , IVF: In vitro fertilization

PAPP-A, and similar β-hCG and NT levels compared with spontaneously conceived pregnancies when both groups consist of uncomplicated singleton pregnancies comparable for maternal age, gestation, weight, BMI, and ethnicity. Also, we find no differences in these parameters between the pregnancies after fresh and frozen ET cycles.

A number of studies examined the possible effects of IVF on first trimester screening test results. These studies are summarized in Table 3. The majority of them reported decreased MoM levels of PAPP-A for both IVF and ICSI pregnancies (3-10) as the most consistent finding (Table 3). As a result of lower PAPP-A levels, higher false-positive rates were reported in the combined screening test of IVF pregnancies (18). PAPP-A is a placental derived protein and its synthesis is defective in Down syndrome due to the impaired differentiation of cyto to syncytiotrophoblasts in the placenta (19). Therefore, maternal PAPP-A levels are lower in fetuses with trisomy 21. However, given that the incidence of births of the fetuses with trisomy 21 was not increased in IVF pregnancies, there must be some other mechanisms that could provide a plausible explanation for the observed decrease in the PAPP-A level and higher false-positive rates of the first trimester screening in these pregnancies. To date, several hypotheses have been put forth to explain this phenomenon. Tul and Novak-Antolic (10) demonstrated that there was an inverse association between the number of aspirated oocytes and PAPP-A MoM values and that inhibin A, a product of the corpus luteum, was increased with decreasing PAPP-A and increasing the number of oocytes retrieved. Based on these findings, the investigators hypothesized that ovarian stimulation was associated with the generation of multiple corpora lutea and higher endogenous levels of inhibin A, which in turns inhibits the secretion of PAPP-A. Currently this hypothesis lacks biologic validation and cannot explain the others' findings showing normal levels of PAPP-A in IVF pregnancies in comparison to controls (13-16). Furthermore, lower maternal PAPP-A levels were also reported in IVF pregnancies after frozen ET cycles, in which the ovaries are not stimulated, and therefore there are no multiple corpora lutea or elevated serum levels of inhibin-A (3,20).

Decreased PAPP-A levels are not specific for Down syndrome because it is also measured at lower levels in euploid pregnancies complicated by defective placentation such as pre-eclampsia and fetal growth restriction (21). This fact raises a question as to whether lower PAPP-A levels may indicate impairment of early implantations of the pregnancies in IVF populations. Currently, there is no good evidence to prove this claim, but it is known that IVF/ICSI pregnancies are more prone to developing adverse obstetric outcomes than natural conceptions. Thus, could lower PAPP-A levels in these pregnancies be the harbinger of poor obstetric events in the

future? The answer is probably no because maternal PAPP-A level continues to remain low even in uncomplicated IVF pregnancies when all cases with obstetric complications were excluded (5,6). Furthermore a recent study comparing first trimester trophoblast volume and placental bed vascular volume between IVF/ICSI (n=70) and normal singleton pregnancies (n=84) using a virtual organ computer-aided analysis system demonstrated no differences in these parameters between spontaneous and IVF pregnancies (22).

Interestingly, it was shown that subfertility itself and the etiology of infertility may also alter the levels of maternal PAPP-A. For instance, time to pregnancy (TTP) is a clinical tool to assess uterine receptivity/subfertility. Ranta et al. (23) demonstrated that the median/geometric mean multiple of MoM of PAPP-A was significantly lower ($p<0.01$) in women with a TTP over 25 months (0.89/0.83 MoM) and in the IVF group (0.95/0.84 MoM) compared with the reference group (1.01/1.03 MoM). However, first trimester β-hCG and NT MoMs were not statistically different between the study groups. Consequently, the proportion of the test screening positives was significantly higher in women with TTP ≥25 months (12.9 vs 2.1%), but not in the IVF group (2.6%). Regarding the effect of infertility on the test results, a record-linkage study showed that PAPP-A levels were reduced when the infertility was reported to be of female-only etiology (0.82 MoM), male-only etiology (0.85 MoM), and when a combination of male and female etiologies were present in the couple (0.82 MoM) (3).

Advanced maternal age among patients who become pregnant after IVF/ICSI appears to be another factor responsible, at least in part, for the higher false-positive rate of the test in these

Table 2. Comparison of the first trimester biomarkers among spontaneous, fresh and frozen cycle IVF pregnancies

	Spontaneous pregnancies	IVF-ICSI pregnancies			p value
		Overall	Fresh ET	Frozen ET	
Free β-hCG (MoM)					
Mean	1.24	1.29	1.26	1.48	
Median	1.00	1.03	1.04	1.00	
Standard deviation	0.87	0.93	0.93	0.62	
Percentiles					a, b, c
25	0.67	0.82	0.82	0.80	
50	1.00	1.03	1.04	1.00	
75	1.53	1.35	1.33	1.71	
PAPP-A (MoM)					
Mean	1.33	1.18	1.19	1.03	
Median	1.06	0.88	0.89	0.80	
Standard deviation	0.98	0.88	0.90	0.69	
Percentiles					a, b, c
25	0.76	0.60	0.61	0.55	
50	1.06	0.88	0.89	0.80	
75	1.51	1.50	1.55	1.38	
NT (MoM)					
Mean	1.06	1.11	1.13	1.01	
Median	1.02	1.00	0.99	1.06	
Standard deviation	0.46	0.57	0.59	0.21	
Percentiles					a, b, c
25	0.86	0.84	0.80	0.85	
50	1.02	1.00	0.98	1.06	
75	1.17	1.19	1.20	1.16	

The MoM of the markers of the first trimester screening (NT, free β-hCG and PAPP-A) were expressed as the mean, median, standard deviation, and the percentile (25, 50, 75). The means of the MoM of PAPP-A were slightly lower in the fresh IVF pregnancies compared to natural conceptions. However, when the medians of the MoMs of PAPP-A and free β-hCG, and their distributions were compared across the mode of conception, IVF pregnancies were not any different from spontaneous ones.

a: $p>0.05$ when the means were compared between spontaneous vs IVF pregnancies (overall) using the Mann-Whitney U test.

b: $p<0.05$ when multiple groups were compared with Kruskal-Wallis and multiple comparison posthoc test. Spontaneous vs fresh IVF: $p=0.25$ for β-hCG; $p=0.056$ for PAPP-A; $p=0.83$ for NT. Spontaneous vs frozen IVF: $p=0.91$ for β-hCG; $p=0.036$ for PAPP-A; $p=0.73$ for NT. Fresh vs frozen IVF: $p=0.27$ for β-hCG; $p=0.31$ for PAPP-A; $p=0.13$ for NT.

c: $p>0.05$ when the medians of the MoMs were compared between spontaneous vs IVF (overall) across the mode of conception with Wilcoxon signed-rank test, Asymptotic significances at a significance level of 0.05 were 0.443 for β-hCG, 0.895 for PAPP-A, and 0.536 for NT.

MoM: Multiple of median; IVF: In vitro fertilization; ICSI: Intracytoplasmic sperm injection; ET: Embryo transfer; PAPP-A: Pregnancy associated plasma protein-A; β-hCG: β-human chorionic gonadotropin; NT: Nuchal thickness; ET: Embryo transfer

Table 3. Summary of the findings of the previous studies evaluating PAPP-A, β-hCG and NT MoM values in spontaneous and IVF pregnancies

Author	n	Mode of conception	PAPP-A (MoM)	hCG (MoM)	NT (MoM)
Liao et al. (24)	220 30 1233	IVF ICSI Control	1.00* 0.86* 1.09	1.21** 1.09 1.06	0.97 1.00 0.98
Niemimaa et al. (31)	49 4265	IVF Control	1.03 0.99	1.25** 1.03	NA
Wojdemann et al. (13)	47 63 3026	IVF OI Control	1.02 0.89 1.00	1.14 1.08 1.00	0.97 1.02 1.00
Maymon and Shulman (33)	71 285	IVF Control	0.96* 1.05	1.16 1.06	1.16 1.06
Orlandi et al. (16)	74 32 42 370	All ART IVF ICSI Control	0.89* 0.79* 0.96 1.00	0.95 0.84 1.13 1.00	1.04 1.10 1.02 1.00
Ghisoni et al. (14)	50 92 429	IVF ICSI Control	0.99 0.98 1.02	1.16* 1.09* 0.99	1.39[d] 1.38[d] 1.50[d]
Hui et al. (20)	92 57 54 31 401	IVF ICSI IVF-FET ICSI-FET Control	0.83* 0.70* 0.95 0.66* 1.00	0.87* 0.82 1.21 0.96 1.00	N/A
Lambert-Messerlian et al. (15)	277 323 247 59 56 37070	IVF-OI IUI-OI IUI IVF-OI-ED IVF-ED Control	0.94 0.91* 0.98 1.09 1.00	1.13 1.06 1.08 0.98 1.22	1.03 1.02 0.97 0.96 0.96
Tul and Novak-Antolic (10)	130 54 914	IVF ICSI Control	0.94* 0.82* 1.04	1.04 0.91 1.00	1.00 0.99 0.99
Anckaert et al. (4)	163 59 31 4088	ICSI IVF FET Control	0.94* 0.75* 1.05 1.10	1.07 0.90 1.12 0.97	N/A
Amor et al. (3)	1739 50253	IVF Spontaneous	0.83* 1.00	0.99 0.98	0.91** 0.90
Gjerris at al. (7)	992 512 396 84 2532	All ART IVF ICSI FET Control	0.80* 0.78* 0.79* 1.03 0.98	0.97 0.96 0.98 1.00 0.99	0.92* 0.90 0.95 0.94 1.00
Engels et al. (6)	203 592 192 572	IVF Control ICSI Control	0.756* 1.029 0.708* 1.061	0.937 1.086 1.041 1.090	0.939 1.013 0.976 0.987
Bender et al. (5)	110 331 1431	IVF ICSI Control	0.86* 0.9* 1.06	1.10 1.10 0.94	1.03 1.02 1.00

Table 3. Continued

Author	n	Mode of conception	PAPP-A (MoM)	hCG (MoM)	NT (MoM)
Matilainen et al. (9)	282	All ART	0.83[a]	0.98	1.00
	176	IVF-ICSI	0.82[b]	1.00	1.03
	87	FET	0.78	0.94	1.00
	19	HRT-FET	0.66	0.83	0.96
	24783	Control	0.94	1.02	0.97

The number of cases and mode of conception sand their test results are shown. *Significantly lower compared with the control group, **Significantly higher compared with the control group, [a]p≤0.03, all ART vs control [b]p≤0.01, IVF/ICSI vs control. NA: Not applicable, IVF: In vitro fertilization, ICSI: Intracytoplasmic sperm injection, ART: Assisted reproduction technologies, FET: Frozen embryo transfer, IUI: Intrauterine insemination, OI: Ovulation induction, ED: Egg donation, [m]Expressed as mean, [d]Expressed as mean in millimeter

patients. However, when age-matched controls were used and age-adjusted analysis was perfomed, the false-positive rate remained persistently high in these IVF pregnancies (3,24). Of particular note, clinically recognized twin pregnancies can be spontaneously reduced to singleton in IVF/ICSI twin pregnancies known as vanishing twin phenomenon. These pregnancies are characterized by higher maternal MoM values of PAPP-A and β-hCG (25,26). Therefore, the results should be carefully analyzed when there is another gestational sac empty or filled with a dead fetus. PAPP-A is a protease of insulin-like growth factor (IGF) binding protein-4 produced by decidua and trophoblastic tissue, and plays critical roles during human implantation such as the regulation of IGF bioavailability in the placental bed (27,28). Therefore, taken together, these findings suggest that IVF pregnancies are likely to be different from spontaneous pregnancies and that IVF treatment itself can modify the implantation process leading to lower PAPP-A levels, which are not always associated with clinically recognized abnormal pregnancy outcomes.

PAPP-A circulates at very low levels in non-pregnant women. Like β-hCG, it is produced at high levels by the placenta during pregnancy (29). We could not find any differences in the temporal relation of β-hCG and PAPP-A with each other and gestational age between natural and IVF conceptions. This situation provides supporting evidence for the notion that IVF pregnancies are not different from spontaneous pregnancies in terms of the first trimester biomarkers.

The other biochemical marker in the first trimester screening test is β-hCG. High levels of β-hCG in the first trimester are associated with increased risk of Down syndrome, whereas its elevated levels in the second trimester are more related to poor obstetric outcomes (30). Although some studies reported increased (5,11,14,15,31) or decreased β-hCG MoM levels in ART pregnancies compared with controls (6), a great majority of the studies including ours found no difference in the levels of β-hCG levels between natural and ART pregnancies (3,4,6,7,9,10,16,20,32). These inconsistent findings have been attributed to small sample sizes, the heterogeneity of study populations, and the differences of β-hCG levels at different gestational weeks (3,18,32).

Another important finding of our study is that IVF pregnancies after fresh ET cycles had similar first trimester screening profiles to those of frozen ET cycles. This information could be relevant because a limited number of studies have thus far analyzed the first trimester screening profiles of ART pregnancies conceived after fresh and frozen ET cycles and reported varying results (3,4,7,9,20). Some of these studies reported significantly reduced median PAPP-A MOM values for pregnancies after fresh IVF and ICSI cycles, whereas median PAPP-A MOM values of pregnancies after frozen cycles were similar to those of spontaneous pregnancies (4,7). Hui et al. (20) studied both IVF and ICSI cycles with fresh and frozen-thawed ET. PAPP-A was significantly decreased in fresh IVF, fresh ICSI, and frozen ICSI pregnancies but not in frozen IVF pregnancies. Fresh and frozen ICSI groups had comparable median PAPP-A MoMs (20). In another study, Matilainen et al. (9) compared spontaneous pregnancies, fresh IVF/ICSI cycles, and frozen-thawed ET with and without hormone stimulation. The median PAPP-A MoM value for fresh cycles was significantly lower than in the control group. Frozen transfer groups, with and without hormone treatment, had lower MoM values than the control group. Interestingly, fresh and frozen-thawed transfer cycles in which exogenous hormones (follicle-stimulating agents, or any combination of estrogen and progesterone) were used had significantly lower PAPP-A values when compared with fresh and frozen-thawed cycles without hormones as shown by Amor et al. (3) who compared 773 fresh cycles with 573 frozen-thawed cycles. A recent meta-analysis documented that free β-hCG tests showed slightly higher values in the ICSI group than controls (RR=1.09, 95% CI: 1.03-1.16) but not in the IVF group (RR=1.03, 95% CI: 0.94-1.12). Pregnancy-associated plasma protein-A values for IVF/ICSI, IVF, and ICSI showed lower values in comparison with controls (RR, 95% CI: 0.85, 0.80-0.90; 0.82, 0.74-0.89 and 0.83, 0.79-0.86, respectively). The nuchal translucency measurement showed no statistical differences between study groups (IVF and ICSI) and controls (RR=1.00, 95% CI: 0.94-1.08 and RR=1.01, 95% CI: 0.97-1.05, respectively) (12).

NT is the only ultrasound marker in the first trimester combined screening test. Most studies have shown similar mean MoM

values for NT in natural and IVF pregnancies (3,5,6,9,10,13,16,24). A few studies found thicker (33) and thinner NT values (7,32) for the general IVF population. However, all studies on fresh and frozen-thawed ET cycles reported comparable NT MoM values for both. In support of this, our results revealed no significant variations in the MoMs of NT between spontaneous and IVF pregnancies.

Our results show that the results of the first trimester combined test did not differ between natural and IVF pregnancies when a homogenous patient population comparable for maternal age, gestation, BMI, ethnicity, and ovarian stimulation protocol was analyzed. On the other hand, test results should be interpreted cautiously in IVF pregnancies because many studies reported that the biochemical markers of the test might be affected by several factors in these pregnancies such as the mode of conception, etiology of infertility, maternal age, ovarian stimulation, and vanishing twins.

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Decoding stillbirths using the Relevant Condition at Death classification: Study from the developing world

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Abstract

Objective: To determine the stillbirth rate in 2017 at Christian Medical College, a tertiary care perinatal center in South India, and to identify causes for the various stillbirths that occurred using the Relevant Condition at Death (ReCoDe) classification.

Material and Methods: Medical records of the women with stillbirths between January 1st, to December 31st, 2017, were retrieved and analyzed using the SPSS software (IBM, version 23). The study was approved by the institutional review board (minute no: 11273, retro dated: 28/3/2018).

Results: Of the total 14696 deliveries between January 1st, 2017, to December 31st, 2017, there were 247 stillbirths, a rate of 16.8 per 1000 births. Maternal factors: 156 (64.2%) women were booked and the rest were un-booked. Hypertensive disorders of pregnancy were detected in 27.5% (n=67). A greater number of un-booked women had gestational hypertension as compared with booked women (41% vs 24%, p=0.005). Fetal characteristics: still births secondary to lethal congenital anomalies were seen in 18.2% (n=45). Lethal congenital anomalies were diagnosed 10 times more in the booked patients than un-booked ones (24.7% vs 2.3%, p=0.001). Obstetric factors: one or two previous miscarriages were seen in 29.5% cases. Seventeen women (6.9%) had a prior stillbirth. ReCoDe Classification: we were able to successfully classify 84.2% of the stillbirths, leaving 15.78% unclassified. Fetal growth restriction secondary to uteroplacental insufficiency was found in 25.9% cases. Of the placental causes, abruption accounted for 10.9% of cases. Medical co-morbidities were seen in 46.5% pregnancies.

Conclusion: The ReCoDe method of classifying stillbirths is useful in the developing world. It helped to elucidate the cause for stillbirths in 84.2% of cases. The majority of cases in our set were due to fetal growth restriction, hypertensive disorders of pregnancy, and uteroplacental insufficiency. Stillbirths can be prevented by a comprehensive antenatal care system, early recognition, and close monitoring of high-risk pregnancies. (J Turk Ger Gynecol Assoc 2019; 20: 106-16)

Keywords: Stillbirth, ReCoDe intrauterine fetal demise, developing world, gestational hypertension, uteroplacental insufficiency

Key message: The ReCoDe classification enabled us to classify 84.2% of stillbirths. A large number of stillbirths in our country remain preventable, due to underlying uteroplacental insufficiency and accompanying fetal growth restriction. A better understanding of the etiopathogenesis may help in the formulation and implementation of clinical guidelines for the management of high-risk pregnancies, which in turn will help alleviate this problem.

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Introduction

The World Health Organization (WHO) defines stillbirth as the delivery of a fetus after 22 completed weeks of gestation, weighing 500 grams or more, with the newborn showing no signs of life at delivery (1). According to the WHO, there were 2.6 million stillbirths in 2015. One out of every 45 babies was stillborn. Nearly three-quarters of them were from South Asia and sub Saharan Africa. The stillbirth rate in India was 23/1000 births in 2015, compared to a worldwide rate of 18.4/1000 births (2).

Since then, the stillbirth rate in our country has declined by 10%, with an annual reduction rate of 2% between 2000-2015. This decline, however, is slow in comparison to the annual reduction in maternal mortality rate and under 5 infant mortality rate at 3% and 3.9%, respectively, during the same period (2). The WHO targets reducing the stillbirth rate to 12/1000 by 2030 by adopting the "Every newborn action plan" (2).

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Socioeconomic factors and lack of appropriate antenatal care both play major roles in the occurrence of stillbirths. However, there are still lacunae in the knowledge of biomedical causes of stillbirth due to a lack of clear, reliable data from the developing world, including India. Stillbirths are traumatic to both the parents and the treating obstetrician. Often there is an element of stigma attached to giving birth to a stillborn baby and the mother holds herself responsible. Elucidating a cause for stillbirth, therefore, becomes quite challenging because parents do not often consent for diagnostic tests such as autopsy or placental biopsy. Hence, the majority of stillbirths remain "unexplained" because a complete evaluation cannot be undertaken.

Although the majority of stillbirths occur in South Asia and Sub Saharan Africa, there are surprisingly few studies on stillbirths from these countries. There is a wide research gap that needs to be filled before the stillbirth rate can be lowered to the desired level.

Relevant Condition at Death (ReCoDe) is a classification derived from a population-based cohort study in West Midlands Perinatal Institute, England. Unlike older classifications, ReCoDe seeks to identify the relevant condition at the time of fetal death – "What went wrong, not necessarily why" (3). It is able to classify nearly 85% of stillbirths, unlike older classifications, which left 50-66% of cases as unclassified (4). It is structured in the form of a hierarchy, starting from conditions that affect the fetus and moving outwards in simple anatomic groups. These are subdivided into pathophysiologic conditions where the primary condition that is applicable to a case, should be first on the list (3). As this classification is more reliant on clinical information and not autopsy/histopathologic data, it has relevance in the developing world where autopsy and/or placental biopsy is not routinely performed due to a lack of expertise and unwilling parents.

Therefore, we performed this study to determine the stillbirth rate over the period of one year at Christian Medical College, a tertiary care perinatal center in South India, and to identify causes for the various stillbirths that occurred using the ReCoDe classification.

Operational definitions

Stillbirth: Delivery of a fetus after 22 completed weeks of gestation, weighing 500 g or more with the newborn showing no signs of life after delivery (5).

Hypertensive disorders of pregnancy include: Pre-eclampsia/eclampsia/syndrome of Hemolysis; Elevated Liver enzymes, Low Platelets (HELLP)/chronic hypertension with superimposed pre-eclampsia (6).

Medical disorders: Including diabetes mellitus, chronic hypertension, autoimmune conditions, anti-phospholipid antibody (APLA) syndrome (7).

Uteroplacental insufficiency: The presence of one or more clinical indicators of maternal vascular malperfusion such as fetal growth restriction; oligohydramnios and abnormal pulsed-flow Doppler studies (8).

Fetal growth restriction: Estimated fetal weight (EFW) measured on scans using Hadlock's formula, less than the 10th percentile based on WHO sex-specific growth charts (9).

Induction of labor: Stimulation of artificial uterine contractions before the onset of labor, with or without ruptured membranes (10). Performed in cases where continuation of pregnancy has potential threat to life of mother and/or baby. May also be performed if the fetus has died or has severe abnormality.

Material and Methods

The hospital numbers of the mothers who gave birth to stillborn babies between January 1st, 2017 to December 31st, 2017, were retrieved from the electronic birth registry maintained by trained nurses. Medical records were then retrieved and data was reviewed by a panel consisting of two senior consultant obstetricians with over fifteen years' individual clinical experience, and two junior consultant obstetricians (with 5 years' individual clinical experience). In the event of any dissent, the records were analyzed by a third senior obstetric consultant, who was blinded to the opinion of the others on the panel, for the final diagnosis. The diagnosis of congenital anomalies on antenatal scans was made by the Fetal Medicine Foundation (FMF) (United Kingdom accredited sonographer in all cases). Information on twin pregnancies was also included. Time of death of one/both twins was noted, and cause of death was investigated.

Ethics committee approval

The study was approved by the Institutional Review Board of the hospital (minute no: 11273, retro dated: 28.03.2018). Consent was not taken, given the retrospective nature of the study and anonymous data collection.

Statistical analysis

Data analysis was performed using SPSS software (IBM, version 23). Descriptive measures such as mean, median, and standard deviation were computed for all continuous variables. Frequency data and cross tables were compared using the chi-square test as appropriate. For all statistical tests, p values <0.05 were considered as statistically significant.

Results

Of the total 14696 deliveries between January 1st, 2017, to December 31st, 2017, there were 243 deliveries, which resulted in 247 stillbirths, a stillbirth rate of 16.8 per 1000 births.

Maternal characteristics

There were 202 (83.1%) mothers from local areas and 41 mothers (16.9%) from other parts of India. Whereas 64.2% (n=156) were booked at our hospital with regular antenatal check-ups since early pregnancy, 35.8% were referred for the first time to our hospital at the time of diagnosis of intrauterine demise in the antepartum or intrapartum period. The majority (75%) of the pregnant women were aged between 21-30 years. Around 9% of the women were aged below 21 years (Table 1). There was no particular association between any subgroup of stillbirths and particular age group of patients.

A body mass index (BMI) of >25 kg/m^2 was seen in 117 (48.1%) of women who had stillbirth. Only 21 (8.6%) patients were underweight. There was no significant correlation, however, between BMI and any particular etiology of stillbirth such as congenital anomalies or hypertensive disorders. Primiparous women constituted 59.3% (n=144) of the study population, whereas 40.7% (n=99) were multiparous women. The majority of the women underwent vaginal delivery (88.9%, n=216). Twenty-five (10.3%) needed lower segment cesarean section (LSCS), and two (0.8%) of them underwent operative vaginal delivery (Table 1).

Of the 25 patients who had a previous LSCS, 60% (n=15) had a vaginal delivery and 40% (n=10) had a repeat surgery (Table 2).

Table 1. Maternal characteristics

	Number of patients	Proportion of total (%)
Domicile		
Tamil Nadu	202	83.1
Rest of India	41	16.9
Booking status		
Booked	156	64.2
Unbooked/irregular visits	87	35.8
Age		
<21 years	21	8.7
21-30 years	183	75.1
>30 years	39	16.2
Body mass index		
<18.9	21	8.6
19-24.9	105	43.2
25-25.9	92	37.9
>30	25	10.3
Parity		
Primiparous	144	59.3
Multiparous	99	40.7
Mode of delivery		
Vaginal	216	88.9
Instrumental	2	0.8
LSCS/hysterotomy	25	10.3

LSCS: Lower segment cesarean section

Obstetric risk factors

Sixteen (6.6%) patients had history of sub-fertility and conceived with the help of artificial reproductive techniques (Table 3). Fifty-five (22.6%) patients had one miscarriage in the past, and 17 (6.9%) patients who had two miscarriages. There were 17 (6.9%) patients who had a prior stillbirth. Ten out of the 17 stillborn babies were diagnosed as having hydrops, requiring induction of labor. The majority (9/10) had non-immune hydrops. Half of the six women with bicornuate uterus had placental abruption leading to stillbirth. Ten percent (n=25) had a history of previous LSCS.

Medical risk factors

Associated medical conditions were present in 46.5% (n=113 pregnancies), Table 4. These included chronic hypertension, diabetes mellitus, APLA, systemic lupus erythematosus, and obstetric cholestasis. The most common medical condition was diabetes mellitus, seen in 59.2% (67/113) of cases. Most women with medical disorders had at least two comorbidities, the most common combination being chronic hypertension and diabetes mellitus.

Hypertensive disorders of pregnancy were found in 54.8% (62/113) pregnancies. The incidence of severe hypertensive disorders (severe pre-eclampsia/eclampsia/HELLP syndrome) among booked patients was almost half of that seen among the un-booked patients (24% vs 41%, p=0.005) (Table 4).

Table 2. Mode of delivery for previous LSCS

	Repeat LSCS/ hysterotomy	VBAC	Total
Previous LSCS	10 (40%)	15 (60%)	25

VBAC: Vaginal birth after cesarean; LSCS: Lower segment cesarean section

Table 3. Obstetric risk factors

	Number of patients	Proportion of total (%) (n=243)
Infertility	16	6.6
Prior miscarriage		
1	55	22.6
>1	17	6.9
Prior stillbirth	17	6.9
Bicornuate uterus	6	2.4
Prior non-immune hydrops	9	3.7
Prior Rh isoimmunization	1	0.4
Previous LSCS	25	10.2
Previous anomalous baby (multiple anomalies)	2	0.8

LSCS: Lower segment cesarean section

The majority of stillbirths occurred in the third trimester (n=161, 66.2%). The majority of stillbirths in the third trimester were due to fetal growth restriction. Across all gestations, the majority of patients were booked. In pregnancies <28 weeks, 74.3% were booked patients, whilst booked patients made up 67.4% of patients in term pregnancies (Table 5).

Induction of labor

There were 148 (60.90%) pregnancies that underwent induction of labor. Most of these cases were induced with prostaglandin E1, and the remaining with intravenous oxytocin. The indications are summarized in Table 6.

Intrauterine death (IUD) was the main indication for induction of labor, comprising 65% of cases. The next most frequent cause was pregnancy-induced hypertension. These women either had severe pre-eclampsia or eclampsia, where continuation of pregnancy was life-threatening for the mother, and the fetus was not salvageable without severe morbidity. These were performed after detailed counselling was undertaken and informed consent was obtained from the parents. Life-threatening congenital anomalies constituted one-fifth of cases, and abruptio placentae, severe fetal growth restriction and non-immune hydrops constituted the remainder.

At <28 weeks' gestation, nearly twice the number of women required labor induction than those who did not (42.5% vs 20%) (Table 7). This was due to the greater prevalence of early-onset pre-eclampsia and lethal congenital anomalies in this group. The maximum number of women in the spontaneous labor group were in the gestational age of 28 to 33+6 weeks (Table 7).

Fetal characteristics: Of the stillborn babies, 51.4% (n=125) weighed less than 1000 g; 34.1% (n=83 babies) weighed between 1001 and 2500 g. Thirty-five (14.4%) babies weighed more than 2500 g (Table 4). Sixty-nine babies (28.3%) were found to be growth restricted based on WHO growth charts.

Lethal congenital anomalies were diagnosed in 45 (18.2%) cases. The incidence of congenital anomalies was significantly greater among the booked patients than the un-booked patients (24.7% vs 2.3%, p=0.001). Almost an equal proportion of babies were fresh and macerated stillbirths (Table 8).

ReCoDe classification

The ReCoDe classification for our cohort of patients is tabulated below (Table 9). We were able to successfully classify 84.2% of stillbirths, leaving 15.78% unclassified.

Labor was induced in 43 pregnancies due to the presence of major congenital anomalies identified in antenatal scans, resulting in stillbirths. Two stillborn babies referred from elsewhere as IUD, were found to have congenital anomalies at birth. The majority of these (n=32, 64%) had multiple major structural anomalies involving two or more systems. There were six cases of open neural tube defects; four had cardiac anomalies, the most common lesion being hypoplastic left heart. Out of four newborn diagnosed as having genitourinary abnormalities, one had bilateral renal agenesis and the rest had infantile polycystic kidneys with anhydramnios. Four cases had lethal skeletal dysplasia. All scans were performed by a

Table 4. Medical risk factors

	Number of patients	Proportion of total (%) (n=113)
Diabetes mellitus	26	59.2
Essential hypertension	17	15.04
PIH	68	60.17
Others (ALL, ITP, Evans syndrome)	3	1.2

PIH: Pregnancy induced hypertension; ALL: Acute lymphoblastic leukemia; ITP: Immune thrombocytopenic purpura

Table 5. Gestational age at delivery

	Booked	Unbooked	Total (n=243)
22-27+6	61 (74.3%)	21 (25.6%)	82
28-33+6	37 (56.9%)	28 (43.07%)	65
34-36+6	29 (54.7%)	24 (45.2%)	53
37-42 weeks	29 (67.4%)	14 (32.5%)	43
Total	156 (61.6%)	87 (35.8%)	243

Table 6. Indications for induction of labor

Indications for induction of labor	Total	Percentage of total (%) (n=148)
Pregnancy induced hypertension	34	22.97
Abruptio placentae with IUD	8	5.40
Severe fetal growth restriction with poor prognosis	6	4.05
Life threatening congenital anomaly	31	20.94
Non-immune hydrops	4	2.70
Intra uterine death, not in spontaneous labor	65	43.91
Total	148	100

IUD: Intrauterine death

Table 7. Induction of labor versus spontaneous labor in women with stillbirths at various gestational ages

Gestation in weeks	Induction of labor	Spontaneous labor	Total n=243
22-27+6	63 (42.5%)	19 (20%)	82
28-33+6	37 (25%)	28 (29.4%)	65
34-36+6	26 (17.5%)	27 (28.4%)	53
37-42	22 (14.8%)	21 (22.1%)	43
Total	148	95	243

Table 8. Fetal characteristics

	Number of patients	Proportion of total (%) n=247
Birth weight		
<1000 gm	125	51.4
1001-2500 g	83	34.1
>2500 g	35	14.4
Congenital anomalies		
Booked	41	93.18
Unbooked	4	9.09
Condition at birth		
Macerated	130	53.5
Fresh still born	113	46.5

sonographer accredited by the FMF, United Kingdom. Most parents, however, did not give consent for fetal autopsy.

Under class A (fetal causes), the maximum cases were classified under fetal growth restriction (n=64, 26.3%). We were able to identify a secondary code in all cases of fetal growth restriction. Uteroplacental insufficiency, by definition, was associated with all cases of fetal growth restriction, either as a secondary or tertiary code. Fetal growth restriction was diagnosed when the EFW measured on scan, was less than the 10th centile, based on WHO sex-specific growth curves. Using customized growth charts would have been a better option; however, we did not have access to these. Moreover, the authors of the study concluded that the lower centiles (10^{th}, 5^{th}, and 2.5^{th}) of a pooled study were more universally applicable than the upper centiles (90^{th}, 95^{th}, and 97.5^{th}), which may vary according to the population being studied (9).

Cord accidents accounted for only 0.4% of cases, whereas placental causes constituted 12.5% (n=31). Among placental causes, the major part of cases was due to abruption (27/31; 87%). Abruption accounted for 10.9% of overall causes of stillbirths. Among the cases of abruption, 14.8% (4/27) had uteroplacental insufficiency. Out of a total of 27 cases of abruption, 29.6% (n=8) were associated with pregnancy-induced hypertension.

Sixteen women had hypertensive disorders of pregnancy as a primary code, this increased to 85 women (34.97%) when secondary and tertiary codes were added. Associated medical conditions were present in 46.5% (113/243 pregnancies). Out of these, 59.29% (n=67) had diabetes. Obstetric cholestasis was diagnosed in 1.76% (2/113) of cases, and APLA was diagnosed in 5.3% of cases (6/113). More than one medical comorbidity was detected in most women, the combination of diabetes and hypertension being the most common.

There were two cases of intrapartum stillbirths. One woman was referred from elsewhere in active labor at 38 weeks with cord prolapse and intrauterine demise and delivered a fresh stillborn baby. Another one was a gravida 4 para 3 referred from elsewhere with obstructed labor and IUD. At laparotomy, there was a uterine rent in the posterior uterine wall with the baby in the peritoneal cavity.

Chorioamnionitis was the assigned primary code in two cases (0.8%), whereas no relevant condition was identified in 39 cases (15.7%).

We were able to identify a secondary code in 49.3% of cases (122/247) (Table 9). The most common secondary code identified was uteroplacental insufficiency 40.16% (49/122). The second most common was pregnancy-induced hypertension 25.4% (31/122).

Tertiary codes were identified in 50 cases (20.2%). Pregnancy-induced hypertension made up 52% of these (26/50) (Table 10).

Twins

There were eleven sets of twins included in our study, of which three were monochorionic diamniotic (MCDA) and eight were dichorionic diamniotic (DCDA) (Table 11). Of these 22 babies, 16 were stillborn. Five of these deaths occurred in relation to hypertensive disease, other causes included diabetes mellitus, lethal anomaly, abruption. Significant growth discordance was seen in 4 sets of twins, two DCDA and two MCDA twins. Of the two MCDA twins, the causes of discordant growth were twin-to-twin transfusion syndrome (TTTS) and selective fetal growth restriction. Two sets of twins had lethal congenital anomalies in one of the twins. In the DCDA twin, selective fetal reduction was performed for the anencephalic fetus, leading to macerated stillbirth. In the MCDA twin, selective cord occlusion was performed for the anomalous twin, resulting in stillbirth.

Discussion

The incidence of stillbirths at our center for 2017 was found as 16.8 per 1000 births. This is lower than that quoted for India (23/1000 live births), but higher than that for the state of Tamil Nadu (7/1000, for 2014). Our center, being a tertiary level perinatal center, often gets referrals of high-risk pregnancies in which the fetus is already compromised.

Using the ReCoDe classification, we were able to classify 84.2% of stillbirths, leaving 15.78% unclassified. This is similar to the findings of the original authors who could not classify15.2% of cases (3).

This system of classification has relevance in the developing world where there is often little information available at the time of delivery. Post mortem of the dead fetus and placental biopsy though routinely conducted in the developed world as a part of the evaluation, is often not performed in third world countries due to unwilling parents and lack of technical expertise. The ReCoDe classification system may be a great boon for elucidating causes of stillbirth in low resource settings

because it does not depend upon the above-mentioned tests.

The most common cause of stillbirths in our cohort was fetal growth restriction (25.9%). All these cases, by definition, were associated with uteroplacental insufficiency. We used the presence of two or more clinical indicators of maternal vascular malperfusion such as FGR, oligohydramnios, and abnormal pulsed-wave Doppler to define cases of uteroplacental insufficiency. Although such cases should ideally be corroborated with findings on placental histopathology, this could not be done due to a lack of expertise and /or unwilling parents. More than half of the cases of uteroplacental insufficiency were also associated with at least one other medical comorbidity such as hypertension, diabetes or APLA. Only half of these cases (n=51; 55.4%) were un-booked pregnancies, the rest had pregnancies supervised in our hospital. Three-quarters of stillbirths due to fetal growth restriction occurred in the third trimester, emphasizing the need for close antenatal surveillance during this period.

The above findings emphasize the need for close antenatal surveillance of pregnancies with medical comorbidities and uteroplacental insufficiency. Optimal treatment of underlying medical conditions may lead to a decrease in the incidence of fetal growth restriction and other associated complications. When diagnosed, optimal management and timely delivery of growth restricted fetuses is of utmost importance. Babies that are growth restricted have less energy reserve, tolerate labor less readily, and are thus more prone to ante/intrapartum asphyxia (3).

Four cases of abruption were associated with fetal growth restriction (and hence some degree of uteroplacental insufficiency). This was not statistically significant but in line with the theory that abruptio placenta is a manifestation of uteroplacental insufficiency (11). Of the six women with bicornuate uterus, 50% had placental abruption. Uterine anomalies are known to have a higher preponderance to abruption (12).

Associated medical conditions were present in 46.5% (n=113 pregnancies). Most women with medical disorders had at least two comorbidities, the most common combination being chronic hypertension and diabetes mellitus. Of these, the most common medical condition was diabetes mellitus, seen in 59.2% (67/113) of cases. The contribution of diabetes mellitus to overall stillbirths was 27.5% (67/243). This is similar to findings by Ajini et al. (13) who found 14.6% had diabetes. This is not surprising, given that India has the highest number of cases with diabetes mellitus in the world (31.7 million cases in 2000) (14). Undiagnosed/uncontrolled diabetes mellitus in pregnancy can contribute to stillbirths in many ways: higher incidence of congenital anomalies, severe growth restriction due to underlying vasculopathy and or/associated hypertension, macrosomia, and sudden intra-uterine demise at term. Thus, the need for universal screening and optimum control of diabetes in pregnancy is particularly relevant in India.

Hypertensive disorders encompassing both chronic hypertension and pregnancy-induced hypertension were found in 25.5% (62/243) pregnancies, making up 54.8% (62/113) of medical comorbidities. Gardosi et al. (3) found an incidence of hypertensive disease of only 0.8%. Ajini et al. (13) found an incidence of 27.6%, and Rajagopal et al. (15) found an incidence of 28%. Notably, the incidence of severe hypertensive disorders (severe pre-eclampsia/eclampsia/HELLP syndrome) among booked patients was nearly half.

In our practice, we often find un-booked mothers seeking medical attention for severe hypertensive disorders at a stage where the disease pathophysiology is so advanced as to endanger the life of the mother, with accompanying severe growth restriction. In such cases, we find induction of labor, unfortunately, to be the only recourse. With regular antenatal visits, gestational hypertension is likely to be picked up at an early stage with optimal treatment, monitoring and timely delivery which, in turn, is likely to prevent stillbirths secondary to utero placental insufficiency.

Preterm births resulting in stillbirths were seen in 2.42% cases (6/247). Most of these were referred from elsewhere with preterm premature rupture of membranes and/or preterm labor. These were classified under I1 (no relevant condition identified) in the ReCode classification, simply for the lack of a relevant category. Currently, we do not offer cervical length screening in low-risk asymptomatic women. In women with a previous history of mid-trimester loss, it would be prudent to monitor cervical length on serial scans and support pregnancy with progestogens. Cervical stitch should be considered when cervical length is ≤2.5 cm in singleton pregnancies (16).

Close monitoring of pregnancies with twins is very important. In monochorionic twins, two-weekly scans to screen for TTTS between 16-26 weeks is of paramount importance. Early diagnosis of TTTS will help by timely interventions such as laser therapy, which can salvage the pregnancy (17). In dichorionic twins, serial growth scans at 2-3-week intervals to pick up discordant growth between the twins is important. Frequent monitoring of such pregnancies will allow timely delivery of both babies before any mishap in the form of intrauterine fetal demise occurs.

Study limitations

The retrospective nature of our study made us reliant on data collection by the treating physician at the time. There were no controls, which would have enabled better qualitative analysis. Fetal autopsy was not performed routinely, neither was placental histopathology.

Table 9. ReCoDe classification, primary and secondary code

Primary ReCoDe	No.	Proportion (%)	Secondary code								
			A2	A3	A4	A5	A6	A7	B1	B2	B3
Fetus											
A1. Anomaly	#	18.2						1			
A2. Infection	8	2.42						1			
A3. NIH	5	3.23									
A4. Isoimmunization	1	2.02						1			
A5. FMH	2	0.40						1			
A6. TTTS	#	0.80									
A7. FGR		25.9								1	
Cord											
B1. Cord prolapses	1	0.40									
B2. Constriction/ Loop/ Velamentous insertion	-	-									
B3. Other	-	-									
Placenta											
C1. Abruption	#	10.9									
C2. Placenta Praevia	-	-									
C3. Vasa Praevia	-	-									
C4. Placental insufficiency	4	1.61									
C5. Other	-	-									
Amniotic fluid											
D1. Chorioamnionitis	2	0.80									
D2. Oligohydramnios	-	-									
D3. Polyhydramnios	1	0.40									
Uterus											
E1. Rupture	1	0.40									
E2. Anomaly	3	1.21									
Maternal											
F1. Diabetes Mellitus	#	6.88									
F2. Thyroid	-	-									
F3. Essential HTN	6	2.42									
F4. PIH	#	4.04									
F5. Lupus/ APLA	2	0.80									
F6. Cholestasis	2	0.80									
F7. Drug induced	-	-									
F8. Others	-	-									

	C1	C2	C3	C4	C5	D1	D2	D3	E1	E2	F1	F2	F3	F4	F5	F6	F7	F8	G1	G2	H2	I1	Total
						1				1	3	6											#
														2				1					4
												1											1
														1	1								3
																							1
	4	1		#		1						1	1	6									#
										1		2	1	8									#
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														3									3
												2	4	4									#
														5	1								6
																		2					2

Table 9. Continued

Primary ReCoDe	No.	Proportion (%)	Secondary code								
			A2	A3	A4	A5	A6	A7	B1	B2	B3
Iatrogenic											
G1. Asphyxia	1	0.40									
G2. Birth trauma	-	-									
Trauma											
H1. External	-										
H2. Iatrogenic	-										
Unclassified											
I1. No relevant condition											
	#	15.7									
I2. No information available											
	-										
Total	#	#						4	-	1	-

NIH: Non-immune hydrops; FMH: Feto-maternal hemorrhage; TTTS: Twin to Twin transfusion syndrome; FGR: Fetal growth restriction; HTN: Hypertension, PIH: Pregnan

Table 10. ReCoDe classification, tertiary code

Tertiary code	Number, n=247 (%)
C4. Placental insufficiency	3 (1.21%)
D2. Oligohydramnios	2 (0.80%)
F1. Diabetes mellitus	2 (0.80%)
F2. Thyroid	5 (2.02%)
F3. Essential hypertension	2 (0.80%)
F4. Pregnancy-induced hypertension	26 (10.5%)
F5. APLA	2 (0.80%)
F8. Other (Evans syndrome, class III obesity)	2 (0.80%)
H2. Iatrogenic trauma	1 (0.40%)
Total	50 (20.24%)

APLA: Anti-phospholipid antibody; ReCoDe: Relevant Condition at Death

We used clinical indicators of uteroplacental insufficiency rather than placental biopsy findings because the latter is not routinely conducted in our hospital due to either a lack of expertise or unwilling parents. This, however, is unlikely to exaggerate the contribution of underlying uteroplacental insufficiency towards occurrence of stillbirths because we used strict clinical criteria, usually more than one, for defining such cases.

A large number of stillbirths in our country can be better defined by using the ReCode classification. The ReCoDe classification enabled us to classify 84.2% of these cases. The largest number of cases were due to underlying uteroplacental insufficiency resulting in fetal growth restriction. A better understanding of etiopathogenesis will help improve health care facilities and development of clinical guidelines, which will work towards alleviating this problem. There was a significantly greater chance of

Table 11. Twins

	Type of twin	Number of stillborn	Primary code	GA at IUD	GA at delivery
Rank number	DCDA	1*	Essential hypertension	25+1	25+1
	DCDA	2	Abruption	25+5	25+5
	DCDA	2	Severe pre-eclampsia	26+1	26+1
	DCDA	1	Lethal congenital anomaly	25+2	37+2
	DCDA	2	DM	32+5	32+5
	DCDA	1	Severe pre-eclampsia	28	28
	DCDA	1	Severe pre-eclampsia	33+3	33+3
	DCDA	2#	Unexplained	28+2	28+2
	MCDA	1	Selective FGR	33+6	34+4
	MCDA	2	TTTS	29+4	29+4
	MCDA	1	Anomalous twin, cord occlusion done	26	35+4

DCDA: Dichorionic diamniotic; MCDA: Monochorionic diamniotic; PIH: Pregnancy-induced hypertension; DM: Diabetes mellitus; FGR: Fetal growth restriction; TTTS: Twin-to-twin transfusion syndrome; END: Early neonatal reath; *The other twin was early neonatal reath and hence was not included in the analysis; #She had spontaneous preterm labor and both twins were stillborn

	C1	C2	C3	C4	C5	D1	D2	D3	E1	E2	F1	F2	F3	F4	F5	F6	F7	F8	G1	G2	H2	I1	Total
	4	1	-	#	-	2	-		-	2	4	#	7	#	2	-	-	3		-	-	-	#

cy induced hypertension; APLA: Antiphospholipid antibody syndrome

having stillbirths secondary to hypertensive disorders in women whose pregnancies were unsupervised or poorly supervised. A more comprehensive antenatal care system, with emphasis on regular visits, may help to diagnose the antecedent causes of avoidable stillbirths and lessen the burden of stillbirth in our country.

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Cystoscopic evaluation and clinical phenotyping in interstitial cystitis/bladder pain syndrome

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Abstract

Herein, we aimed to review, report, and discuss the role of cystoscopy and clinical phenotyping in interstitial cystitis/bladder pain syndrome (IC/BPS). For this purpose; a comprehensive nonsystematic review of the relevant literature was conducted. We reviewed articles published in English and indexed in the PubMed, Embase, and Google Scholar databases. Original manuscripts, review articles, case series, and case reports were taken into consideration. Data regarding the indications for, technique, and possible findings of cystoscopy with hydrodistension (HD) and biopsy, as well as clinical implications of cystoscopic information and the concept and use of clinical phenotyping within the context of IC/BPS were extracted and discussed. IC/BPS is diagnosed based on symptomatic assessment and exclusion of confusable diseases. There is no universal agreement upon the evaluation and diagnostic algorithm of IC/BPS. The majority of the guidelines recommend cystoscopy with HD and biopsy as a diagnostic prerequisite. Various different techniques have been described for cystoscopy with HD. General or epidural anesthesia is more commonly preferred and advocated while assessing endoscopic alterations in patients suspected of having IC/BPS. Cystoscopy with HD and biopsy enables more objective exclusion of confusable diseases. It also provides the basis of the European Society for the Study of Interstitial Cystitis classification. Patients with IC/BPS who demonstrate positive cystoscopic (glomerulations and/or Hunner lesion) and histologic findings have a more severe symptomatology and may benefit from lesion-targeted endoscopic treatments. Clinical phenotyping has been implemented for IC/BPS and may be used for individualized assessment and treatment. (J Turk Ger Gynecol Assoc 2019; 20: 117-22)

Keywords: Bladder pain, cystoscopy, hydrodistension, biopsy, phenotyping

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Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disorder of unknown etiology and is one of the most debilitating conditions in urologic practice. It is characterized by pain, pressure or discomfort perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks' duration, in the absence of any identifiable cause such as infection (1,2). IC/BPS can be recognized by the presence of consistent symptoms and signs. Disorders that may lead to a similar symptomatology should be excluded in order to confirm the diagnosis of IC/BPS (2).

There are significant variations regarding the evaluation and diagnosis of IC/BPS (3). The role of cystoscopy in the diagnosis and classification of IC/BPS has long been a matter of debate, with some authorities such as the European Society for the Study of Interstitial Cystitis (ESSIC) indicating cystoscopy as a diagnostic prerequisite, whereas some others, such as the American Urological Association (AUA) reserve it for complex cases (4).

Clinical phenotyping, which categorizes the disorder according to the presence or absence of clinically relevant domains, has been implemented in IC/BPS after its success for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in an effort to optimize diagnosis and treatment (5). The main purpose of phenotype mapping in IC/BPS is to better understand the multifactorial etiology of the disorder and enable multimodal and phenotype-directed targeted therapy (6).

Herein, we review and discuss the contemporary English literature about cystoscopic evaluation and clinical phenotyping in IC/BPS.

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Indications for cystoscopy with hydrodistension and biopsy in IC/BPS

Indications for cystoscopy within the context of IC/BPS evaluation and management exhibit considerable variation. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established cystoscopic discovery of glomerulations or Hunner lesions as an unchallenged diagnostic criterion for IC/BPS (7). However, NIDDK criteria were used mainly for the purpose of standardization in scientific studies and the strict application of these criteria would miss a significant proportion of patients who actually have IC/BPS (8). Many experts agreed that the absence of glomerulations or Hunner lesions did not rule out IC/BPS (9).

The ESSIC proposal highlighted the importance of excluding confusable diseases (such as carcinoma in situ) as the cause of symptoms and indicated cystoscopy under anesthesia with hydrodistension (HD) and eventual biopsy as a diagnostic prerequisite (2). Furthermore, cystoscopic and histopathologic findings would enable further documentation and classification of IC/BPS (2). The European Association of Urology (EAU) (10) and the Japanese Urological Association guidelines (11), conjoint expert opinions from East Asia (12), and the Bladder Pain Syndrome Committee of the International Consultation on Incontinence (13) follow the recommendations of the ESSIC. Conversely, the AUA guidelines do not indicate cystoscopy as an integral part of the initial diagnostic evaluation for IC/BPS (1).

Technique of cystoscopy + hydrodistension in IC/BPS

Similar to its indications, the technical protocol of cystoscopy and HD in IC/BPS is subject to considerable variation and lacks consensus. The NIDDK recommended cystoscopy and HD to be performed under anesthesia, at a pressure of 80-100 cm H20, lasting 1-2 minutes, and up to 2 cycles. The presence of Hunner lesions or glomerulations that are diffuse in at least three quadrants with ten glomerulations per quadrant were considered positive findings in favor of IC/BPS (14). The ESSIC and EAU guidelines did not specify technical details about the cystoscopic evaluation for IC/BPS (2,10). According to the AUA guidelines, cystoscopy and HD should be performed under anesthesia, at a pressure of 60-80 cm H20, and be no longer than 10 minutes when the aim is therapeutic (1). The Japanese guidelines recommended lumbar anesthesia at the level of T6 during cystoscopy, with 80 cm H20 pressure, and to stop the infusion when the volume is between 800-1000 mL despite low pressures (11).

Apart from the guideline recommendations, some authors have proposed individual protocols. Turner and Stewart suggested a pressure of 100 cm H20 with a maximum infused volume of 1000 mL, and the distension being maintained for 1 minute. According to their technique, bladder cycling should not be repeated more than 5 times and cystoscopic assessment should be performed ideally at the initial and last distensions (15).

According to Nordling et al. (16), possible urethral urine leaks around the cystoscope should be blocked digitally. They also suggested that the bladder should be filled with a pressure of 80 cm H20 until the infusion stops dripping, without any specification about the volume limit. Emptying should be started after waiting for 3 minutes with the bladder fully distended. During filling and emptying, which can be repeated one more time, endoscopic assessment is performed. However, they recommend not to reach the maximum capacity during the second cycle to better visualize lesions and optimize tissue sampling (16).

The majority of the published series about IC/BPS stated general or spinal anesthesia as the preferred and recommended type of anesthesia to be applied during cystoscopy with HD. However, some investigators suggested that glomerulations or Hunner lesions could be visualized under local/regional anesthesia (17). Yamada et al. (18) supported the feasibility of epidural anesthesia in an effort to perform additional HDs on the next day following the initial cystoscopy +HD. Aihara et al. (19) used local anesthesia via intravesical administration of lidocaine 10 minutes prior to the start of the infusion, which was terminated when the patient reported intolerable pain or other local symptoms. They reported favorable results in terms of the safety and efficacy of this approach (19).

Cystoscopic findings in IC/BPS

Hunner lesions and glomerulations represent the most characteristic findings that might be encountered during the cystoscopic evaluation for IC/BPS. Hunner lesions were initially called ulcers. However, it is actually an inflammatory lesion that ruptures through the mucosa and submucosa when the bladder is distended. Hence, the suffix 'lesion' would more precisely define its characteristics. Hunner lesions encompass tiny vessels radiating towards a central scar, which is covered by coagulum. When they rupture upon bladder distension, petechial oozing of blood occurs in a waterfall manner (Figure 1) (2). Hunner lesions are not common, with only around 10-15% of patients with IC/BPS showing consistent cystoscopic signs (19-21). Narrow band imaging, which helps to distinguish the vascularity of a given bladder mucosal abnormality, has been proposed as an aid to better identify Hunner lesions endoscopically (22). However, more studies are needed to advocate its routine use for this purpose.

Glomerulations are a separate entity and they are defined as small submucosal petechial lesions that become visible after bladder HD (23). They are classified into five grades according

to the extent of submucosal bleeding and the presence/absence of mucosal disruption (16). The term 'glomerulation' was introduced by Walsh who linked these mucosal changes to early stage disease and also highlighted that they were not pathognomonic for IC because other bladder pathologies, such as dyskinesia, might lead to similar alterations in the bladder mucosa (24). Being mainly related to IC/BPS, glomerulations are neither specific nor sensitive enough when used solely for diagnostic purposes. Patients with chronic inflammation of the urothelium, urinary tract stone disease, and benign prostate hyperplasia can exhibit endoscopic signs consistent with glomerulations (25,26). Furthermore, Waxman et al. (27) showed that glomerulations could even be discovered in otherwise healthy women. On the contrary, the proportion of patients with a clinical diagnosis of IC/BPS but with no cystoscopic changes can be in the range of 24-34% (28,29).

Classification of ic/bps according to findings at cystoscopy with hydrodistension and biopsies

According to the ESSIC, cystoscopy and HD with biopsy is an integral part of the diagnostic evaluation for IC/BPS. Cystoscopic positive signs in favor of IC/BPS are glomerulations grade 2-3 or Hunner lesions or both. Infiltration of inflammatory cells and/or formation of granulation tissue and/or overexpression of mast cells and/or intrafascicular fibrotic changes represent the histopathologic findings that are interpreted in favor of IC/BPS (2). IC/BPS subtypes are defined on the basis of cystoscopic and histopathologic findings (Table 1). If cystoscopy or biopsy are not performed, then the letter X is assigned. Biopsy findings are categorized as follows: normal (A), inconclusive (B), and positive (C). Cystoscopic findings are interpreted as follows: normal (1), glomerulations (2), and Hunner lesion (3). This type of classification could not be possible if only clinical findings were used. Moreover, such a distinction would have implications regarding prognosis and treatment outcome.

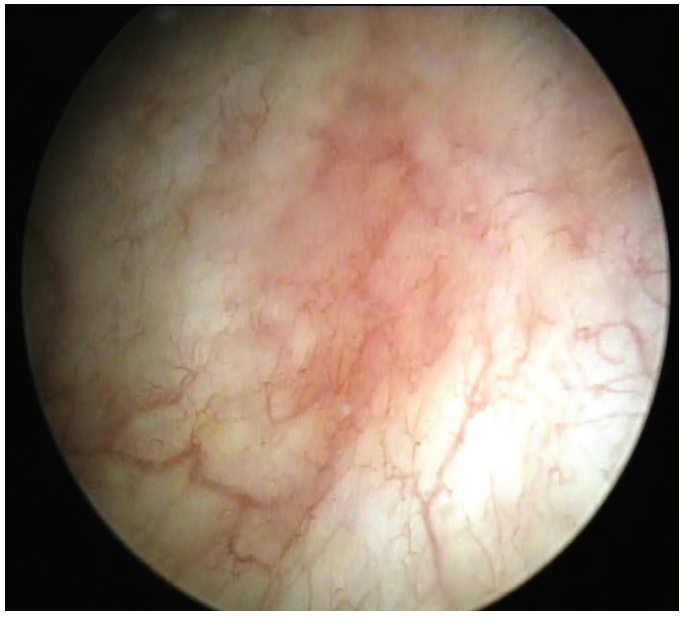

Figure 1. Cystoscopic view of Hunner lesion (courtesy of Dr. Tufan Tarcan)

Clinical implications and correlations regarding cystoscopy with hydrodistension and biopsy findings in IC/BPS

The clinical relevance of IC/BPS subtypes has long been questioned. However, the information gathered through cystoscopic examinations and histopathological assessments of bladder biopsy samples in IC/BPS offer several advantages regarding optimizing patient management and treatment outcomes. First of all, IC/BPS is essentially a diagnosis of exclusion. Cystoscopy with HD +/- biopsy offers the unique opportunity to exclude some confusable diseases such as carcinoma in-situ and bladder stones in a more reliable manner (2,30).

Moreover, patients with Hunner lesion IC/BPS may benefit from targeted endoscopic interventions. Transurethral resection of Hunner lesions has been associated with symptomatic improvement rates in the range of 90% (31,32). Hunner lesion-directed endoscopic treatment options were further enriched by studies investigating the potential utility of Nd: YAG laser, electrocoagulation, and instillation of triamcinolone (33-35), all of which reported impressive improvement rates ranging from 70-90%. This therapeutic benefit would not have been possible if these patients were not identified via cystoscopy +/- biopsy. It has been shown that a reliable distinction between Hunner lesion IC/BPS and non-Hunner lesion IC/BPS is not possible via clinical assessment only (36,37). Furthermore, cystoscopy

Table 1. Classification of types of IC/BPS according to findings at cystoscopy with hydrodistension and biopsies

Cystoscopy with hydrodistension					
		Not done	**Normal**	**Glomerulations**	**Hunner lesion**
Biopsy	Not done	XX	1X	2X	3X
	Normal	XA	1A	2A	3A
	Inconclusive	XB	1B	2B	3B
	Positive	XC	1C	2C	3C

IC/BPS: Interstitial cystitis/bladder pain syndrome

under local anesthesia can be used to monitor the effect of bladder distension and emptying on pelvic symptoms. Despite the limitation that might be induced by pain and/or discomfort, functional bladder capacity can also be assessed in the same setting (17).

Regarding the correlation between cystoscopy and clinical findings; recent studies have shown that patients with Hunner lesion IC/BPS are more severely symptomatic than patients without Hunner lesions. In their study in which 393 patients with IC/BPS (55% with type 3C) were enrolled, Logadottir et al. (38) investigated the potential clinical similarities and dissimilarities between the main disease subtypes. They found that patients with type 3C disease were older (62 vs 42 years, $p<0.001$), with a lower average maximal voided volume (206 vs 289 mL, $p<0.001$), and a lower average bladder capacity under anesthesia (459 vs 743 mL, $p<0.001$). Boudry et al. (39) assessed the use of a bladder diary for discriminating between Hunner lesion vs nonHunner lesion IC/BPS. For this purpose, they used the clinical data of 54 consecutive (39 women and 15 men) patients and discovered an association between the bladder diary parameters and cystoscopic alterations such that those with positive cystoscopic findings had lower functional bladder capacities, an increased rate of frequency and nocturia, and greater relief of symptoms upon voiding when compared with those who had normal cystoscopic findings (39). Ahn et al. (40) studied the differences between Hunner lesion IC/BPS and nonHunner lesion IC/BPS with regard to bladder diary findings and urodynamic parameters in a cohort of 55 female patients. According to bladder diary data, the frequency of micturitions was higher in the Hunner lesion group (16.65 vs 12.53, $p=0.045$) together with a smaller amount of maximal voided volume (143.48 vs 244.53 mL, $p<0.001$). Regarding the urodynamic recordings, the desire to void and maximum cystometric bladder capacity (MBC) (182.09 vs 286.59 mL, $p<0.001$) corresponded to significantly lower volumes in the Hunner lesion group. The authors identified cut-off values for urodynamic parameters to predict the presence of Hunner lesions on cystoscopy and suggested that endoscopic evaluation of the bladder should be offered to patients with a strong desire to void volumes ≤210 mL or with an MBC ≤236 mL (40).

Finally, cystoscopy is not a morbid procedure, having a fairly low incidence of complications. Relatively few publications have focused on the complications of cystoscopy and HD performed primarily within the context of IC/BPS management. Apart from anecdotal reports of bladder rupture, bladder necrosis, and acute pyelonephritis, the procedure seems to be safe and well tolerated (41,42).

Clinical phenotyping in IC/BPS

IC/BPS is a disorder without a universal agreement upon its etiology, diagnostic algorithm, and management strategy. IC/BPS may be regarded as a component of a more generalized somatic problem, reflections of which may affect the urinary bladder and other pelvic organs via several proposed mechanisms. The release of mediators such as leukotriene from activated mast cells located close to the neural/perineural structures along the bladder wall is the most widely studied etiopathogenetic explanation for IC/BPS (43).

Diverse clinical phenotypes might be encountered within the context of IC/BPS (44,45). The concurrent existence of IC/BPS with other chronic pain and symptom-based syndromes have been documented (45,46).

The main aim of phenotype mapping for IC/BPS has been to provide more individualized and phenotype-directed clinical assessment and treatment. The urinary symptoms,

Table 2. Treatment options which can be recommended based upon the predominant clinical phenotype of the patients with IC/BPS

Clinical phenotype		Treatment options
Urinary		Behavioral treatments, antimuscarinic drugs, intravesical treatment (heparin, DMSO, HA, CS, PPS), hydrodistension, botulinum toxin A, sacral neuromodulation, radical surgery
Psychosocial		Stress management and psychosocial support
Organ-specific	Hunner lesion (-)	Amitriptyline, cimetidine, hydroxyzine, cyclosporine A, PPS, quercetin, intravesical treatment (DMSO, heparin, HA, CS, alkalinized lidocaine, PPS), hydrodistension, botulinum toxin A, radical surgery
	Hunner lesion (+)	Endoscopic treatment (fulguration, laser ablation, resection, steroid injection), hyperbaric oxygen, radical surgery
Infectious		Antibiotics
Neurologic/systemic		Gabapentanoids, cimetidine, hydroxyzine, sacral neuromodulation
Tenderness		Pelvic floor physiotherapy, massage therapy, acupuncture, trigger point injections

IC/BPS: Interstitial cystitis/bladder pain syndrome; CS: Chondroitin sulphate; DMSO: Dimethyl sulfoxide; HA: Hyaluronic acid; PPS: Pentosan polysulfate

psychosocial dysfunction, organ specific findings, infection, neurologic/systemic and tenderness of muscle (UPOINT) schema, which provides better classification and treatment for CP/CPPS (45), has been extrapolated for IC/BPS. Nickel et al. (44) categorized patients with IC/BPS into 6 domains: the urinary domain, which includes patients with bothersome lower urinary tract symptoms; the psychosocial domain, which is characterized by patients with clinical depression or an identifiable maladaptive coping mechanism; the organ-specific domain, which mainly comprises patients with typical cyclic pain provoked by bladder filling and temporary relief with voiding and/or demonstrating positive cystoscopy + biopsy findings; the infection domain, which consists of patients with urine culture-documented urinary tract infections within the last 2 years that provoked/exacerbated baseline symptoms, the neurologic/systemic domain hallmark of which being prior diagnoses of disorders involving some degree of neuropathy or neural upregulation (e.g. irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, vulvodynia); and the tenderness domain, which includes patients who demonstrate trigger point tenderness during physical examination. Patients with more UPOINT-positive domains experienced more severe symptoms of longer duration as determined by the interstitial cystitis symptom index (ICSI) (44). Treatment options that can be recommended based upon the UPOINT classification are summarized in Table 2 (47).

Doiron et al. (17) investigated the use of clinical phenotyping in distinguishing Hunner lesion IC/BPS from nonHunner lesion IC/BPS in their cohort composing 359 patients (12.3% with Hunner lesions) with documented cystoscopic findings. The Hunner lesion group reported higher ICSI scores together with higher rates of pain, frequency, and nocturia when compared with the nonHunner group. However, the difference between the two groups was not statistically significant in terms of the number and distribution of UPOINT phenotypes. Despite the lack of statistical significance, there was a trend towards a more prevalent urinary domain in the Hunner lesion IC/BPS group (17). The authors concluded that patients with Hunner lesion IC/BPS could not be identified by clinical phenotyping alone and cystoscopy was inevitable for such a discrimination.

IC/BPS is diagnosed based on symptomatic assessment and exclusion of confusable diseases. There is a lack of consensus regarding the evaluation and diagnostic algorithm of IC/BPS. European and Asian guidelines recommend cystoscopy with HD and biopsy as a diagnostic prerequisite. On the other hand, cystoscopic examination is not a routine part of the diagnostic evaluation according to the AUA. Considerable variation exists about the technique of cystoscopy with HD. General or epidural anesthesia is usually preferred while examining the bladder in patients with clinical signs of IC/BPS. However, certain authorities support the feasibility and have highlighted the advantages of local anesthesia for the same purpose. Cystoscopy with HD and biopsy enables exclusion of the confusable diseases in a more reliable manner. It also forms the basis of the ESSIC-proposed classification of IC/BPS. The identification of patients who demonstrate positive cystoscopic signs and histopathologic alterations in favor of IC/BPS might have implications regarding treatment outcome because lesion-targeted endoscopic treatment has yielded promising results. Patients with Hunner lesion IC/BPS tend to be older with a more severe symptomatology in terms of pain and lower urinary tract symptoms when compared with those with nonHunner lesion IC/BPS. Clinical phenotyping has been implemented in IC/BPS. Categorizing patients according to UPOINT domains might enable individualized treatment.

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Step-by-step ligation of the internal iliac artery

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Abstract

The internal iliac artery is the main vascular supply of pelvic visceral structures. All pelvic surgeons must know the anatomic landmarks and basic steps of internal iliac artery ligation in order to stop massive pelvic hemorrhage. This cadaveric demonstration and clinical review of the internal iliac artery shows the anatomic landmarks and basic steps of internal iliac artery ligation. (J Turk Ger Gynecol Assoc 2019; 20: 123-8)

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Introduction

The anatomy of the internal iliac artery (IIA) has been well documented previously and it is the major blood supply of pelvic structures. It arises from the common iliac artery and runs infero-medially in the pelvis. An enormous number of small vessels, collateral circulation, and variations exist in pelvic vasculature (1,2).

The role of IIA ligation to control intractable pelvic hemorrhage has been described by Kelly (3) for the first time in 1893 for a cervical carcinoma case. Ligation of the IIA could also be a life-saving procedure during peripartum bleeding (4,5). In selected cases, ligation of IIA is also an option during intraperitoneal bleeding where the exact location could not be identified because IIA is the main blood supply of the pelvic viscera (6). During a massive pelvic hemorrhage or peripartum bleeding, bilateral ligation of the IIA reduces the pelvic arterial blood flow by 49% and pulse pressure by 85% (7). After bilateral ligation of IIA in the long term period, the collateral circulation will maintain the re-functioning of the IIA. The deep femoral artery is the principal vascular supply to provide re-vasculature to the IIA. Anastomosis between the medial femoral circumflex and obturator artery, and the lateral femoral circumflex and superior gluteal artery are the main connection areas (8). Additionally, the ovarian artery also provides blood flow to the uterus. Despite bilateral ligation of the IIA, future reproductive potential is not affected totally and term pregnancies have also been reported in the literature (9,10).

Despite some technical difficulties with regard to anatomic relationships and potential complications, ligation of IIA provides a rapid way to decrease the pelvic arterial blood flow. This clinical and photographic review shows the step-by-step surgical technique used in ligation of the IIA because all pelvic surgeons need to know how to ligate the IIA.

Material and Methods

The figures of this study were obtained during cadaveric dissections at the Consultants in Obstetrics and Gynecology-Management of Peripartum Bleeding and Morbidity Cadaveric Course, Bahçeşehir University Faculty of Medicine, İstanbul,

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2017, and the Management of Peripartum Hemorrhage Cadaveric Course, Kafkas University Faculty of Medicine, Kars, 2018.

Probable indications of internal iliac artery ligation

Ligation of the IIA has a proven success rate in controlling massive pelvic hemorrhage, varying between 40% and 100%, and obstetric pathologies occupy the first place as the leading factor (11,12). Table 1 shows the obstetric and gynecologic indications of IIA ligation.

Probable complications during ligation of the internal iliac artery

The risk of operative injury beyond success is the major gap beneath the feasibility of the procedure (Table 2). A detailed knowledge of the anatomy is required along with good exposure to achieve the procedure with the maneuver of traction and counter-traction. Bilateral ligation of the IIA is better to control the total blood flow in the pelvis and the surgeon would prefer to change the operative side for a comfortable surgical practice.

Basic anatomy of the internal iliac artery

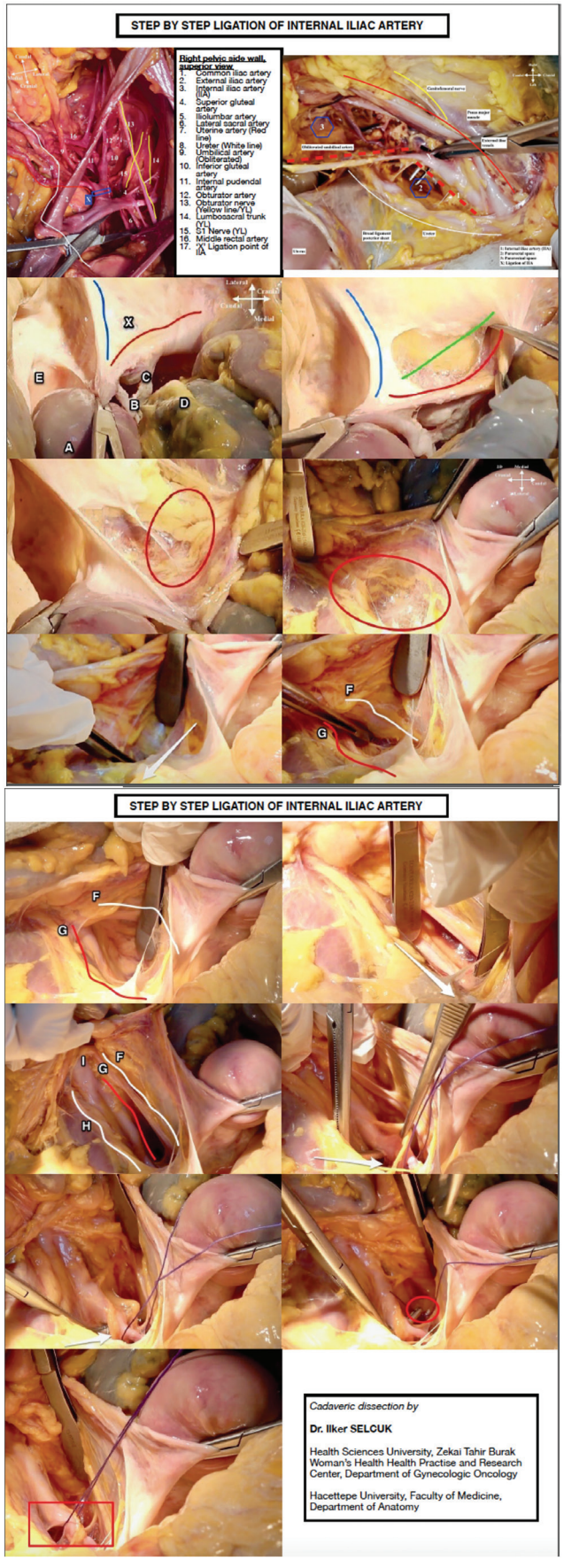
The aorta is divided into left and right common iliac arteries at the level of the fourth and fifth lumbar vertebra (L4-5) and after a pathway of 4.0-5.0 cm the common iliac artery gives the

Table 1. Indications of internal iliac artery ligation

A. Obstetric factors
Uterine atony
Uterine laceration or rupture
Abruptio placenta
Placental adhesion disorders
Placenta accreta, increta, percreta
Cervical pregnancy
B. Gynecologic factors
Gynecologic oncologic procedures
Mass/tumor at the deeper part of pelvis
Exenteration surgery
Radical hysterectomy
Extended radical operations
Postoperative unknown site for pelvic hemorrhage

Table 2. Operative complications during ligation of internal iliac artery

Injury to the external iliac vein
Injury to the internal iliac vein
Ligation or laceration of the external iliac artery
Injury to the internal iliac artery
Ligation or laceration of the ureter



branches of external iliac artery and IIA. The IIA runs inferomedially after the pelvic brim (Figure 1) and has two divisions, posterior and anterior (Table 3). The anterior division starts after 3.5-5.0 cm from the origin of the IIA and branches of the posterior division diverge before that part. The anterior division is the main blood supply of the pelvic viscera.

Accurate identification of adjacent anatomic structures (Table 4) will make the procedure easier and decrease the risk of complications during the surgical approach (13).

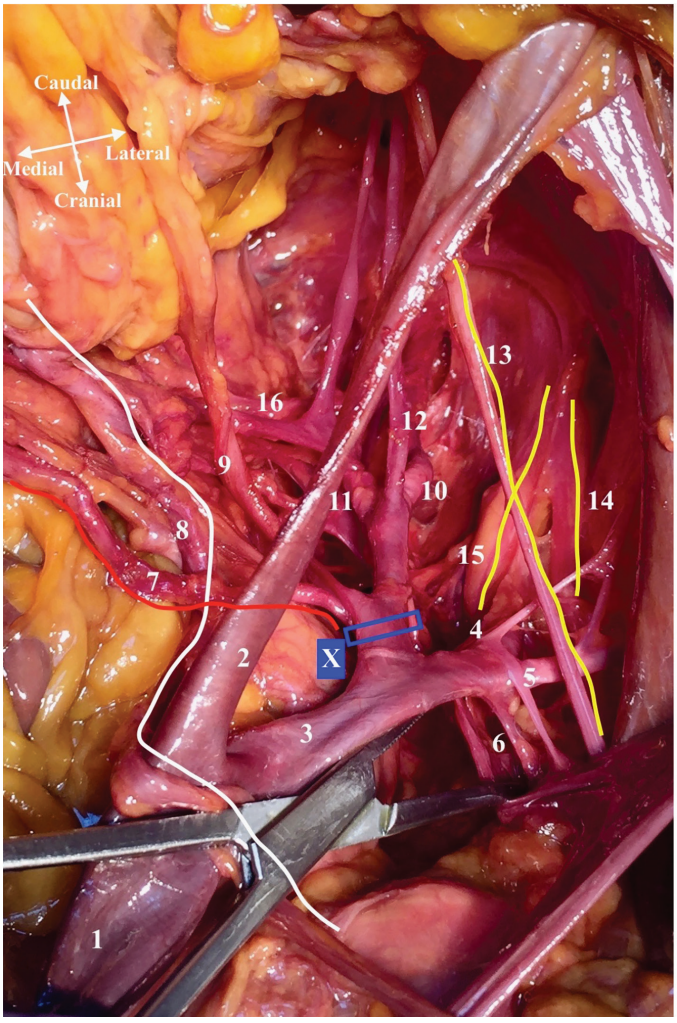


Figure 1. Anatomy of the internal iliac artery. Basic anatomic structures and branches of the internal iliac artery; Right pelvic side wall, superior view (1. Common iliac artery, 2. External iliac artery, 3. Internal iliac artery (IIA), 4. Superior gluteal artery, 5. Iliolumbar artery, 6. Lateral sacral artery, 7. Uterine artery (red line), 8. Ureter (white line), 9. Umbilical artery (obliterated), 10. Inferior gluteal artery, 11. Internal pudendal artery, 12. Obturator artery, 13. Obturator nerve (yellow line), 14. Lumbosacral trunk (yellow line), 15. S1 Nerve (yellow line), 16. Middle rectal artery, X. Ligation point of IIA)

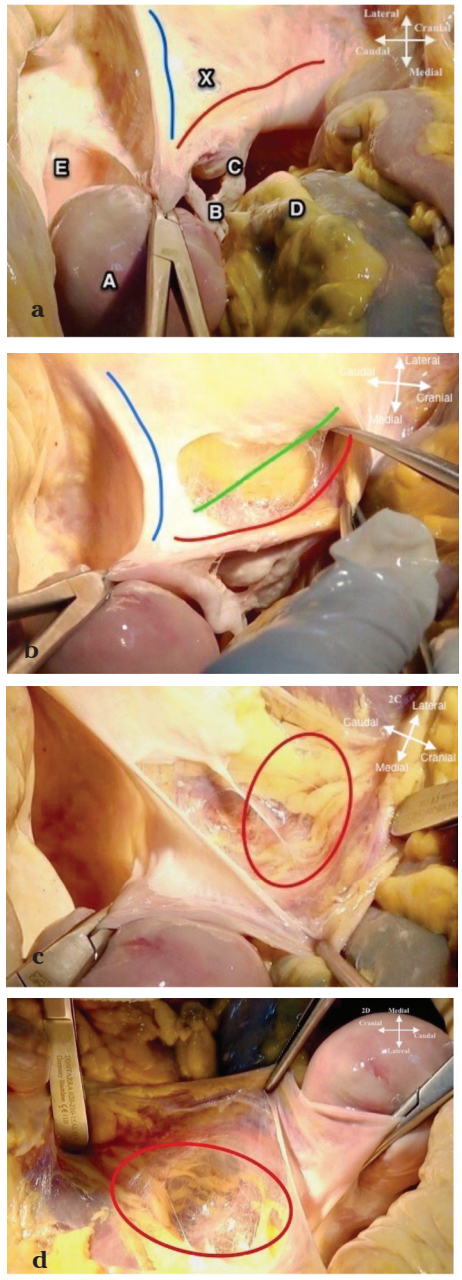


Figure 2. Entering the retroperitoneum (2a-d). a. The lateral parietal peritoneum over the pelvic side wall (over the psoas major muscle and external iliac artery) between the round ligament (ligamentum teres uteri) (blue line) and infundibulopelvic ligament (ligamentum suspensorium ovarii) (red line) is cut (X). During this step the uterus is pulled towards the counter side (caudally) of the pelvic wall where we plan to enter the retroperitoneum. (A: Uterus, B: Right fallopian tube, C: Right ovary, D: Rectum, E: Bladder), b. The incision is extended cranially to the level of pelvic brim (green line) parallel to the infundibulopelvic ligament, c. superior view, d. lateral view: Posterior leaf of the broad ligament (ligamentum latum uteri), (the peritoneum with the ovarian vessels), is retracted medially so the retroperitoneal area (red circle) is visualized

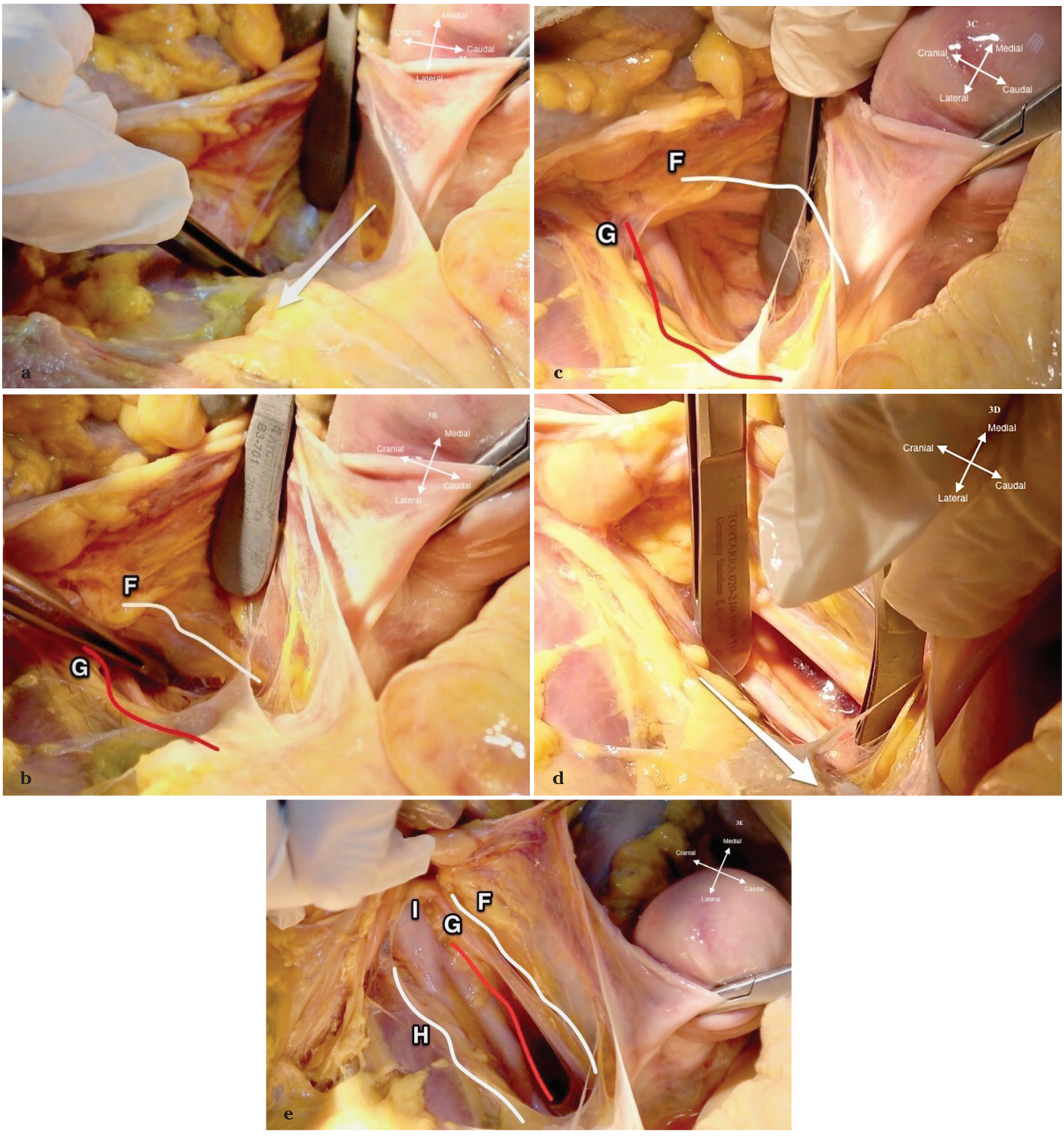


Figure 3. Identification of the ureter and internal iliac artery (3a-e). a. The ureter runs on the posterior leaf of the broad ligament under the ovarian vessels, medial to the anterior branch of internal iliac artery; therefore, holding the posterior leaf and making a blunt dissection towards sacrum (white arrow) targeting the deeper part of posterior leaf will guide to identify the ureter; b, c. The ureter (F, white line) is identified on the base of the broad ligament, medial to the internal iliac artery (G, red line); d, e. The adipose and lymphatic tissue over the internal iliac artery is dissected with a caudal movement (white arrow) (3d). The ureter (F, white line), internal iliac artery (G, red line), external iliac artery (H), and the common iliac artery (I) will be noticed just over the pelvic brim at the upper part of pararectal space (3e) [borders of pararectal space: posteriorly sacrum, medially ureter and rectum, laterally internal iliac artery and anteriorly uterine artery and cardinal ligament (ligamentum transversum cervicis)]

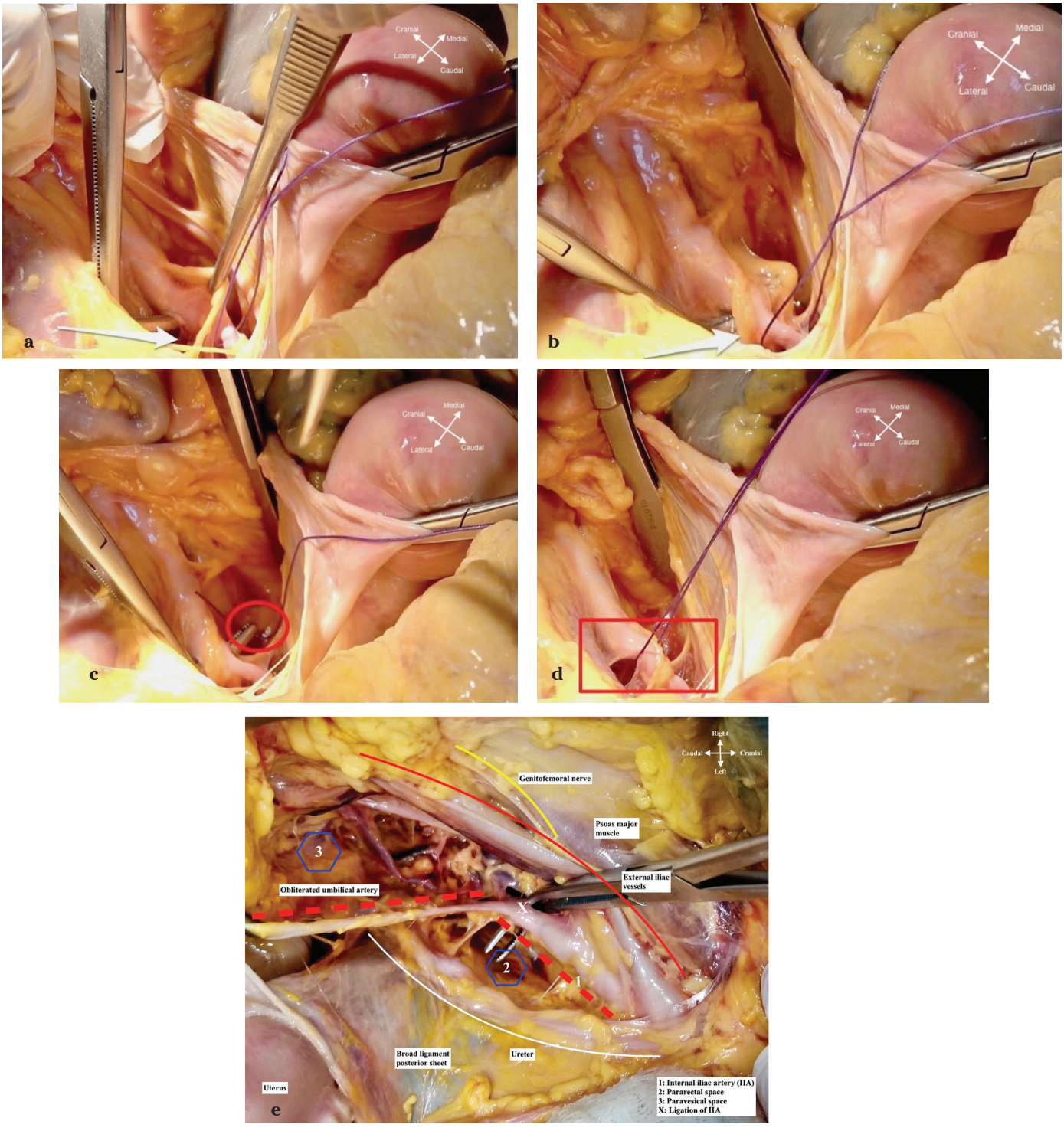


Figure 4. Ligation of internal iliac artery (4a-e). a. A right-angle clamp is placed under the anterior division of internal iliac artery (white arrow), after the main trunk gives the branches of the posterior division (3.5 cm after the origin of internal iliac artery); b. Care should be taken not to harm the underlying external iliac vein, located on the infero-lateral part of the internal iliac artery. Accordingly, the right-angle clamp should be moved from lateral to medial under the internal iliac artery (white arrow) while holding the end point of clamp upperly; c. After getting on the other side beneath the internal iliac artery, the suture material is grasped (red circle) and pulled backwards in the same direction; d. The ureter, external iliac artery, and other important anatomic landmarks are re-checked and finally the suture is tied carefully (red rectangle); e. Superior view of right pelvic side wall, how to ligate the internal iliac artery, with close anatomic structures

Table 3. Branches of internal iliac artery with regard to divisions

Posterior division
Iliolumbar artery
Lateral sacral artery
Superior gluteal artery
Anterior division
Internal pudendal artery
Inferior gluteal artery
Obturator artery
Uterine artery
Middle rectal artery
Vaginal artery
Superior vesical artery
Inferior vesical artery

Table 4. Anatomic relations of internal iliac artery

Anterior	Peritoneum
Medial	Ureter
Inferomedial	Internal iliac vein
Lateral	Psoas major muscle, internal obturator muscle
Inferolateral	Obturator nerve

Clinical tips

Monopolar or bipolar electrocoagulation could also be used during dissection of the surgical field, bleeding from small veins will stop spontaneously; nevertheless, care must be taken. Before ligation of the IIA, dissection of the ureter is extremely important and inspection is better than just palpation of the ureter in the context of preventing any probable injury. Although ligation of IIA could be performed at any side of the patient either right or left, the surgeon must be careful during dissection and traction of the IIA because movement of the right-angle clamp from medial to lateral will cause a laceration on the external iliac vein.

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What is your diagnosis?

A 53-year-old female patient was admitted to Hacettepe University Faculty of Medicine, Department of Urology outpatient clinic with dysuria, swelling in the left inguinal region, and severe urinary incontinence symptoms. Informed consent was gained from the patient before the study. The patient had stress-type urinary incontinence and a history of midurethral sling surgery 10 years ago due to her symptoms. Incontinence symptoms reduced in the first three postoperative months but there was recurrence afterwards. The patient had hypertension but no other comorbidities. According to the physical examination, there was grade I-II cystocele and vaginal atrophy. The Bonney stress test was positive and there was erosion in the left inguinal region due to the previous sling operation. Ultrasonography revealed abscess formation and mesh erosion in the left inguinal region. The same findings were observed with computed tomography. Afterwards, cystometry was performed; the maximum vesical capacity was 637 mL and the maximum vesical pressure was 33 cm H2O. Simultaneously, cystography revealed urine leakage while standing and there were no trabeculations. The uroflowmetry result was normal and there was no residual volume. The abscess formation was thought to be as a result of the mesh inflammation. Mesh excision, abscess drainage, and fascial transobturator sling operation was planned for the patient. During the operation, an approximately 4 cm-diameter mass due to mesh inflammation was excised from the left inguinal region, reaching to the retropubic area (Figure 1).

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Answer

Stress urinary incontinence is a commonly seen pathologic entity with a rate of 13% among women aged 19-44 years, and 22% among women aged 45-64 years (1,2). Unfortunately it is an underdiagnosed and underreported medical problem. SUI can be assessed with physical examination, leak abdominal pressure point, and some other tests. Patients must undergo basic evaluation with a voiding diary, cotton swab test, cough stress test, cystoscopy, post-voiding residual volume, and urodynamic studies. There are many treatment methods that are used for the treatment of patients with SUI. Basically, these methods can be divided into surgical and nonsurgical modalities. Duloxetine is a recent treatment choice as a medical treatment option and studies have shown its positive effects in treatment (3). Physical exercise also has positive effects and must be considered as a treatment option. Apart from these treatment modalities, surgery is also widely used in the treatment of SUI (4). Pubovaginal sling is a commonly used surgical procedure because it has many advantages. This procedure has an excellent overall success and it is a good option with longer curative rates (5). Midurethral slings

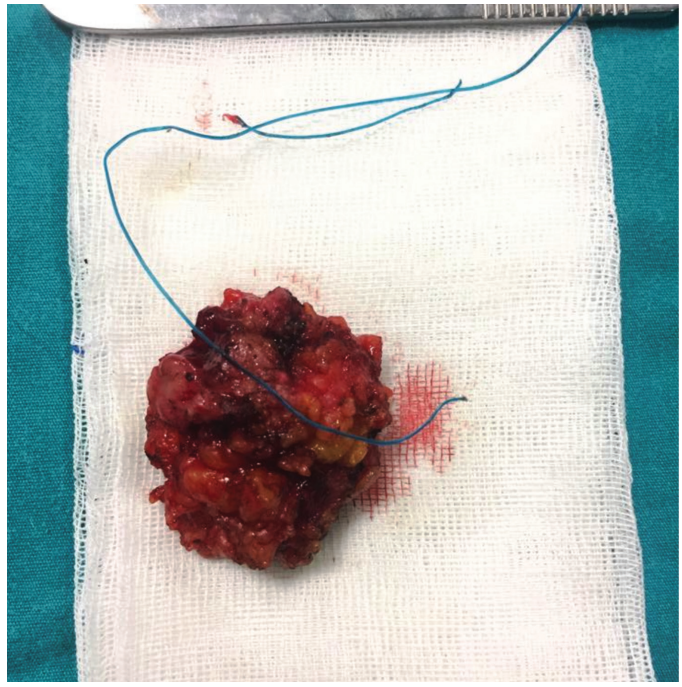

Figure 1. Macroscopic view of the excised abscess formation

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have been used more often than pubovaginal slings recently with good success rates because it has become the gold standard for the treatment of SUI (5,6). Despite the positive outcomes, sometimes there are complications regarding this procedure. Infection and abscess formation would be seen as serious complications. Sometimes these complications can be corrected via excision of mesh.

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Step-by-step colpotomy in total laparoscopic hysterectomy: a technique to avoid apical support damage to the upper vagina

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Abstract

The purpose of this video article is to demonstrate our colpotomy technique that enables maximal protection of the cervical ring, helps to prevent the ureteral injury by distancing, and avoids shortening of the vagina at total laparoscopic hysterectomy. Step-by-step explanation of the colpotomy technique is presented using educational video setting in university-affiliated private hospital. After the uterine artery transection, a VECTEC surgical uterine manipulator (VECTEC, Hauterive, France) was inserted into the vagina in place of the sharp curette. The plastic rotating blade of uterine manipulator was strongly pushed forward into the anterior vaginal fornix. Colpotomy incision was started from the uppermost middle point of an anterior vagina, and extended to both sides with a monopolar L-hook electrocautery at 40 watts cutting mode. Then the manipulator's blade was maneuvered into the right lateral fornix, and THUNDERBEAT platform (Olympus Medical Systems Corp, Tokyo, Japan) was chosen as the modality of energy for the transection of the rest of the vagina. At the posterior part of colpotomy, the vaginal wall was cut from the uppermost part of uterosacral ligaments, as well. Finally, the left lateral fornix was cut by the same principles, and colpotomy was completed circumferentially. In conclusion, maximal preservation of paracervical ligaments with this technique preserve the apical support of vagina, and avoids shortening of vaginal length. The technique also minimizes the ureteral injury by distancing. (J Turk Ger Gynecol Assoc 2019; 20: 131-2)

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Introduction

The purpose of this video article is to demonstrate our colpotomy technique that enables maximal protection of the cervical ring, helps to prevent the ureteral injury by distancing, and avoids shortening of the vagina in total laparoscopic hysterectomy. The operation was performed under general anesthesia in the dorsal lithotomy position. The abdominal cavity was insufflated, and a 5-mm primary trocar was placed through the umbilicus. A 30-degree telescope was used for visualization of the peritoneal cavity. A 2.4 mm percutaneous instrument (MINILAP® SYSTEM WITH MINIGRIP® HANDLE) was placed to the upper right quadrant, a 3-mm port to the left lower quadrant, and a 5-mm port to the right lower quadrant. Our hysterectomy technique has been described previously (1, 2). A colpotomy incision was started from the uppermost middle point of anterior vagina, and extended to both sides with a monopolar L-hook electrocautery at 40 watts cutting mode (3). Then the manipulator's blade was maneuvered into the right lateral fornix, and THUNDERBEAT platform (Olympus Medical Systems Corp, Tokyo, Japan) was chosen as the modality of energy for the transection of the rest of the vagina. After rotating the blade of the manipulator into the lateral fornix, it was pushed forward delineating the connection between the vagina and cervix and then retracted backward to allow space for the THUNDERBEAT. One jaw of the THUNDERBEAT was inserted into the fornix. The vagina was cut from the uppermost part leaving cardinal ligaments maximally on the vaginal side (Figure 1). At the posterior part of colpotomy, the vaginal wall was also cut from the uppermost part of uterosacral ligaments (Figure 2). Finally, the left lateral fornix was using the same

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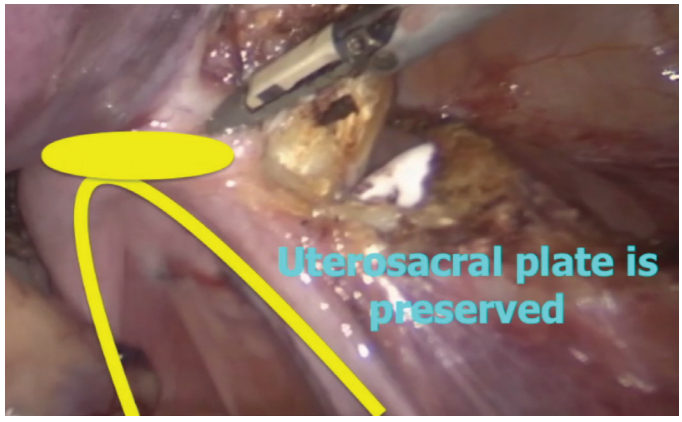

Figure 1. Preservation of uterosacral plate

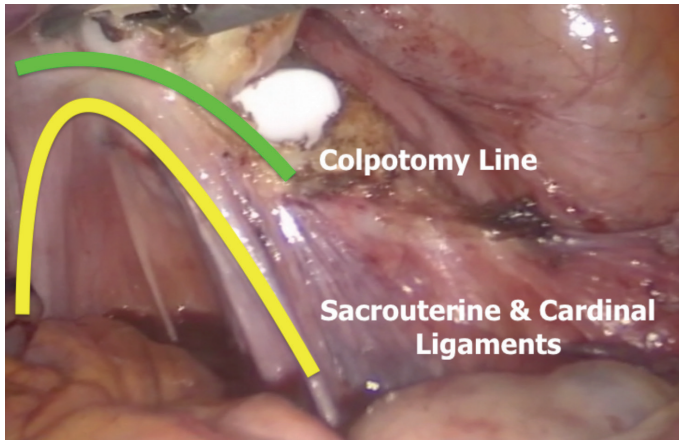

Figure 2. View of colpotomy line

principles, and colpotomy was completed circumferentially. By using the manipulator's blade, at the uppermost margin of the vagina, the ureters remained apart from the transection area, the uterosacral and cardinal ligaments were protected, and the vaginal length was preserved maximally (4). After the detachment of the uterus, the specimen was removed vaginally. The vaginal cuff was closed horizontally by using a unidirectional barbed suture (1,5). In our technique, colpotomy starts immediately after the transection of the bilateral uterine artery. In the absence of unnecessary paracervical tissue dissection below this level, the possibility of ureteral injury can be minimized, and the sacrouterine and cardinal ligaments can be maximally preserved (6). Colpotomy is carefully performed above the blade of the uterine manipulator after accessing the anterior vaginal fornix. Transection of cervicovaginal connection from the uppermost part warrants maximal preservation of the cervical ring. A detachment of vagina above the cervical ring can be accomplished via effective uterine manipulation. Stretching tissues by applying enormous pressure on the uterine manipulator is pivotal for exposure of vaginal fornices, which allows easy transection of the uppermost vagina. Maximal preservation of paracervical ligaments with this technique preserves the apical support of the vagina, and avoids shortening of vaginal length. The technique also minimizes ureteral injuries by distancing.

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

June 5-8, 2019	**3rd Nordic Congress on Gynecological Endoscopy 2019, Helsinki, Finland**
June 11-14, 2019	**Society of Obstetricians and Gynaecologists of Canada 75th Annual Clinical Meeting 2019, Halifax, Canada**
June 13-15, 2019	**43rd National Congress of the Italian Society of Urodynamics 2019, Roma, Italy**
June 25-29, 2019	**18th World Congress in Fetal Medicine 2019, Alicante, Spain**
June 26-28, 2019	**Swiss Society Of Obstetrics And Gynaecology Annual Congress 2019, Gallen, Switzerland**
July 4-5, 2019	**British Menopause Society 29th Annual Conference 2019, Kenilworth, United Kingdom**
July 11-12, 2019	**British Gynecological Cancer Society Annual Scientific Meeting 2019, Cambridge, United Kingdom**
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August 26-29, 2019	**Swedish Society of Obstetrics and Gynecology 2019, Sweden**

CONGRESS CALENDER

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(for detailed International Meeting please go website:
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September 12-15, 2019	**10. Ulusal Haseki Tıp Kongresi ve 9. Haseki Hemşirelik Sempozyumu, Sakarya, Turkey**
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October 3-6, 2019	**VII. Üreme Tıbbı ve Cerrahisi Derneği Kongresi, Antalya, Turkey**