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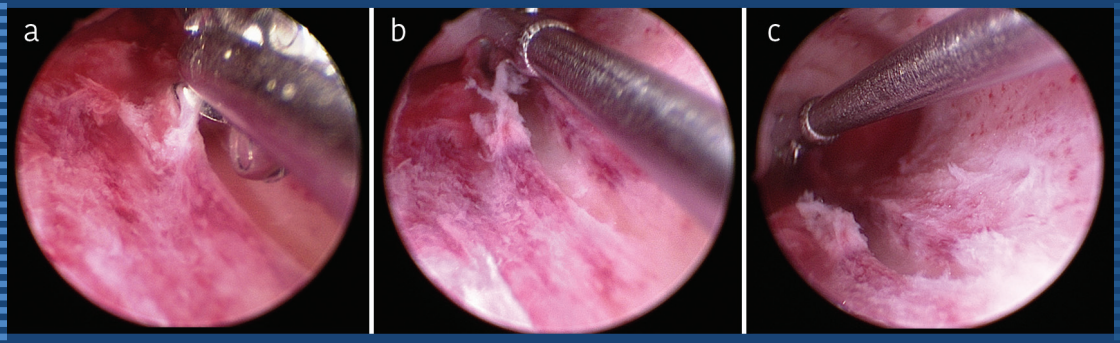

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Cover Picture: Günther et al. Endometrial "Scratching"

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Şiddetli menstrüel kanama yaşayan kadınların SORUNLARI AYNI FAKAT İHTİYAÇLARI FARKLI

BAYER

Oral tedaviyi tercih eden kadınlarda[1]

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Rahim içi sistem tercih eden kadınlarda[2]

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

QLAIRISTA® tablet: Her biri 3 mg estradiol valerat içeren 2 adet koyu sarı renkli, 2 mg estradiol valerat ve 2 mg dienogest içeren 5 adet kırmızı renkli, 2 mg estradiol valerat ve 3 mg dienogest içeren 17 adet açık sarı renkli, 1 mg estradiol valerat içeren 2 adet koyu kırmızı renkli, 2 adet beyaz film kaplı (hormon içermeyen) toplam 28 tablet. **Terapötik endikasyonlar:** Oral kontrasepsiyon Pozolojiuygulama sıklığı, süresi ve şekli: Tablet almına doğal sıklusun (menstrüel kanamanın) birinci gününde başlanmalıdır. Tabletler kuturun üzerinde belirtilen sırayla, her gün günün aynı saatinde, yeterli miktarda su ile alınmalıdır. Birbirinin 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: Erzim 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, ravınapin ve St. John bitkisi (Hypericum perforatum) gibi CYP 3A4 indükleyicileri ya da azol grubu antifungaller, simetidin, verapamil, makrolidler, diltiazem, protez 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 kontrasepsiftler 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 kontrasepsitifler (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 trombozya 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, etkeni ya da yardımcı maddelere karşı aşırı duyarlılık. **Özel kullanım uyarıları ve önlemler:** 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'tanın 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 çıkartır. 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 kullanılarda son derecede ender olarak diğer kan damarlarında, örn. hepatik, mezenterik, renal, serebral ya da retinal veriler 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, ártmış olan bu riski daha da artırabileceğine işaret edilmiştir; ancak bu bulgunun diğer bazı sonuca ulaşmayı güçleştirici faktörlere (örn. servikal tarama ve bariyer kontrasepsiftlerin 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 enderi 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'tanın biyolojik etkilerine ya da bu ikisinin bir kombinasyonuna bağlı olabilir. Yaşanılanın herhangi bir döneminde KOK kullananlarda tanısı konulan meme kanseri, hiç kullanmamış kadınlarda tanısı konulanlardan, klinik olarak daha az ilerlemiş olma eğilimindedir. KOK kullanılarında 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 önemi taşıyan artışlar enderdir. Aşağıdaki tabloların hem gebelik hem de KOK kullanımı sırasında ortaya çıktığı ya da kötüleştiği bildirilmiştir, ancak KOK kullanımı ile aradaki ilişkiye yönelik veriler kesin değildir; kolestaza bağlı sarılık ve/veya pruritus, safra taşı oluşumu, porfiri, sistemik lupus eritematozus, hemolitik üremik sendrom, Sydenham koresi, herpes gestasyonis, otosklerozia bağlı işitme kaybı. Hereditter 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 klozorna gravidarum olan kadınlarda, zaman zaman klozorna ortaya çıkabilir. Klozorna eğilimi taşıyan kadınlar, KOK kullanırken güneşe maruz kalmaktan veya ultraviyolee 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, kontrasepsif 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, kontrasepsif 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, emilimi 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 malabsorpsyon problemi olan hastaların bu ilacı kullanmaması gerekir. Gebelikte kullanım kontrendike olup gebelik kategorisi X'tir. Kullanım sırasında gebelik oluşursa, ilaç alımı kesilmelidir. Ancak etinil estradiol içeren KOK'tarla yapılan kapsamlı epidemiyolojik çalışmalarda, gebelik öncesinde KOK kullanmış olan kadınların doğurduğu çocuklarda doğum defekti riskinde artış görülmemiştir. Laktasyon döneminde kullanılmamalıdır 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 bilinen kapılı tabletlerin doz aşımı oluşturacak şekilde alınması sonucunda olugabilecek semptomlar bulantı, kusma ve genç kızlarda hafif vajinal kanamadır. Antidotu yoktur ve tedavi semptomatik olmalıdır. **Raf ömrü:** 60 ay. Saklahaya yönelik özel tedbirler: 30°C'nin altında, oda'sıcaklığında saklanmalıdır. Ambalajın niteliği ve içeriği: Polivinil klorürden yapılı transparan filmler ve sayla işlanmış alumınyumdan yapılı metalik folyolardan oluşan blister ambalajda 28 tablet. **Ruhsat sahibi:** Bayer Türk Kimya San. Ltd. Şti., Çakmak Mah. Balkan Cad. No:53 34770 Umraniye - Istanbul Tel: (0216) 528 36 00 Faks: (0216) 538 36 12 **Ruhsat numarası:** 131/95 **İlk ruhsat tarihi:** 17.08.2011 Daha geniş bilgi için firmamıza başvurunuz. **Fiyatı:** 55,46 TL (19.02.2020)

MİRENA® Levonorgestrel rahim içi sistemi **Formülü: MİRENA®** rahim içi sistemi, 52 mg levonorgestrel içerir. Başlangıç salım miktarı 20 mikrogram/24 saattir. Endikasyonları: Kontrasepsiyon (gebeliğin önlenmesi), İdiyopatik menoraji, Estrogen replasman tedavisi sırasında endometriyal 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; **MİRENA®**'nın içeriğine karşı olabilecek aşırı duyarlılık durumu. **Uyarılar / Önlemler:** Aşağıdaki durumlardan herhangi biri varsa ya da ilk kez ortaya çıkıyorsa, **MİRENA®** ancak uzman tarafından 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; aleplıtmışın dışında şiddetli baş ağrısı; sarılık; belirgin tansiyon yüksekliması; 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. **MİRENA®** enfekte endokardit riskine yol açan konjenital kalp hastalığı ya da valvüler kalp hastalığı olan kadınlarda dikkatle kullanılmalıdır. Bu hastalarda rahim içi sistem takılır veya çıkartılırken antibiyotik profilaksisi yapılmalıdır. Düşük-doz levonorgestrel glukoz toleransını etkileyebileceğinden, **MİRENA®** kullanan diyabetik kadınlarda kan şekeri izlenmelidir. Düzensiz kanamalar, endometrium polliperinin ve kanserinin bazı belirtilerini gizleyebilmektedir. Bu olgılarda tanısal girişimlerde bulunulmalıdır. **MİRENA®** genç ve doğum yapmamış kadınlarda ve ileri uterus atrofisi olan postmenopozal kadınlarda ilk seçenek değildir. **Uygulama ve çıkarma/tekrar uygulama:** Uygulamadan önce, kadın **MİRENA®**'nın etkinliği, riskleri ve yan etkileri hakkında bilgilendirilmelidir. Pelvik muayene/ve ve meme muayenesinin içeren bir fizik muayene ve servikal smear yapılmalıdır. Gebelik ve cinsel yolla bulaşan hastalıklar ekarte edilmeli ve genital enfeksiyonlar tamamen tedavi edilmelidir. Uterus pozisyonu ve uterus boşluğunun büyüklüğü belirlenmelidir. **MİRENA®**'nın fundal yerleşimi, progestagenin endometriyuma eşit olarak dağılmasının sağlanması, kazayla çıkmanın önlenmesi ve etkinliğin artırılması açılarından özellikle önem taşır. Bu nedenle uygulama talimatlarına dikkatle uyulmalıdır. Kullanıcı uygulamadan 4-12 hafta sonra tekrar muayene edilmeli ve bundan sonra yılda bir ya da klinik endikasyonu varsa daha sık aralıklarla kontrol edilmelidir. Fertil yaştaki kadınlarda **MİRENA®** uterus boşluğuna menstruasyonun ilk yedi günü içinde yerleştirilmelidir. **MİRENA®** bir yenisiyle sıklusun herhangi bir gününde değiştirilebilir. Sistem ilk trimestr düşüklerini takiben hemen uygulanabilir. Postpartum uygulamalar doğum sonrası altıncı haftaya kadar ertelenmelidir. **MİRENA®**'nın post kolitsi bir kontrasepsiftir olarak kullanılması uygun olmayabilir. Estrogen replasman tedavisi sırasında endometriyal koruma için kullanılacaksa, **MİRENA®** amenorelk bir kadına herhangi bir zamanda, ya da menstruasyonun veya çekilme kanamasının son günlerinde takılabilir. Tedavinin ilk aylarında düzensiz kanama ve lekelenme kanamalarının sık görülmesi nedeniyle **MİRENA®** takılmadan önce endometriyal patolojinin ekarte edilmesi önerilir. **MİRENA®** bir forseps yardımıyla 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 ayrı yöntemi kullanmaya devam etmek isterse, yeni bir sistem aynı zamanda takılabilir. Eğer gebelik arzu edilmiyorsa, **MİRENA®** fertil yaşlardaki kadınlarda bir sıklusun varlığından emin olunması amacıyla menstruasyon sırasında çıkarılmalıdır. Eğer sistem sıklus ortasında çıkarıldıysa ve kadın bir hafta içinde ilişkiye girmişse, çıkarılmayı takiben yeni bir sistem takılmadığı takdirde gebelik riski mevcuttur. Uygulama ve çıkarmaya bir miktar ağrı ve kanama eşlik edebilir. Prosedür vazovagal reaksiyonda olduğu gibi bir bayılmaya ya da epileptik bir hastada nöbet geçirmeye yol açabilir. **Oligo-/amenore: MİRENA®** kullanan fertil kadınların %20'sinde zamanla oligomenore ve/veya amenore çekilmektedir. 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. **MİRENA®**'nın kesintisiz estrogen replasman tedavisi ile birlikte kullanıldığı durumlarda, birçok kadında ilk yıl içinde kanamasız bir düzen oluşur. **Pelvik enfeksiyon:** Pelvik enfeksiyonun ciddi sonuçları olabilir; fertilitaye zarar verebilir ve ektopik gebelik riskini artırabilir. Tekrarlanan endometrit veya pelvik enfeksiyonunda ya da tedaviye birkaç gün içinde olumlu yanıt vermeyen veya şiddetli akut bir enfeksiyon durumunda **MİRENA®** çıkarılmalıdır. Enfeksiyon düşündüren en küçük bir belirtide bile bakteriyolojik tetkikler ve ölem önerilir. Yeniden oyrnarsa/çıkrsa; **MİRENA®** yeniden oyrnarsa çıkarılmalıdır. İsteniyorsa o sırada yenisi takılabilir. Kullanıcıya **MİRENA®**'nın iplliklerini 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 serviksde geri çekme iplikleri görülmüyorsa, gebelik ekarte edilmelidir. **Geciken foliküler atrezi: MİRENA®**'nın kontrasepsif etkisi başlıca lokal etkisine bağlı olduğundan, fertil yaştaki kadınlarda folikül çatlamasının görüldüğü ovulatuar sikluslar sıklıkla gerçekleşir. Bazen folikülün atrezisi geciktir ve folikülogenez devam edebilir. **Yan etkiler/Advers etkiler:** Çok sik (kullanıcıların %10'undan daha fazlasında) görülen yan etkiler, kanama paterninde değişiklikleri ve ilk huylu ovaryal kistlerdir. Farklı kanama değişiklikleri tüm **MİRENA®** kullanıcılarında görülür. İyi huylu ovaryal kist görülme oranı kullanılan tanısal yönteme bağlıdır. Klinik çalışmalarda **MİRENA®** kullanan kadınların %12'sinde büyümüş folliküllere rastlanmıştır. Folliküllerin çoğu asemptomatiktir ve üç ay içinde kaybolur. **İstenmeyen etkilerden bazıları:** duygu durum değişkenliği, başağrısı, migren, abdominal ağrı, abdominal şişkinlik, akne, saç dökülmesi, hirsutizm, kasıntı, kızarıklık, ürtiker, sırt ağrısı, pelvik ağrı, dismenore, pelvik enflamatuvar hastalık, uterus perforasyonu, vajinal akıntı, vulvovajinit, servisit, endometrit, memede gerginlik, mastalji, değin atrima, 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. **MİRENA®**'nın kontrasepsif etkisinin bu tür ilaçlar ile etkileşimi bilinmemektedir, ancak lokal etki mekanizması nedeniyle büyük bir öneme sahip olduğu düşünülmemektedir. **Kullanım şekli ve dozu: MİRENA®** rahim boşluğuna yerleştirilir. Beş yıl boyunca etkilidir. Salım hızı başlangıçta 20 mikrogram/24 saattir. Beş yılın sonunda bu hız 11 mikrogram/24 saate düşer. Beş yıllık kullanım süresi boyunca ortalama salım hızı 14 mikrogram/24 saattir. Hormon replasman tedavisi alan kadınlarda **MİRENA®** progestagen içermeyen oral veya transdermal preparatlarla birlikte kullanılabilir. **MİRENA®** takılacağı zamana kadar açılmaması gereken steril bir paket halinde sunulmaktadır. Açılmış ürün aseptik koşullara uyularak kullanılmalıdır. Steril paketin ambalajında hasar/açılma mevcutsa, rahim içi sistem tıbbi atık muamelesine tabi tutulmalıdır. Çıkarılmış bir rahim içi sistem de, hormon kalıntıları içerebileceğinden tıbbi atık muamelesine tabi tutulmalıdır. **MİRENA®** aplikatörü hastane atığı, ambalajlar ise evsel atık kabul edilir. **MİRENA®** uygulaması ile ilgili ayrıntılı bilgi "Teknik Bilgiler" bölümünde bulunmaktadır. 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Editorial Office

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

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Aims and Scope

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

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Book chapter;

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

Book;

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

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3 Ovül

Trivag

300 mg/200 mg/100 mg
Ovül

Tinidazol
Tiokonazol
Lidokain

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

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

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

▶ **Mikst vajinal enfeksiyonların**

ampirik tedavisinde tek form ile etkilidir.*

Tedavide rahatlık için*

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

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Editorial

Dear Colleagues,

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

As you know, modeling and simulation is breaking away from traditional uses (e.g., aviation and research) and emerging as an increasingly important tool for education and training. Educational simulation focuses learners on specific facts, concepts, or applications of the system. Simulators are useful tools in providing powerful learning experiences. Integrating simulations into an educational program is a perfect opportunity to put theory into practice through role playing, Here you will read a paper investigating the suitability of an in-house conisation simulator for teaching medical students the practical performance of conisation.

You will also read an interesting paper investigating whether testis magnetic resonance spectroscopy predicts the success or failure of micro-dissection testicular sperm extraction (micro-TESE) in patients with non-obstructive azoospermia. As you appreciate, the development of a non-invasive imaging technique which can identify infertile men with non-obstructive azoospermia where a successful sperm retrieval outcome in micro-TESE can be expected is of great clinical significance.

Also you will get the occasion to read a review examining the current literature to find if there was any possible benefit of endometrial scratching.

Dear reviewers and researchers,

As editors we are in function to provide scholarly communication. As a team our aim is to elevate our journal and continue to nurture its growth through every stage of the publishing process. Thank you for your valuable support.

Best regards,

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

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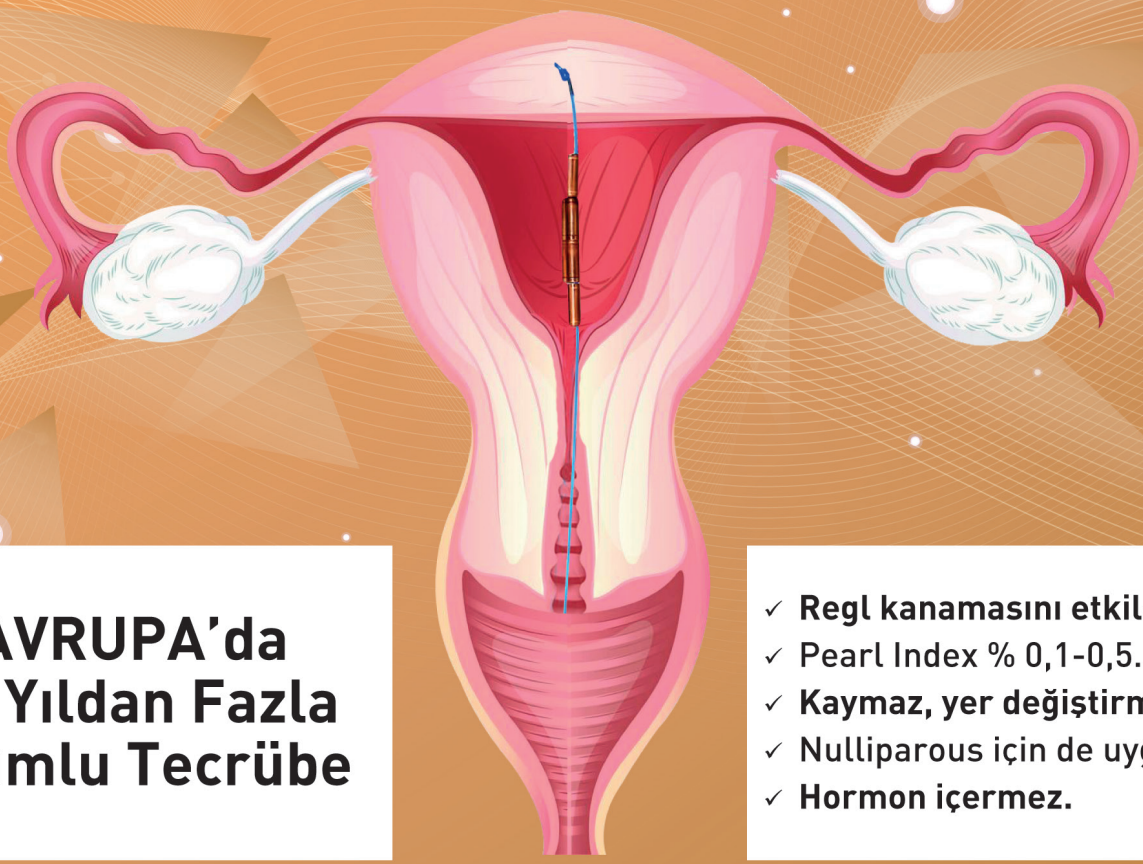

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Testis spectroscopy may predict sperm retrieval rate in men with non-obstructive azoospermia undergoing micro-TESE: A pilot study

Önder Çelik[1], Şafak Hatırnaz[2], Aynur Erşahin[3], Alper Başbuğ[4], Gonca Yetkin Yıldırım[5], Vahit Özener[6], Neslihan Gürpınar[6], Sudenaz Çelik[7], Nilüfer Çelik[8], Tansu Küçük[9], Cihat Ünlü[9]

[1]Department of Obstetrics and Gynecology, Private Office, Uşak, Turkey
[2]In Vitro Fertilization Unit, Medicana International Hospital, Samsun, Turkey
[3]In Vitro Fertilization Unit, Medicalpark Göztepe Hospital, İstanbul, Turkey
[4]Department of Obstetrics and Gynecology, Düzce University Faculty of Medicine, Düzce, Turkey
[5]Clinic of Obstetrics and Gynecology, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
[6]Department of Radiology, Barış Radiology Center, İzmir, Turkey
[7]Kent College High School, İzmir, Turkey
[8]Clinic of Biochemistry, University of Health Sciences, Behçet Uz Children's Training and Research Hospital, İzmir, Turkey
[9]Department of Obstetrics and Gynecology, Acıbadem University Faculty of Medicine, İstanbul, Turkey

Abstract

Objective: To investigate whether prior testis magnetic resonance spectroscopy predicts the success or failure of micro-dissection testicular sperm extraction (micro-TESE) in patients with non-obstructive azoospermia (NOA).

Material and Methods: Nine men with NOA who were scheduled for micro-TESE for the first time, 9 NOA men with a history of previous micro-TESE and 5 fertile men were enrolled. All NOA patients and fertile controls underwent testis spectroscopy. A multi-voxel spectroscopy sequence was used. Testicular signals of choline (Cho), creatine (Cr), myo-inositol (MI), lactate, and lipids were analyzed quantitatively and compared with the results of the micro-TESEs.

Results: The most prominent peaks were Cho and Cr in the fertile controls and NOA subjects with positive sperm retrieval in the micro-TESE. A high Cho peak was detected in 87% of the NOA men with positive sperm retrieval. NOA men without sperm at the previous micro-TESE showed a marked decrease in Cho and Cr signals. For positive sperm retrieval in micro-TESE, the cut-off value of Cho was 1.46 ppm, the cut-off value of Cr was 1.43 ppm, and the cut-off value of MI was 0.79 ppm.

Conclusion: Testis spectroscopy can be used as a non-invasive screening method to predict the success or failure of micro-TESE. (J Turk Ger Gynecol Assoc 2020; 21: 70-8)

Keywords: Testis, magnetic resonance spectroscopy, sperm retrieval, micro-TESE, non-obstructive azoospermia

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Introduction

The fertility management of patients with non-obstructive azoospermia (NOA) involves micro-dissection testicular sperm extraction (micro-TESE) combined with intracytoplasmic sperm injection (ICSI) (1). Micro-TESE is not only a diagnostic tool for the presence of spermatozoa, but also a therapeutic procedure for retrieving sperm for ICSI. The sperm retrieval rate in men with NOA is reported to be 50% (2,3). However, micro-TESE is an invasive procedure that requires anesthesia.

Address for Correspondence: *Önder Çelik*
e.mail: celiksudenaz@gmail.com ORCID: orcid.org/0000-0003-4053-0770

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Moreover, repeated unsuccessful micro-TESE procedures can be devastating for fertility outcome. Concordantly, excessive and repeated tubule harvesting to retrieve spermatozoa may lead to complications, including testicular atrophy and hemorrhage, and a decline in serum androgen levels (4). In addition to being a surgically invasive procedure, there can be a severe psychological blow for infertile couples when sperm cannot be obtained during micro-TESE.

The development of non-invasive imaging techniques which can identify infertile men with NOA where a successful sperm retrieval outcome in micro-TESE can be expected is of great clinical significance. An evaluation of serum or seminal fluid biomarkers provides a minimally invasive diagnostic approach to predict the presence of spermatozoa in the testes of men with NOA. Allied to this, several predictors such as age, testicular volume, testicular histology, serum follicle stimulating hormone (FSH), inhibin and testosterone concentrations, and Y chromosome microdeletions have been used to test for the presence of spermatozoa in testicles (5-9). Nevertheless, each test has its own shortcomings and there are many examples of the limitations of these predictors, some of which are described below. Testicular biopsy and histology is the best predictor of micro-TESE outcome. However, it is not practical to perform a biopsy before micro-TESE, and recurrent surgery adds to the patient cost and increases the risk of complications. It has been reported that serum FSH levels indicate the status of seminiferous epithelium and can be used to predict spermatozoa status. A study conducted by Khelaia et al. (9) in 2015 reported that the sperm retrieval rate in NOA men with serum FSH levels between 10 and 15 mU/mL was 0%. Moreover, despite normal levels of circulating FSH, subjects may exhibit sperm maturation defects (10). Likewise, FSH levels show wide variations among infertile and fertile men (11). In spite of a strong positive correlation between testis volume and sperm retrieval rates, the calculation methods of testis volume are not standardized (12). In addition, despite normal testis volumes, subjects may show defects in spermatogenesis (10). While sperm recovery is possible in subjects with azoospermia factor c (AZFc) microdeletions, complete deletions in the AZFa or AZFb loci are not compatible with the presence of sperm (5,6).

In addition to biological predictors, some imaging techniques have been developed to predict the presence of spermatozoa in the testes of azoospermic men. Tsili et al. (13) assessed differences of apparent diffusion coefficient (ADC), fractional anisotropy (FA) and the association with the presence of spermatozoa after TESE. They reported that both ADC and FA are increased in NOA testes compared to age-matched controls. Multiphoton microscopy and Raman spectroscopy are further imaging techniques evaluating the testis and its content. However, each method requires either testis biopsy or biological fluid samples. In vitro techniques are also available (14). More importantly, DNA damage to sperm may occur if high laser intensity is used during these procedures. In short, globally accepted non-invasive biological or radiological tests that can predict the presence of spermatozoa in the testes of men with azoospermia undergoing micro-TESE have not been reported.

It is known that isolated regions of spermatogenic tissue may exist in the testicles of men with NOA (15). In the absence of non-invasive methods for the identification of these regions of spermatogenic tissue, invasive procedures such as testis biopsy and micro-TESE are the only diagnostic methods that are available to retrieve spermatozoa. Magnetic resonance spectroscopy (MRS) is a non-invasive imaging method that provides qualitative and quantitative information about the biochemical and molecular composition of living tissues, including testes. Any alteration in the molecular and cellular status of living tissues translate into signal intensity, which can be detected by MRS. Because each living tissue has a unique spectrum, spectral signal intensity or a chemical shift might predict the different in vivo pathological processes at a cellular level (16). The feasibility of MRS for evaluating female and male reproductive organs has been shown by our team and others (16-18). However, it remains to be determined whether spectroscopy of the testes before micro-TESE can predict the presence of sperm in harvested testis specimens. A comprehensive literature search did not reveal any studies investigating the predictor effects of testicular MRS in NOA men undergoing micro-TESE. The present study thus aimed to determine whether prior testis MRS can predict the success or failure of micro-TESE, as well its value in the management of NOA patients undergoing initial or repeat micro-TESE.

Material and Methods

This pilot study was approved by the Ethical Commitee of Kanuni Sultan Süleyman Training and Research Hospital (approval number: KAEK/2017.1.13). In total, 18 men with NOA with a mean age of 37 (range: 27-48 years) and five fertile controls were included in the study. Azoospermia was defined as the absence of sperm cells in the seminal fluid. All patients were confirmed to be azoospermic through at least two semen analyses. Nine of the 18 patients had previously undergone micro-TESE, and these cases were evaluated retrospectively. Three patients were sperm positive on micro-TESE, but sperm was not found in the other six patients. Due to weak choline (Cho) and creatine (Cr) signals in their spectra, the six NOA men with negative micro-TESE anamnesis were not recommended for repeat micro-TESEs. Some of the patients provided more than one negative micro-TESE history. The remaining nine patients underwent micro-TESE for the first time. They had

diagnostic testis spectroscopy prior to the planned micro-TESE. The nine NOA men with a history of previous micro-TESE and the fertile controls underwent MRS following three days of sexual abstinence. The men with NOA were scheduled for micro-TESE after spectroscopy. Detailed information about the surgical technique used for the micro-TESE procedure can be found elsewhere (4,8). The micro-TESE specimens were analyzed by an experienced embryologist to determine whether the materials contained sperm or not. The testis spectroscopy results of the NOA men were analyzed quantitatively and then correlated with the results of subsequent micro-TESE attempts. Possible associations between the metabolite peak intensities obtained from the spectra of the NOA subjects and the sperm retrieval rates in their micro-TESE were assessed. In addition to testis MRS, the testicular long axis and serum concentrations of FSH, luteinizing hormone (LH), prolactin (PRL), and testosterone were measured in each study group. Participants with unilateral testes due to surgical resection or undescended testes were excluded. Subjects with a history of benign or malignant testicular tumors, testicular torsion, and abnormal karyotypes were also not included.

Magnetic resonance spectroscopy technique

Both the men with NOA and the fertile controls underwent testis spectroscopy before micro-TESE. Spectroscopy analysis of each testis was performed using a 3-T system (Achieva; Philips, Best, Netherlands). T1-weighted images (WI) [time repetition/time echo (TE), 500/20] and T2-WI (1600/80) with 4 mm thick sections were obtained in the axial and coronal planes. A single and a multi-voxel point-resolved spectroscopy sequence (16), both with short (35 ms) and long (140 ms) TEs were used. Multivoxel point-resolved spectroscopy sequence was used for detecting testes metabolites. The metabolite ratios of the peaks were determined using magnetic resonance user Interface software. The quantified metabolites of the spectra were Cho, Cr, myo-inositol (MI), lactate, and lipids in both NOA groups and the fertile controls. The metabolites in the spectrum were measured in units and converted to parts per million (ppm). The testes were first visualized using magnetic resonance imaging before the voxels were prescribed accordingly (17,18). Due to the critical importance of the voxel locations in the appropriate testicular area for investigating spermatogenesis, the volume of interest was placed to the center of the testicular parenchyma (Figure 1). The absence of neighboring organs or tissue parts that could affect the signals obtained from testes make testis spectroscopy easy and objective, thus resulting in good quality metabolite signals. Possible associations between the metabolite intensities obtained from the spectra of the NOA subjects and the sperm retrieval rates in their micro-TESEs were assessed. The spectroscopy results were also compared with other predictors, including age, FSH, LH, PRL, testosterone, and the long axis of the testes.

Statistical analysis

SPSS version 23.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis of the data. The conformity to normal distribution of the data was tested using the Shapiro-Wilk test. Quantitative data were expressed as mean ± standard deviation, median and range (minimum-maximum), and percentage (%). For comparison of the groups, ANOVA test was used with the corresponding Tukey contrast test. The chi-square or Fisher's exact tests were performed to compare the frequencies of the categorical variables, as appropriate. The correlations between age, reproductive hormones, and tissue metabolites were evaluated using Pearson correlation coefficients. Receiver operating characteristic curve analysis was used to determine the best cut-off values for the testes metabolites for the evaluation of the success rates of sperm retrieval. Cho and Cr are the two main metabolites indicating the vital function of living cells. In our previous study, it was shown that the metabolic function of reproductive tissues is either absent or pathological when Cho and Cr signals are below the expected physiological values (16). Therefore, these two metabolites were used to determine the cut-off values for the prediction of spermatogenesis in NOA men undergoing micro-TESE. Initially, it was thought that micro-TESE for NOA cases could be recommended where the Cho and Cr signals were greater than the cut-off values. However, due to the

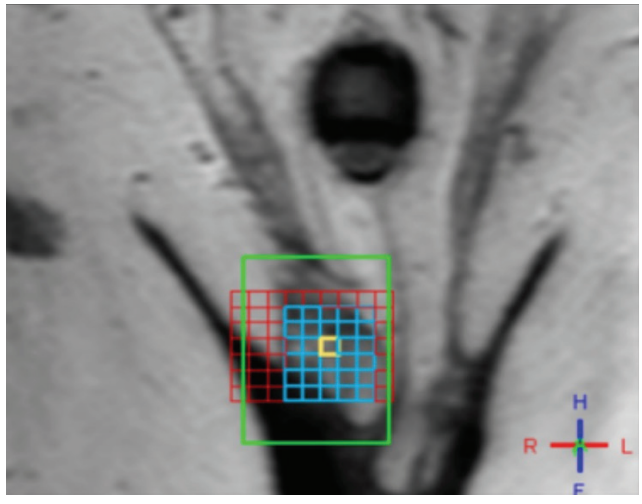

Figure 1. Multivoxel point-resolved spectroscopy sequence was used for detecting testis metabolites. The volume of interest was placed to the center of the testicular parenchyma. Lack of neighbouring organs or tissue parts that could affect signals obtaining from testes make testis spectroscopy easy and objective for obtaining good quality metabolite signals.
R: Right, L: Left, H: Head, F: Foot

novelty of the diagnostic use of spectroscopy in NOA and to determine the cut-off values, micro-TESE was offered for all participants, regardless of their metabolite values. A value of $p<0.05$ was accepted as statistically significant.

Results

Demographic characteristics of each group are presented in Table 1. A total of 18 subjects with NOA and five fertile men underwent single/multi-voxel MRS at 3 T. MRS was feasible for in all subjects with NOA, as well as the control subjects. All the patients had two testes; thus, 36 testes were investigated in terms of their peak characteristics. Since the right and left testes signal characteristics were similar, only the right testis data are presented here. As there are no previous studies investigating the effects of spectroscopy on spermatogenesis, all the patients were sent for micro-TESE regardless of their peak intensities. Five different testicular metabolites, including Cho, Cr, Lac, MI, and lipids, were detected via spectroscopy. Cho, Cr, and MI were the most prominent metabolites detected in the fertile group (Table 2 and Figure 2) and this was also the case with the NOA men with active spermatogenesis. The Cho and Cr signals of the fertile group were significantly higher than those in the NOA groups. The MI and lactate metabolites of the fertile group were similar to those of the NOA men with or without sperm in micro-TESE. Although a low lactate signal was detected in the fertile cases compared to the NOA groups, the difference was not statistically significant. When the subgroup analysis was performed, the lactate peak of the NOA men with negative sperm retrieval in micro-TESE was higher than that of the NOA men with positive sperm retrieval (1.515±0.675 ppm vs 0.525±0.193 ppm; $p=0.001$). Cho, Cr, and MI were highly sensitive peaks to predict the presence of sperm in micro-TESE. The cut-off value of Cho was 1.46 ppm [area

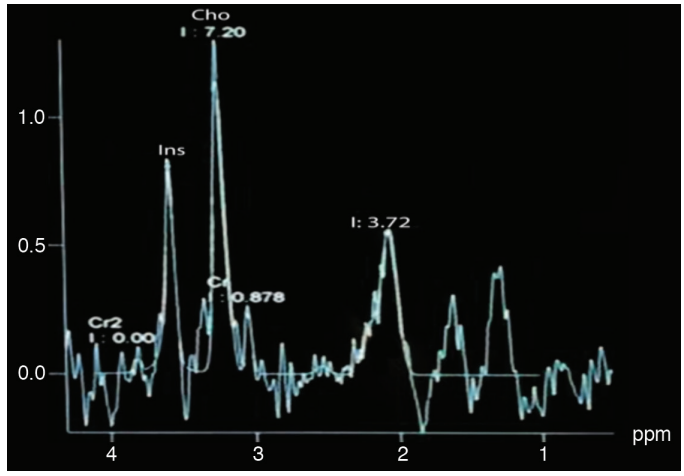

Figure 2. The spectral pattern of a fertile man showing high Cho and MI signals depicting normal
Cho: Choline, MI: Myo-inositol, Cr: Creatine

Table 1. Characteristics of study subjects

	Fertile group (n=5)	Previous micro-TESE group (n=9)	First micro-TESE group (n=9)	p
Age (year)	31.5 (28-37)	40.5 (29-44)	32.5 (27-41)	0.408
FSH (IU/L)	15.75±5.96	13.75±5.61	19.50±5.74	0.204
LH (IU/L)	8.50±1.29	7.25±0.95	9.75±4.11	0.932
Prolactin (ng/mL)	14.50±2.38[↓]	19.50±4.04	23.50±4.79[↓]	0.018
Testosterone (ng/dL)	422.00±34.22	393.25±8.99	396.00±30.50	0.299
Right testis long axis (mm)	41.25±2.75	36.25±2.98	33.25±4.19	0.062
Left testis long axis (mm)	41.00±2.58	36.25±2.98	35.50±3.69	0.175
Y chromosome microdeletions	0	3 (33.3%)	1 (11.1%)	0.236

micro-TESE: Micro-dissection testicular sperm extraction, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, [↓]: Significant difference between groups

Table 2. Testis metabolites levels

	Fertile group (n=5)	Previous micro-TESE group (n=9)	First time micro-TESE (n=9)	p
Cho (ppm)	2.328±0.309[↓]	0.946±0.572	1.232±0.780	0.003
Cr (ppm)	2.196±0.625[↓]	1.158±0.473[↓]	1.532±0.704	0.021
Lac (ppm)	0.362±0.128	1.043±0.610	0.788±0.441	0.060
Lip (ppm)	0.618±0.345	0.643±0.220[↓]	0.455±0.237	0.001
MI (ppm)	1.032±0.110	0.584±0.182	1.064±0.309	0.283

Cho: Choline, Cr: Creatine, Lac: Lactate, Lip: Lipid, MI: Myo-inositol, [↓]: Significant difference between groups, micro-TESE: Micro-dissection testicular sperm extraction

under the curve (AUC): 0.938, 95% confidence interval (CI): 0.811-1.00; p=0.002], the cut-off value of Cr was 1.43 ppm (AUC: 0.900, 95% CI: 0.730-1.00; p=0.004), and the cut-off value of MI was 0.79 ppm (AUC: 0.794, 95% CI: 0.547-1.00; p=0.037) for positive sperm retrieval in micro-TESE (Table 3). In five of the nine NOA cases, the Cho and Cr signals were found to be greater than the cut-off values while in the remaining four cases, these were lower than the cut-off values. Sperm was found in four of the five cases with Cho and Cr signals greater than the cut-off values in the initial MRS (Figure 3). In one case, despite high Cho and Cr signals, no sperm was found on micro-TESE. Sperm was not found in three of four cases with Cho and Cr signals lower than the cut-off values in the initial MRS (Figure 4). Despite the low Cho and Cr signals in the initial spectroscopy, sperm was found in one man with NOA. In total, sperm was harvested from five of the nine subjects with NOA during micro-TESE (Table 4). The sperm retrieval rate for the NOA group was 55.5%. A low Cho peak was detected in 100% of the NOA men with negative sperm retrieval in micro-TESE (Figure 5). In contrast, a high Cho peak was detected in 87% of the NOA men with positive sperm retrieval in micro-TESE (Figure 5). A low Cho peak had high specificity thus indicating inactive spermatogenesis. The peak intensities of the measured metabolites in the fertile men were similar to the spectra of the NOA men with sperm in micro-TESE (Cho p=0.059; Cr p=0.917; lactate p=0.530; MI p=0.117; lipid p=0.310). Conversely, the signal characteristics of the fertile men were significantly different than those of the NOA men without sperm in micro-TESE (Cho p=0.001; Cr p=0.017; lactate p=0.002; MI p=0.007). The mean testicular lengths were similar in the fertile and NOA groups. No correlations were detected between the FSH, LH, PRL, and total testosterone levels, long testicular axis, and measured spectral signals (Table 5). However, a significantly positive correlation was detected between age and lactate signal. When the nine men who had a history of previous micro-TESEs were examined retrospectively, the Cho and Cr signals were found to be greater than the cut-off value in three patients with positive sperm retrieval. The Cho and Cr signals were either absent or under the cut-off values in six patients with negative sperm retrieval in previous micro-TESEs.

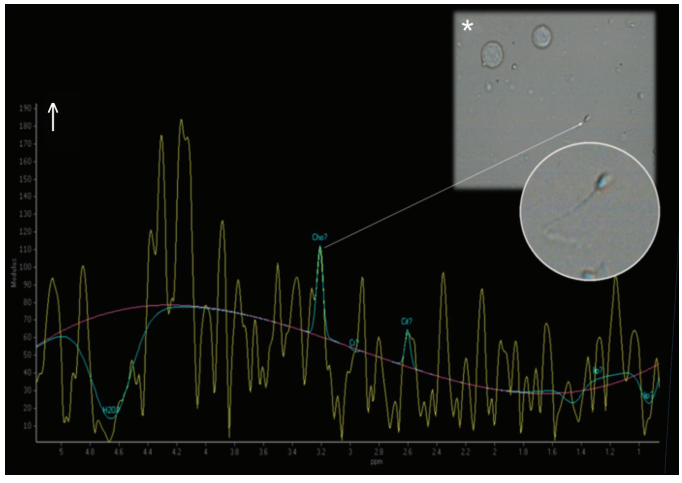

Figure 3. (*) The spectral pattern of an NOA man with positive sperm retrieval following micro-TESE. (↑) Note the high Cho signal depicting active spermatogenesis
NOA: Non-obstructive azoospermia, micro-TESE: Micro-dissection testicular sperm extraction, Cho: Choline

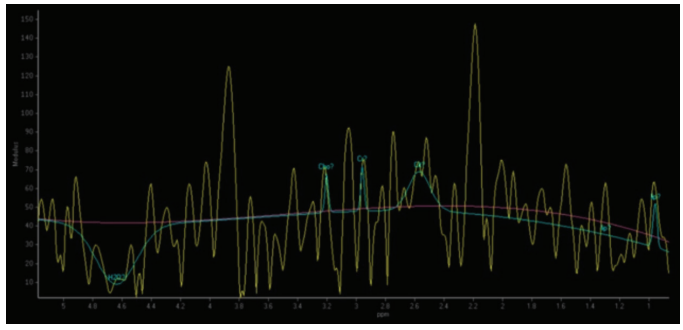

Figure 4. The spectral pattern of an NOA man with negative sperm retrieval following micro-TESE. Note the low Cho and Cr signals depicting pathological spermatogenesis
NOA: Non-obstructive azoospermia, micro-TESE: Micro-dissection testicular sperm extraction, Cho: Choline, Cr: Creatine

Table 3. Diagnostic performance of testes metabolite leves for positive sperm retrieval

	Sensitivity (%)	Specificity (%)	Positive predictivity of the test (%)	Negative predictivity of the test (%)
Cho↑	87.5%	100%	100%	90%
Cr↑	87.5%	90%	87.5%	90%
MI↑	75%	80%	66.6%	77.7%
Cho↑ Cr↑	87.5%	100%	100%	90%
Cho↑ MI↑	62.5%	100%	100%	77%
Cr↑ MI↑	62.5%	100%	100%	77%
Cho↑ Cr↑ MI↑	62.5%	100%	100%	77%
Cho: Choline, Cr: Creatine, MI: Myo-inositoli, ↑: Increase				

Discussion

There is no single clinical or laboratory finding that can accurately predict positive or negative sperm retrieval before micro-TESE. In the present study, the diagnostic accuracy of in vivo spectroscopy signals obtained from the testicles of NOA men undergoing micro-TESE and the concomitant success rates for finding spermatozoa were investigated. The most crucial result of this study was the powerful relationship between a high Cho peak and the chance of sperm retrieval in micro-TESE. An increased Cho signal intensity was very sensitive for predicting positive sperm retrieval when using

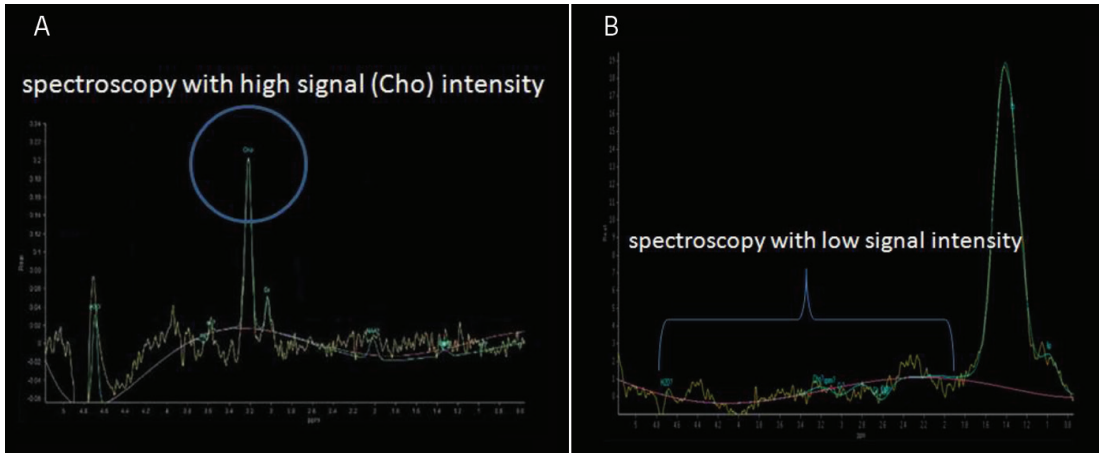

Figure 5. Comparison of a spectroscopy with a high (A) and low (B) signal intensity. It is expected to be a healthy metabolic process in the testis of a man with high Cho peak (A). There is a high probability that the metabolic process is disturbed in the testis of a man with low signal. The first case belongs to a fertile case (A) and the second is a spectroscopy of a TESE negative case (B)
Cho: Choline, TESE: Testicular sperm extraction

Table 4. Magnetic resonance spectroscopy analysis of testes of men with negative or positive sperm retrieval in previous or first micro-TESE

NOA men	TESE results	Cho	Cr	Lac	Lip	MI	Comment
Previous micro-TESE	Negative sperm retrieval	0.40	1.0	0.93	0.20	0.55	Note the low signal intensity of Cho and MI
Previous micro-TESE	Negative sperm retrieval	0.67	1.2	1.05	1.01	0.79	Note the low signal intensity of Cho and high Lac
Previous micro-TESE	Negative sperm retrieval	0.71	0.9	1.61	0.83	0.56	Note the low signal intensity of Cho, Cr, MI and high Lac
Previous micro-TESE	Positive sperm retrieval	1.63	1.66	0.22	0.74	0.65	Note the high signal intensity of Cho, Cr and low Lac
Previous micro-TESE	Positive sperm retrieval	1.59	1.75	0.52	0.57	0.80	Note the high signal intensity of Cho, Cr and high Lac
Previous micro-TESE	Positive sperm retrieval	1.82	1.78	0.40	0.61	0.23	Note the high signal intensity of Cho and Cr and low Lac
Previous micro-TESE	Negative sperm retrieval	0.80	0.65	1.78	0.60	0.70	Notet the low Cho and Cr, high Lac signal
Previous micro-TESE	Negative sperm retrieval	0.34	0.98	1.90	0.59	0.41	Note the low Cho Cr and high Lac signal
Previous micro-TESE	Negative sperm retrieval	0.56	0.51	0.98	0.64	0.57	Note the absence of remarkable signals
First micro-TESE	Positive sperm retrieval	2.12	1.98	0.67	0.43	1.31	Note the high signal intensity of Cho, Cr and MI
First micro-TESE	Positive sperm retrieval	1.76	2.01	0.33	0.77	1.25	Note the high signal intensity of Cho, Cr and MI
First micro-TESE	Positive sperm retrieval	0.55	0.82	0.97	0.80	1.33	Note the high signal intensity of MI
First micro-TESE	Negative sperm retrieval	0.32	0.98	1.02	0.53	0.87	Note the low Cho, Cr signals and high Lac
First micro-TESE	Positive sperm retrieval	2.09	2.11	0.31	0.40	1.40	Note the high signal intensity of Cho, Cr and MI
First micro-TESE	Positive sperm retrieval	1.99	2.65	0.40	0.12	1.29	Note the high signal intensity of Cho, Cr and MI
First micro-TESE	Negative sperm retrieval	1.33	1.67	1.49	0.47	0.60	Note the high signal intensity of Cho, Cr, Lac
First micro-TESE	Negative sperm retrieval	0.54	0.87	1.30	0.46	0.80	Note the high signal intensity of Lac

NOA: Non-obstructive azoospermia, micro-TESE: Micro-dissection testicular sperm extraction, Cho: Choline, Cr: Creatine, Lac: Lactate, Lip: Lipid, MI: Myo-inositol

Table 5. Correlation between age, reproductive hormones and testis metabolites

	Cho		Cr		Lac		Lip		MI	
	p	r	p	r	p	r	p	r	p	r
Age (year)	0.053	-0.464	0.407	-0.208	0.007[‡]	0.610	0.344	-0.237	0.891	0.035
FSH (IU/L)	0.783	-0.081	0.802	0.074	0.747	-0.095	0.217	0.352	0.294	-0.302
LH (IU/L)	0.136	0.377	0.287	0.274	0.579	-0.145	0.620	0.130	0.931	-0.023
Prolactin (ng/ML)	0.126	-0.446	0.246	-0.346	0.293	0.316	0.650	0.139	0.752	-0.097
Testosterone (ng/DL)	0.601	0.169	0.339	0.303	0.891	0.044	0.558	0.188	0.211	-0.389
Right testis long axis (mm)	0.389	0.261	0.703	0.117	0.300	-0.312	0.826	-0.068	0.840	0.062
Left testis long axis (mm)	0.109	0.431	0.294	0.290	0.093	-0.450	0.653	-0.127	0.778	-0.080

[‡]Significant difference between groups
Cho: Choline, Cr: Creatine, Lac: Lactate, Lip: Lipid, MI: Myo-inositol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

micro-TESE technique. The chance of sperm retrieval using micro-TESE was very high when the cut-off value for Cho was over 1.46 ppm and the cut-off value for Cr was over 1.43 ppm. Sperm was retrieved by micro-TESE in 80% of the NOA men whose Cho and Cr signals were greater than the cut-off values. Nevertheless, despite high Cho and Cr signals on spectroscopy, sperm could not be detected in one patient. Of the four men with NOA who exhibited a high Cho signal and had successful retrieval of spermatozoa, three of their partners became pregnant. One woman delivered a healthy baby while the remaining two women had ongoing pregnancies during the study period. Accordingly, if the Cho and Cr signals are lower than 1.46 and 1.43 ppm, respectively, the chances of sperm retrieval in micro-TESE are very low. No sperm was found using micro-TESE in 75% of the patients whose Cho and Cr signals were lower than 1 ppm. In fact, 75% of azoospermic patients with low Cho signal did not have any foci of spermatogenesis that were sufficient to find spermatozoa on micro-TESE. Only one NOA man with low Cho signal in prior testis spectroscopy had successful spermatozoa retrieval. This may be due to a technical error in evaluating the spectroscopy signals or a fault in the MRS procedure. Interestingly, his partner did not become pregnant.

Our findings suggest that, irrespective of the overall state of spermatogenesis, determining high Cho and Cr signals may predict positive sperm retrieval in men with NOA. In light of this, we suggest that the best predictor of positive sperm retrieval in micro-TESE is a high Cho peak. A Cho signal at least greater than 1.46 ppm should be present in the MRS of a testicle to find spermatozoa on micro-TESE. Similar to the Cho signal, the Cr signal in the NOA men with active spermatogenesis was found to be greater compared to the Cr signals in the NOA men without spermatogenesis. As Cr is an indicator of the energy status of living cells, a decreased Cr signal in the NOA men without sperm may indicate a defective metabolism within the testis. In contrast to the Cho and Cr signals, the lactate levels were significantly higher in the negative sperm retrieval group when compared to the positive sperm retrieval group (1.515±0.675 vs 0.525±0.193, respectively). As is well known, high lactate levels indicate the presence of anaerobic glycolysis at the cellular level. It is therefore not expected that sperm can survive in an oxygen-free environment. It was observed that the NOA men with active spermatogenesis had high Cho peaks when compared to the NOA men without spermatogenesis. Although the exact mechanism for this difference was unclear, we propose that it may be associated with the disturbed cellular integrity of the Leydig and/or Sertoli cells. The absence of any signal or weak signal intensity in NOA men with Sertoli cells only, maturation arrest, or orchitis support our idea. Albrecht (19) reported that the testes of NOA men showed an increased deposition of collagen fibers and an extracellular matrix. They also noted that by increasing the thickness of the lamina propria, this pathological accumulation may cause defective spermatogenesis. We therefore propose that decreased Cho peak intensity in NOA men without sperm on micro-TESE may be related to excessive thickness of the lamina propria of the seminiferous tubules. The greatest support for our hypothesis comes from the study conducted by Tsili et al. (18), which showed a decline in the intensity of Cho signals with advancing age. When taken together, our findings and previous results suggest that NOA men without active spermatogenesis exhibit the signal properties of elderly men. Conversely, as Cho is a marker of cell membrane turnover, a high Cho peak in NOA men with sperm on micro-TESE may indicate that they have healthy cellular function. A similar Cho peak intensity in fertile men and NOA men with active spermatogenesis further supports our hypothesis. When a routine clinical application of testicular spectroscopy before micro-TESE is possible, this may lead to more cost-effective ICSI cycles because ovarian stimulation will only be started in NOA patients with positive spectroscopy, which

predicts the presence of sperm in the testicles. With the use of this non-invasive tool, an infertile man undergoing micro-TESE will know whether their testes contain sperm or not. If the initial micro-TESE is negative for finding sperm, spectroscopy will help in the decision of whether to offer a repeat micro-TESE. If testicular mapping can be performed according to the signal intensities of Cho and Cr, it may help determine in which regions sperm will be found by micro-TESE. Thus, it may be possible to avoid unnecessary surgical procedures in the sperm-free regions of testicular tissue. As a consequence, NOA patients with favorable spectroscopy that predicts the presence of sperm may undergo micro-TESE, confident in the knowledge that sperm will be retrievable during the procedure. In contrast, subjects with unfavorable spectroscopy results can be counseled about the low sperm retrieval rates in micro-TESE. NOA men with unfavorable metabolites at spectroscopy can abstain from micro-TESE attempts and redirect their attention to other assisted reproductive technology options. Although only in a small proportion of NOA patients, spectroscopy can also help detect benign and malignant testicular lesions as well as congenital and acquired causes of obstructive azoospermia (20).

The current investigation was carried out because of two contrasting hypotheses; high Cho and Cr signals were proposed as being indicators of the presence of spermatozoa while low Cho and Cr signals would be indicators of the absence of spermatozoa on micro-TESE. We found that low Cho and Cr signals on spectroscopy indicated that spermatozoa will not be found on micro-TESE while the presence of high Cho and Cr signals in spectroscopy indicated a strong likelihood that sperm will be found in micro-TESE. The real value of prior testis spectroscopy is its ability to correctly predict whether spermatozoa will be present or absent on micro-TESE.

Conclusion

Analysis of our results demonstrates for the first time that high Cho and Cr signals are the best predictors of positive sperm retrieval in NOA men undergoing micro-TESE. Moreover, MI may also be used as a predictive factor. In addition to evaluating AZF deletions, testicular volume, and serum FSH levels, spectroscopy of the testes before micro-TESE can improve the prediction of sperm retrieval rates in men with azoospermia. Bilateral testicular spectroscopy can not only provide significant information with regard to the possibility of retrieving sperm in micro-TESE, but can also prevent unnecessary surgical interventions. Studies with larger sample sizes are warranted to enable a more adequate assessment of the impacts of in vivo spectroscopy on sperm retrieval rates. If our results are confirmed by other studies, testis spectroscopy could be used in ART practice to distinguish between testes with active or inactive spermatogenesis. In addition to being inexpensive and non-invasive in nature, the quick results of spectroscopy make it an ideal candidate tool for the screening of NOA men before micro-TESE. Testicular MRS is best coupled with an initial micro-TESE before starting the ICSI cycle. This non-invasive technique may serve as a novel and useful predictive method for guiding urologists and IVF specialists on whether to perform or not perform micro-TESE.

Ethics Committee Approval: *This pilot study was approved by the Ethical Commitee of Kanuni Sultan Süleyman Training and Research Hospital (approval number: KAEK/2017.1.13).*

Informed Consent: *Written informed consents obtained.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices - Ö.Ç., A.E., V.Ö., N.G.; Concept - Ö.Ç., Ş.H., G.Y.Y., A.B.; Design - Ö.Ç., S.Ç., N.Ç., Ş.H., C.Ü., T.K.; Data Collection or Processing - Ö.Ç., Ş.H., A.B., G.Y.Y., C.Ü.; Analysis or Interpretation - Ö.Ç., A.B., Ş.H.; Literature Search - Ş.H., A.B., G.Y.Y., Ö.Ç.; Writing - Ö.Ç., Ş.H., N.Ç., T.K., C.Ü.*

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Conisation course for medical students-experience from a German University Hospital

Ferenc Zoltan Takacs, Erich-Franz Solomayer, Amr Hamza Ingolf Juhasz-Böss, Panagiotis Sklavounos, Julia Caroline Radosa, Sebastian Findeklee

Department of Gynecology, Obstetrics and Reproductive Medicine, Saarland University Hospital, Homburg, Germany

Abstract

Objective: Conisation of the cervix is one of the most common surgical procedures in gynaecology. Nevertheless, surgical expertise is required because if the cone is too small, the oncological risk increases and if the cone is too large, the obstetric risk increases. The aim of this prospective study was to investigate the suitability of an in-house conisation simulator for teaching medical students the practical performance of conisation.

Material and Methods: Following a demonstration, students performed a loop conisation with a target depth of 8-10 mm using the simulator. Cone biopsy dimensions were analysed and a loop electrosurgical excision procedure (LEEP) score was calculated. The students were surveyed using a questionnaire of 12 items with five possible responses for each in order to investigate the suitability and realism of the teaching experience.

Results: Eighty-nine students participated in the course. The median (range) cone depth was 8 (3-25) mm with a standard deviation of 3.3 mm. The observed LEEP score amounted to 1.5. The questionnaire was answered by 88 students and completed by 86. Survey results showed the course was consistently rated as positive, especially towards the increase in practical skills. The questionnaire item producing the highest score was “I enjoyed the course” while the statement “I have gained enough self-confidence for the application of high-frequency surgery” received the lowest approval score. Students considered the course to be realistic and a helpful teaching exercise.

Conclusion: Practical surgery exercises on the surgical simulator were received positively. Simulation training could be extended to other gynaecological operations and to other medical subjects. (J Turk Ger Gynecol Assoc 2020; 21: 79-83)

Keywords: Conisation simulator, student teaching, questionnaire

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Introduction

Conisation is one of the minor gynaecological operations and in addition, it is one of the most common surgical procedures in gynaecology. Therefore, it is considered a typical operation for beginners but the procedure cannot be regarded as trivial. The removal of a too small a cone when excising diseased tissue may be at the expense oncological safety, thus requiring follow-up operations and/or therapies (1). Conversely, removing too large a cone will increase the oncological safety but will also increase the patient's obstetric risk in the event of a subsequent pregnancy. It has been reported that the risk of cervical insufficiency and consecutive premature birth in pregnancy after conisation is about 25% (2,3). This is aggravated by the fact that cervical dysplasia in need of treatment mostly occurs in young women aged 30-35 years (4).

How should one deal with this dilemma in clinical practice? Preventing young colleagues from performing conisations is not possible - because eventually there would not be the specialists capable of conisation. However, patient safety is paramount.

Therefore, a simulator for practicing conisation with an electric loop was developed at our center (5). This was then used during gynaecological and obstetric practical clerkship training. Students were asked to attempt an optimal conisation, following a demonstration by the doctor in charge of the study (study doctor). The students were then surveyed concerning the experience of practical training.

Address for Correspondence: *Sebastian Findeklee*
e.mail: Sebastian.Findeklee@uks.eu ORCID: orcid.org/0000-0002-2921-0664

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Material and Methods

The conisation simulator was used as part of the gynaecology and obstetrics practical clerkship at our gynaecology clinic in the summer semester 2018 (examination period: 13.04.2018-13.07.2018). This was a prospective study with fifth year medical students. The only inclusion criterion was participation in the conisation simulation course. The students were informed in detail about the study before participating. Participation was voluntary and anonymous. The study was previously approved by the Local Ethics Committee (approval number: 259/17).

Conisation simulator

A loop electrosurgical excision procedure (LEEP) was performed on the simulator. The conisation simulator was a table-top model with a self-holding speculum. A stone slab formed a stable surface, and a polystyrene plate lying on top of it conformed well to the shape of the speculum. A self-holding speculum with smoke evacuation was ideal for performing a LEEP under local anaesthesia and realistic conditions. For the simulation of the portio the end of a sausage was used. The cervical canal was visualized by the injection of red dye. Thus, the fragmentation and thickness of the cone could be better illustrated. The sausage was placed directly on the neutral electrode and fixed with a Velcro bandage (see Figure 1, 2). This allowed numerous quick repetitions. The LEEP was performed with the monopolar power device ERBE Vio300D (Erbe Elektromedizin GmbH, Tübingen, Germany) with a loop electrode (Erbe Elektromedizin GmbH, Tübingen, Germany) under colposcopic view (Olympus OCS-500, Olympus Europe, Hamburg, Germany) as previously described (5).

The course took place on the last day of the one-week practical clerkship and lasted 30 minutes. First, the study doctor carried out a loop conisation. Subsequently, the students in groups of around eight at a time, had the opportunity to make a loop conisation and up to two post-resections on their own under supervision by the study doctor.

After the course, the study doctor, who was a specialist in obstetrics and gynaecology employed at the study center, was asked if the simulator was suitable for everyday use and the course as realistic and if he could imagine assisting the students in a LEEP.

Loop electrosurgical excision procedure score for excision

To enable measuring the desired learning effect in the handling of the loop electrode after demonstration of the procedure by the study doctor, the participants were asked to perform an excision between 8 and 10 mm deep in a single cut. The specimens were measured with a digital calliper in the area of the cervical canal and visualized with dye. Depending on the depth and shape of the specimen, the students were able to perform a subsequent resection. The thickness of each specimen was added to obtain the total cone thickness. Thus

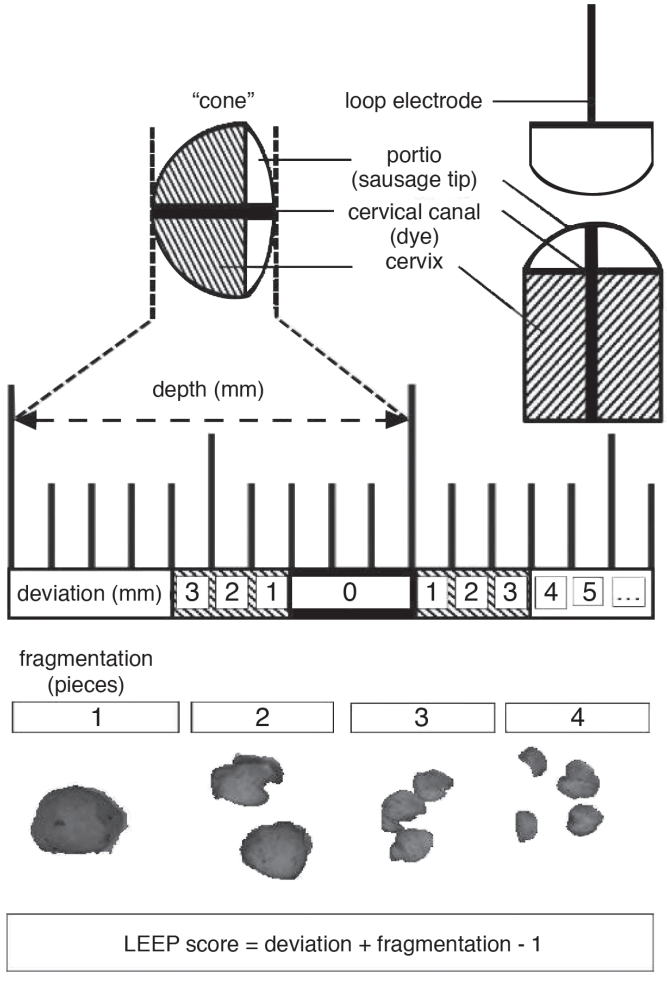

Figure 1. Scheme of the loop electrosurgical excision procedure simulator
LEEP: Loop electrosurgical excision procedure

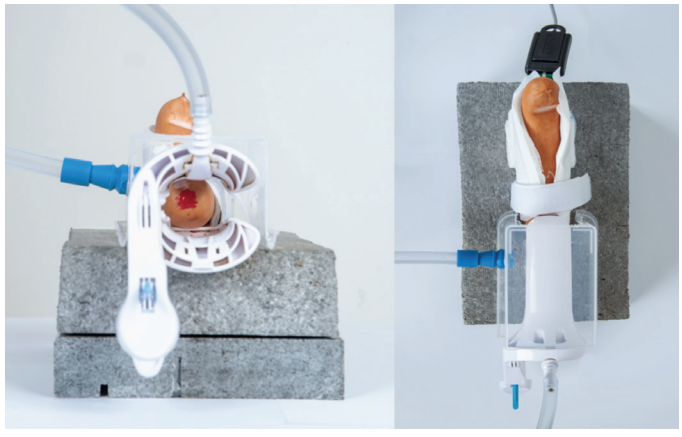

Figure 2. Construction of the conisation simulator

even if each individual cut showed a large deviation from the target range, resections could still result in a normal mean thickness. To record the excisions that missed the target range of 8-10 mm, deviations were recorded separately. The deviation from the desired cutting depth was calculated as follows. If the specimen thickness was between 8 and 10 mm, the deviation was 0. For superficial cuts, that is those less than 8 mm, deviation from the desired minimum was recorded so that a 6 mm specimen would have a depth deviation of 2 mm. Similarly for a cut that was too deep, that is greater than 10 mm, deviation from the desired maximum was recorded so that an 11 mm specimen would have a deviation of 1 mm. In order to account for both fragmentation and deviation together, a LEEP score was calculated as recently described (5).

Statistical analysis

All variables were analysed descriptively using median and standard deviation (SD) for continuous variables. Data was analysed using an electronic database (Microsoft Office Professional, Excel version 2007, Redmond, Washington, USA).

Study questionnaire

Students were asked to complete a self-developed anonymous questionnaire for the evaluation of the event, directly after performing the conisation. Participants were asked to rate the following statements using five possible grades (“agree”, “agree somewhat”, “neutral”, “disagree somewhat” and “disagree”). The following 12 statements used to evaluate the course:

1. The course has improved my operational skills.
2. The course helps me in dealing with patients.
3. The course has improved my medical study quality.
4. I wish to do more operation simulation exercises in the practical year.
5. I wish to perform more operation simulation exercises in other subjects.
6. The surgical simulation improves my understanding of the subject gynaecology and obstetrics.
7. The course improves my competence in gynaecology and obstetrics.
8. The surgical simulation has expanded my competence in gynaecological examination.
9. I have received sufficient knowledge about high-frequency surgery.
10. I have enough confidence to perform high-frequency surgery myself due to the course.
11. I could carry out a LEEP under supervision myself.
12. I enjoyed the course.

Results

A total of 89 out of 90 medical students performed a conisation with the simulator. One person could not attend for health reasons.

The median (range) total cone depth during the 89 conisations was 8 (3-25) mm and the SD was ±3.3 mm with 34 (38.2%) conisations being too superficial and 14 (15.7%) too deep. Thus, 41/89 students (46.1%) achieved the target range for cone depth of 8-10 mm with one conisation and 64/89 students (71.9%) reached the target range with additional subsequent resection. A total of 34 subsequent resections with a median (range) depth of 5 (2-10) mm and a SD of ±1.9 mm were performed. 25/89 (28.1%) did not reach the target range. We observed a LEEP score of 1.5 for the 89 medical students.

Out of the 89 students, 88 completed questionnaire and 86 forms were completely filled. On two questionnaires one answer was missing.

The study doctor assessed the conisation simulation course in all 89 cases as suitable for everyday use as part of normal student teaching. Furthermore, the course was perceived as realistic and the study doctor was confident in assisting a loop conisation in the operation room for all 89 medical students after the course.

The students’ conclusions regarding the teaching experience were consistently positive. Table 1 summarizes the results of the course evaluation by the medical students. The highest rated aspect of the course was enjoyment of the course with nearly 91% complete approval. The item with the worst assessment by the students concerned having enough self-confidence for performance of high frequency surgery on their own, with only 30% complete approval.

Discussion

To our knowledge, this is the first study ever examining a conisation simulator in the context of student teaching. The conisation exercises with the Homburger conisation simulator were rated almost entirely positive by both the study doctor and the participating students. An indication of this finding can be seen in the fact that for all questions, the first answer category (“agree”) was most often chosen although this was equal with the neutral response to the statement “self-confidence in the application of high frequency surgery”. However, it also seems interesting that the students’ answers were by no means homogeneous. This increases the validity of the answers, since evaluations within the framework of student teaching run the risk that the same answer will always be chosen or overestimated because of a lack of interest, in order not to disappoint the teachers.

Three basic tendencies can be seen in the analysis. First of

Table 1. Evaluation of the conisation course by the medical students (n=88)

Item	Agree	Agree somewhat	Neutral	Disagree somewhat	Disagree
1. Improvement of surgical abilities due to conisation course	45 (51.1%)	30 (34.1%)	12 (13.6%)	1 (1.1%)	-
2. Surgical simulation aid in daily treatment of patients	52 (59.1%)	26 (30.0%)	9 (10.2%)	1 (1.1%)	-
3. Improvement of study quality	58 (65.9%)	25 (28.4%)	4 (4.5%)	-	1 (1.1%)
4. Students' desire for more surgical exercises in the practical year	74 (84.1%)	12 (13.6%)	1 (1.1%)	-	1 (1.1%)
5. Students' desire for more surgical exercises in other subjects	77 (87.5%)	9 (10.2%)	-	-	1 (1.1%)
6. Improvement of understanding for the subject gynaecology and obstetrics	51 (58.0%)	29 (33.0%)	5 (5.7%)	2 (2.3%)	1 (1.1%)
7. Improvement of the medical expertise in the subject gynaecology and obstetrics	41 (46.6%)	37 (42.0%)	8 (9.1%)	2 (2.3%)	-
8. Improvement of expertise in gynaecological examination	44 (50.0%)	34 (38.6%)	7 (8.0%)	1 (1.1%)	1 (1.1%)
9. Extent of gained knowledge in high frequency surgery	38 (43.2%)	29 (33.0%)	14 (15.9%)	17 (19.3%)	-
10. Self-confidence in the application of high frequency surgery	26 (30.0%)	25 (28.4%)	26 (30.0%)	5 (5.7%)	6 (6.8%)
11. Self-confidence to perform a LEEP on your own	31 (35.2%)	27 (30.7%)	15 (17.0%)	7 (8.0%)	8 (9.1%)
12. Fun with conisation exercises	80 (90.9%)	7 (8.0%)	-	-	1 (1.1%)

LEEP: Loop electrosurgical excision procedure

all, the practical operation simulation exercise was very well received by the students, were perceived as a lot of fun and there was a strong desire to implement more simulation exercises during their studies. Second, they seem to bring about a global increase in knowledge, both in the theoretical and practical fields, with the practical gain in knowledge appearing to be greater than the theoretical one. Third, the students still expressed reservations about the practical application of surgical techniques to the patient under everyday clinical conditions as was evident by the lowest positive response (35.2%) concerning the self-confidence gained in using the methods of high frequency surgery in real practice. It must be emphasized that this can hardly be expected from a 30 minute course. It should also be kept in mind that, from experience, only half of the students will be interested in working in an operative subject later. Among future gynaecologists, the approval rates might have been higher.

The fact that the majority of students were able to reach the target range for conisation, with the aid of a subsequent resection if required, can be regarded as an encouraging result. However, the conisation simulator should be evaluated in further studies, in particular the impact of repetitive training on conisation depth, LEEP score and surgeon's self-confidence should be investigated further.

In this study practical exercises as an element of medical student teaching were investigated. These practical exercises can take several forms. They can be performed on humans (usually patients) as well as on animals, for example the practice of complex surgeries or interventional procedures such as heart valve replacement, as well as on models specially created for an intervention, as in this study (6-8). Undoubtedly, a non-living model is the most favourable solution, because it minimises ethical concerns. Additionally, most models would have unlimited reusability. An open question is the financing of simulation training. Unfortunately, not all university hospitals have a sufficient teaching budget to provide such models in sufficient numbers. One reason for this could be that practical exercises, especially of surgical interventions, are not yet an integral part of the curriculum within the clinical section of medical studies. If this were the case, medical schools would have a greater incentive to provide funding for it.

Alternative teaching concepts for practical exercises using simulation models also provide theoretical knowledge transfer, for example in the context of a lecture or a seminar and showing techniques with the help of various media, such as pictures or videos (9,10). In this case a practical simulation exercise was deliberately chosen because we believe that surgical procedures are best learned by actually experiencing the procedure and by repeating the procedures in a work or simulation setting. The publication by Spüntrup et al. (11) which showed that endoscopic surgery can be learned through repeated practice, confirmed the feasibility of the concept.

In addition, we believe it is unethical to practice operations primarily on humans or animals.

Conclusion

It is suggested that the conisation simulator for learning LEEP by medical students as well as physicians in further education has merit and further study is warranted.

We conclude that surgical simulation exercises, including exercises for the implementation of loop conisations, can be carried out without problems under everyday conditions in a university hospital and are rated positively by both the teacher and the students. With the aid of simulators practical surgical skills as well as theoretical knowledge can be taught efficiently. We propose that operation simulation exercises should be used much more widely, not only in gynaecology but also in other subjects, and that it may be possible to extend them to other operations or scientific issues.

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A comparison of antenatally and intraoperatively diagnosed cases of placenta accreta spectrum

Rahila Imtiaz, Zubaida Masood, Samia Husain, Sonia Husain, Rubina Izhar, Saba Hussain
Department of Gynaecology and Obstetrics, Karachi Medical and Dental College, Karachi, Pakistan

Abstract

Objective: To assess the effect of antenatal diagnosis of placenta accreta spectrum (PAS) on fetomaternal outcomes.

Material and Methods: This was a retrospective cohort study conducted from January 2017 to December 2018. Women with PAS diagnosed antenatally were designated as group A and those where diagnosis was suspected during operation and confirmed on histopathology (PAS diagnosed perioperatively) were designated as group B. Outcome in terms of uterine conservation, maternal death, admission of mother to intensive care unit (ICU), perinatal death and neonatal ICU (NICU) admission were recorded.

Results: During the study, PAS was confirmed in 96 cases which were included. Out of these, 34 (35.4%) cases were included in group A while 62 (64.6%) were diagnosed intraoperatively (group B). The median number of units of blood transfused was lower in group A compared to group B (4 vs 6, $p<0.001$). The uterus was conserved more often in group A compared with group B (67.6% vs 43.5%, $p=0.024$) while admission to ICU occurred significantly more often in group B (26.5% vs 59.7%, $p=0.002$). Maternal death ($p=0.038$) and perinatal death ($p=0.008$) were also significantly higher in group B. More neonates delivered to mothers in group B were admitted to NICU (85.7% vs 24%, $p=0.033$). Survival analysis showed a statistically significant increase in uterine conservation rate in group A compared with group B (log rank, $p=0.04$).

Conclusion: PAS diagnosed antenatally has better fetomaternal outcome than intraoperative detection of PAS. Diagnosing PAS antenatally is therefore crucial to improve management and achieve a better outcome. (J Turk Ger Gynecol Assoc 2020; 21: 84-9)

Keywords: Placenta accreta spectrum, antenatal diagnosis, fetomaternal outcomes

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Introduction

Placenta accreta spectrum (PAS) is a well-known entity that has become far more common than previously reported (1). This is partly due to the rising cesarean section rates in the region. However, the effect of sophisticated techniques for diagnosing this condition is also noteworthy.

PAS is associated with significant maternal morbidity and mortality. The condition, when diagnosed antenatally, allows mobilization of suitable clinical resources and helps to reduce poor outcomes (2). It was previously believed that the final diagnosis could only be confirmed retrospectively by histological examination of the specimen. This position is now in doubt and studies have reported that novel techniques such as power Doppler and magnetic resonance imaging have up to 100% sensitivity in diagnosing PAS cases (3).

An urgent problem arises when PAS cases are diagnosed intrapartum and the expertise, though available at tertiary centers, cannot be mobilized rapidly enough (4). Diagnosis of PAS can be dependent on assessment of risk factors but this is not always sufficient so that sometimes cases are missed, especially in facilities with high patient workloads. When an undiagnosed PAS is encountered morbidity has been reported to increase (5).

Despite antenatal diagnosis of PAS being associated with decreased morbidity, the evidence remains sparse, as PAS is not frequently encountered worldwide. Most evidence has been gathered in regions where antenatal care is optimal and cesarean sections rates are not very high (6,7). This report

Address for Correspondence: *Samia Husain*
e.mail: samiahusain_scorpio@hotmail.com ORCID: orcid.org/0000-0003-4301-4544

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originates from a region where antenatal care is suboptimal and cesarean section rates are at an all-time high which results in cases of PAS being seen more frequently. This aim of this study was to assess the effect of antenatal diagnosis of PAS on morbidity seen in such cases.

Material and Methods

This was a retrospective cohort study, conducted from 1st January 2017 to 31st December 2018. Consent for the use of hospital records was obtained from the department head. All labor room and obstetrics theatre records were analyzed to calculate the delivery rate at the hospital. The incidence of accreta was then calculated for the facility. All women who were diagnosed with PAS on histopathology report were included in the analysis. Women whose histopathology was not sent and PAS was not confirmed were excluded. All cases were scrutinized for diagnosis; women who were diagnosed before they underwent anesthesia for cesarean delivery were included as antenatally diagnosed PAS (group A). Cases where PAS was suspected during operation and confirmed on histopathology were included as PAS diagnosed peroperatively (group B).

For cases diagnosed antenatally, the surgery was performed by a senior obstetrician and a consultant anesthetist while a consultant pediatrician was present. Four units of blood were arranged and continuous communication was maintained with the onsite blood bank. The patient's hemoglobin was regularly assessed antenatally and hemoglobin of above 11 g/dL was maintained. All patients received antenatal steroids to promote lung maturation in the fetus after 26 weeks. For this purpose, injection betamethasone (Betnesol) was used at a dose of 12 mgs. Each patient was given two doses, intramuscularly, 24 hours apart. The incision was made avoiding the placental location, which was assessed preoperatively by an ultrasound assessment. The baby was delivered by going around the placenta and was immediately handed over to the consultant pediatrician for ongoing neonatal care.

A proforma was used to collect data that included: Age of woman, her parity, duration of surgery in minutes and number of units of blood transfused. The primary outcome measure was uterine conservation. Secondary outcome measures included maternal death, admission of mother to intensive care unit (ICU), perinatal death or neonatal ICU admission. Duration of surgery in cases where the uterus was conserved was also assessed.

Data was coded and confidentiality was ensured. The hospital head gave permission to the investigators for reporting the study. In lieu of formal ethical approval, the principles of the Declaration of Helsinki were followed.

Statistical analysis

All data were analyzed using SPSS, version 15 (IBM Inc., Chicago, IL, USA). Shapiro Wilk's test was used to assess the normality of data. Women's age, parity, duration of surgery and number of units transfused were not normally distributed and were presented as median and range. Mann-Whitney U test was used to compare non-parametric data sets. Frequencies and percentages were calculated for qualitative variables including uterine conservation, diagnosis antepartum/intrapartum, ICU admission and neonatal death. Chi-square test and Fisher's exact test were used to compare these variables at $p<0.05$ level of significance.

Time to uterine conservation was analyzed for both groups using the Kaplan-Meier survival plot and curves were compared by means of Mantel Haenszel log rank test. A significance level of 5% was chosen.

Results

During the study period, 8979 deliveries took place at the facility. PAS was confirmed in 96 of those women, giving an incidence of 1.06% (1 in 100). Of these, 34 (35.4%) cases were antenatally diagnosed (group A), while 62 (64.6%) were diagnosed intraoperatively (group B).

The median (range) age of the study population, time of surgery and number of units of blood transfused was 28 (21-35) years, 55 minutes (50-140) minutes and 6 (2-12) units, respectively. Only 34 (35.4%) cases were diagnosed antepartum. When risk factors were assessed, the median (range) number of previous section in the study population was 1 (0-4) and only 16 (16.7%) had a history of dilation and curettage while 40 (41.7%) gave history of bleeding. Uterus was conserved in 50 (52.1%) of all women. ICU admission was required for 46 (47.9%) of women and 23 (23.59%) women died. Regarding perinatal outcomes, perinatal mortality rate was 44.8%. Of these, 31 (72.09%) were fresh stillbirths and 12 (27.91%) were neonatal deaths. Only 18 (33.96%) neonates had Apgar score below 7 after 5 minutes and ICU admission was required for 30 (56.6%) of the neonates. Table 1 summarizes the characteristics of the whole study population.

When stratified according to groups, there was no significant difference between the groups with regards to age ($p=0.865$), parity ($p=0.289$) and duration of surgery ($p=0.588$). There was no difference between the groups in terms of risk factors including the median number of cesarean sections ($p=0.304$), history of bleeding ($p=0.703$) and history of prior dilatation and curretage ($p=0.427$). However, antenatally diagnosed PAS required a lower median number of units of blood transfused compared to those with intrapartum diagnosed PAS (4 vs 6, $p<0.001$).

Uterus was conserved in 23 (67.6%) women in group A and 27 (43.5%) women in group B ($p=0.024$). Nine (26.5%) women

required admission to ICU in group A which was significantly fewer (p=0.002) than the 37 (59.7%) of women from group B who required ICU care. Maternal death (p=0.038) and perinatal death (p=0.008) were also significantly more frequent in cases diagnosed perioperatively (p=0.008). More neonates delivered to women in group B (85.7% vs 24%, p=0.033) were admitted to ICU for cases diagnosed intraoperatively (see Table 2).

Survival analysis showed a statistically significant difference in the duration of surgery with antenatal diagnosis between the two groups (log rank, p=0.04; see Figure 1).

Table 1. Demographic and clinical characteristics of the whole study population

Age in years	-	28 (21-35)
Time in minutes	-	55 (40-140)
No of units of blood	-	6 (2-12)
Parity	-	2 (1-5)
Number of previous cesarean sections	-	1 (0-4)
History of dilation and curretage	Yes	16 (16.7)
	No	80 (83.3)
History of bleeding	Yes	40 (41.7)
	No	56 (58.3)
Diagnosis of PAS	Antenatal	34 (35.4)
	Intraoperative	62 (64.6)
Uterine conservation	Yes	50 (52.1)
	No	46 (47.9)
ICU stay	Yes	46 (47.9)
	No	50 (52.1)
Maternal death	Yes	23 (23.95)
	No	73 (76.0)
Perinatal death	Yes	43 (44.8)
	No	53 (55.2)
	Fresh stillbirths/ perinatal deaths	31 (72.1)
	Neonatal deaths/ perinatal deaths	12 (27.9)
Apgar score below 7 at 5 minutes (n=53)	Yes	18 (34.0)
	No	35 (66.0)
ICU admission of baby (n=53)	Yes	30 (56.6)
	No	23 (43.3)

Values are median (range) or n (%) unless otherwise specified
ICU: Intensive care unit

Discussion

Main findings

The present study shows that feto-maternal outcomes are better in cases of PAS where diagnosis is made antenatally. Women need fewer units of blood when diagnosed antenatally and are more likely to retain their uterus. Duration of surgery is also shorter in antenatally diagnosed cases of PAS and there is a significantly lower likelihood of admission to ICU following surgery while perinatal death is also less likely.

Study Limitations

As placenta accreta is seen frequently due to higher cesarean rates, the strength of this study is its sample size. Another strength of the study is the clear clinical definition of PAS as all cases that were included were histologically confirmed.

The biggest limitation of the study was the retrospective design.

Table 2. Demographic and clinical characteristics by group

	Groups		p
	A (antenatal diagnosis) (n=34)	B (intraoperative diagnosis) (n=62)	
Age in years	29 (21-35)	27 (21-35)	0.865
Time in minutes	55 (45-140)	55 (40-140)	0.59
No of units of blood	4 (2-12)	6 (2-12)	<0.001*
Parity	2 (1-4)	2 (1-5)	0.29
Gestational age at diagnosis	24 (20-26)	-	-
Previous cesareans	1 (0-2)	1 (0-4)	0.30
Previous history of dilation and curretage	5 (14.7)	11 (17.7)	0.43
History of bleeding	16 (47.1)	24 (38.7)	0.70
Uterine conservation	23 (67.6)	27 (43.5)	0.02*
ICU stay	9 (26.5)	37 (59.7)	0.002*
Maternal death	4 (11.8)	19 (30.6)	0.04*
Perinatal death	9 (26.5)	34 (54.8)	0.008*
Fresh stillbirths	8 (88.89)	22 (64.7)	0.04*
Neonatal death	1 (11.12)	12 (35.29)	0.006*
Apgar score below 7 at five minutes	5 (20.0)	13 (46.4)	0.45
ICU admission of babies (after excluding perinatal deaths)	6/25 (24.0)	24/28 (85.7)	0.03*

Data are shown as median (range) or count (percent).
*The chi-square or Mann-Whitney U test is significant at the 0.05 level
ICU: Intensive care unit

As cases were assessed retrospectively, patient reported outcomes could not be assessed.

Interpretation

Rates of placenta accreta have increased markedly in recent times. Placenta accreta was previously only seen occasionally. In developed countries the rates of PAS are lower than those reported from developing countries. The estimated incidence from the UK was 1.7 per 10000 maternities (8) while that from Australia was 44.2/100000 women giving birth (9). The prevalence varied from 0.01% to 1.1% according to a large database review (10). These rates are alarming as proportion of cesarean sections of all deliveries is also increasing and this could potentially mean more cases would be encountered in the near future. The rate in our study was 0.010% which is very high in comparison to the data previously reported. Another reason for this rate could be the fact that the facility is a tertiary care center and deals with all high-risk cases that are referred from all parts of the city.

Increased maternal age, previous cesarean section and increased parity are among the commonly recognized risk factors for PAS (11). The median age of the study population was 28 years and they had a median parity of 2 which shows that the women were below the advanced maternal age range and might have not completed their families. The median maternal age reported for placenta accreta was approximately 34 years and the median parity was 2.5 (12). This suggests that placenta accreta may soon affect younger women, as PAS in the most commonly reported indication of peripartum hysterectomy.

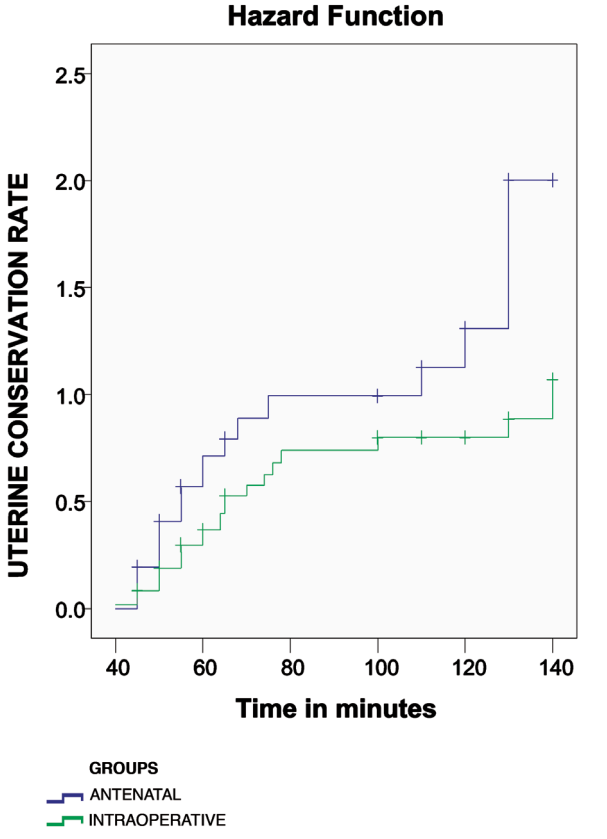

Figure 1. Kaplan meier survival curve of women whose uteri were conserved (log rank test, p=0.04)

Antenatal diagnosis of PAS can substantially reduce morbidity. Only 35.4% of our series were diagnosed antepartum. This is lower than the 57% of cases diagnosed antenatally in a study reported from Australia (9). In that study, 36% of the cases were diagnosed solely on ultrasound. Our hospital records showed that all cases of PAS that were antenatally diagnosed, were suspected on grey scale ultrasound and confirmed on color Doppler. 3-D power Doppler has been shown to have the best prediction of antenatal PAS (13). Since 3-D power Doppler was not available at our center, our cases were diagnosed by color Doppler.

Availability of senior colleagues or experts has been shown to improve outcome in difficult and complex cases (14). Multidisciplinary team involvement and specialized centers for managing PAS have been reporting better outcomes. However, these resources can only be mobilized in antenatally diagnosed patients. In cases where accreta is diagnosed on the operating table, such expertise is difficult to arrange at very short notice (15). Our study highlights the importance of preparedness for such emergencies as antenatally diagnosed cases had significantly better outcomes.

The duration of surgery is an important morbidity marker. Women with prolonged surgeries are more likely to require ICU transfer, have a longer duration of stay in hospital, and suffer wound infections and other post-operative complications (16). Duration of surgery was not significantly different between the groups in our study but women who had PAS diagnosed antenatally had a lower transfused blood volume requirement. In addition, in cases where the uterus was conserved, time to uterine conservation was also less. This finding may be explained by the fact that these cases were optimized antenatally, hemoglobin was kept in check and the operation was performed by more experienced surgeons under more favorable conditions. The planning and anticipation of complications in cases of PAS is associated with improved outcomes overall (17).

Fetomaternal outcomes were also influenced by the timing of diagnosis in the study. Only 26.5% of group A compared with 59.7% of group B were admitted to ICU which was a significant difference (p=0.002). Perinatal death was also significantly higher in cases diagnosed intrapartum (p=0.008). These findings are in agreement with the studies reported previously (18,19).

Our study shows the beneficial effect of diagnosing PAS antenatally. This diagnosis becomes even more important in regions where antenatal care remains suboptimal because these women have far worse fetomaternal outcomes than women who receive better care. The importance of a scan to localize the placenta antenatally in all women and confirm invasion, especially in cases with a previous scar, cannot be emphasized enough.

Simply diagnosing PAS is not sufficient, in our opinion. We believe there is a need for dedicated centers for PAS. Women in our study, despite delivering at a tertiary care center, did not achieve as good an outcome as reported by studies from the developed world.

If PAS is diagnosed antenatally, women are counseled and optimized prior to delivery and delivery subsequently takes place in a dedicated center with sufficient expertise, much better outcomes can be expected. Development of dedicated PAS centers in developing countries can be expected to make a significant difference in reducing morbidity and both maternal and fetal mortality. After establishment of such centers, a larger study with prospective design would be capable of assessing the outcomes with better and more prevalent antenatal diagnosis.

Conclusion

PAS diagnosed antenatally has better fetomaternal outcomes than intraoperative detection of PAS. Our results show that diagnosing PAS antenatally will significantly improve management and result in better outcome. We propose adoption of antenatal localization of placenta in all cases, especially where risk factors for PAS are present.

Ethics Committee Approval: *Retrospective study.*

Informed Consent: *Consent for the use of hospital records was obtained from the department head.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: Ra.I., Z.M., Sam.H., So.H., R.I.; Concept – Ra.I., Z.M., Sam.H., So.H., R.I.; Design – Ra.I., Z.M., Sa.H., So.H., R.I.; Data Collection or Processing – Ra.I., Z.M., Sam.H., So.H., R.I., S.H.; Analysis or Interpretation – Ra.I., Z.M., Sam.H., So.H., R.I., S.H.; Literature Search – Ra.I., Z.M., Sam.H., So.H., R.I., S.H.; Writing – Ra.I., Z.M., Sam.H., So.H., R.I., S.H..H.*

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Association of sexual function and psychological symptoms including depression, anxiety and stress in women with recurrent vulvovaginal candidiasis

Zeinab Moshfeghy[1], Somayeh Tahari[2], Roksana Janghorban[3], Fatemeh Sadat Najib[4], Arash Mani[5], Mehrab Sayadi[6]

[1]Student Research Committee, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Student Research Committee, Department of Midwifery, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Department of Midwifery, School of Nursing and Midwifery, Community Based Psychiatric Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[4]Department of Obstetrics and Gynecology, School of Medicine, Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[5]Department of Psychiatry, School of Medicine, Community Based Psychiatric Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[6]Student Research Committee, Department of Biostatistics, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Objective: Recurrent vulvovaginal candidiasis (RVVC) is a common vaginal infection which could affect the quality of life, romantic relationships, and sexual performance. There is some evidence that psychological problems result in an increased incidence of RVVC by changing the immune systems of individuals. The aim of this study was to determine the association of sexual function and psychological factors including depression, anxiety, and stress in women with RVVC.

Material and Methods: Study design was case controlled. Equal numbers of women with RVVC and uninfected women referred to gynecology clinics were selected, using convenience purposive sampling. Two samples of vaginal discharge were prepared from each person. One sample was examined microscopically and the second was cultured on Sabouraud Agar. Data collection tools used for this study included demographic questionnaire, Female Sexual Function Index, Depression Anxiety Stress Scales-21. Data were analyzed using SPSS software (version 19).

Results: Less sexual satisfaction [odds ratio (OR): 0.608, 95% confidence interval (CI): 0.421-0.878] and less orgasm (OR: 0.741, 95% CI: 0.530-0.998) was associated with RVVC. In patients with RVVC, the levels of depression, anxiety and stress were significantly higher compared to those of healthy individuals.

Conclusion: Depression, anxiety and stress in the past four weeks are related to an increased risk of RVVC. There is an association between depression, anxiety and stress, sexual satisfaction, and orgasm with RVVC. It may be that psychological interventions and sexual counseling can be effective in improving RVVC. (J Turk Ger Gynecol Assoc 2020; 21: 90-6)

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Address for Correspondence: *Roksana Janghorban*
e.mail: janghorban@sums.ac.ir ORCID: orcid.org/0000-0002-7831-8401

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Introduction

Genital tract infections are common problems in women (1,2). Vaginitis is an inflammation and infection of the vagina and its symptoms include itching or irritation, unusual and malodorous discharge, leukorrhea and dyspareunia (3). According to the World Health Organization candida, trichomonas, and bacterial infection are considered to be the main factors causing vaginitis and these three pathogens constitute approximately 90% of vaginal infections (1).

Candida albicans is responsible for 85-95% of vaginal yeast infections (4). This disease is mostly seen in women of reproductive age (5). Studies have shown that the occurrence of this problem is rare before the age of menarche and has been observed less commonly at postmenopausal ages (6,7). This indicates the existence of a hormonal dependency for the infection (8).

It is estimated that 75% of women will have a vaginal yeast infection at least once in their lifetime and around 45% of women will experience this type of infection two or more times (4). Causes of the vaginal yeast infections are various species of Candida, with Candida albicans being the most common cause accounting for 80-90% of the disease. Nevertheless, in patients with recurrent vaginal candidiasis, 15-47% of cases are caused by non-albicans species (9).

In studies carried out in different countries, the rate of infection with candidiasis is different. The rate in Nigeria was reported to be 6.5% and in Turkey, with culture method and clinical diagnosis, it has been reported as 17.4 and 14.1%, respectively (10,11). In a further study from Nigeria, the prevalence of this infection was reported as 18.9% (12). In Iran, in the cities of Tabriz, Sanandaj, Hamedan, Yazd, and Shiraz, the prevalence was reported to be between 25-45% (9). The occurrence of four episodes or more of candidiasis per year is called recurrent vulvovaginal candidiasis (RVVC) (4). The prevalence of RVVC, reported in a study from five European countries and the United States, was between 29% and 49% (13). In another study in Sweden in 2009, the incidence of RVVC, using fungal culture for diagnosis, was estimated as 29.8% (14). In Iran, in Sari, the incidence was reported as 24.2% (15).

Several factors play a role in the incidence of vaginal candidiasis, including antibiotics, pregnancy, diabetes mellitus, taking oral contraceptive pills, human immunodeficiency virus infection, wearing tight and nylon underwear with inadequate ventilation, vaginal douching, immunosuppression drugs, use of an intrauterine device, many sexual activities, local vaginal immune deficiency, using tampons instead of sanitary napkins, and oral sex. However, each of these factors could have an effect on incidence of recurrent chronic candida (4-6,16).

There is also some largely indirect evidence that psychological problems contribute to the incidence of RVVC (5). Depression, helplessness, hopelessness, and stressful life events may lead to the disease by inhibiting the immune systems of individuals. Studies have shown that there is a relationship between the central nervous system and the immune system, and consequently, the incidence of various stresses affects immune function and associated diseases (17-19). Chronic stress may reduce cellular immunity and affects the hypothalamic-pituitary-adrenal (HPA) axis reactions. If the HPA axis is active chronically, normal reaction to external acute stress may fail, and this will increase the susceptibility to inflammation and, crucially, infections (16,20).

In addition studies have shown that there was a significant relationship between sexual dysfunction in individuals with a diagnosis of depression, anxiety, and stress (21,22). Psychosocial factors, such as exposure to factors causing stress in daily life, can lead to disruption of the sexual response cycle (23). The results of a study from Brazil revealed that women with RVVC had lower scores in the domains of orgasm and sexual satisfaction in comparison to women with localized vulvar vestibulitis syndrome (24).

Therefore, the present study was conducted to investigate the possible influence of psychological factors on the incidence of RVVC, the role of the psychological condition on women's sexual function and to address the lack of a study which could demonstrate an association between psychological factors (anxiety, stress, and depression) and sexual function in women with RVVC (5,16,25).

Material and Methods

In this case control study, participants consisted of married Iranian women attending gynecology clinics and who had been sexually active in the past four weeks. The women were of reproductive age, and were able to complete the questionnaire or interview. Exclusion criteria included pregnant and lactating women, having a previous or current history of cancer, patients undergoing chemotherapy, having immune deficiency diseases, and being under treatment for sexual and/or psychological problems. In addition, women who were in their menstrual period, women who had intercourse in the past 24 hours, and those who used vaginal creams during the week prior to the study and used vaginal douching within 48 hours of the study were excluded, as were those not willing to participate in the study.

Fifty women with RVVC and 50 healthy women, referred to gynecology clinics were selected using convenience purposive sampling. From October 2015 to June 2016, the female researcher attended clinics every day. After explaining the objectives of the project and obtaining written informed consent from individuals who were willing to participate in

the study, samples were obtained. After preliminary review, if a selected individual was not included in the study because of exclusion criteria, a further suitable recruit was obtained until the desired number of cases and of controls was achieved.

The participants in the case group were married women with a history of at least four episodes of vulvo-vaginal candidiasis per year. All cases had a documented diagnosis of symptomatic episodes of infection in their clinic records. The diagnosis was suggested clinically by gynecologists working at the recruitment clinics, according to the presence of external dysuria together with vulvar pruritus, pain, swelling, and/or redness and signs include vulvar edema, fissures, excoriations, and thick "curdy" vaginal discharge and microscope examination of a smear from the vagina using a potassium hydroxide mounting. Additionally, an experienced laboratory microbiologist gave a definitive diagnosis of recent candida infection using fungal cultivation and direct observation under a microscope slide. The control group consisted of healthy individuals who were referred to clinics for routine screening. After direct observation under a microscope slide preparation and taking samples of vaginal discharge culture, all of the controls were shown not to have RVVC.

The data were collected via three questionnaires. The first questionnaire included demographic characteristics, pregnancy and childbirth information, contraceptive methods, history of fungal infections, bacterial vaginosis and trichomonas, history of drug use, menstrual history, and each participants' health information. The second questionnaire was the Female Sexual Function Index (FSFI) which was designed by Rosen et al. (26) and validated for use in an Iranian population by Mohammadi et al. (27). The FSFI is a 19-item questionnaire designed to determine the sexual function status in women in the last four weeks. It assesses six domains: Sexual desire (two questions); sexual excitation (four questions); lubrication (four questions); orgasm (three questions); satisfaction (three questions); and pain (three questions). The FSFI has 6 Likert options relating to sexual activity (never, rarely, sometimes, often, always), which are scored for each domain. Therefore, at least the total scale score is 2 and maximum has been considered as 36. Generally, higher score indicates better sexual function. According to Mohammadi et al. (27), reliability of scale and subscales for all the individuals was calculated as 0.85 for total score, 0.76 for sexual desire, 0.88 for sexual excitation, 0.88 for lubrication, 0.9 for orgasm, 0.71 for satisfaction and 0.87 for pain (27). The third questionnaire was the Depression Anxiety Stress Scales (DASS-21). The questionnaire, which is the short form, contains 21 questions and measures three domains of depression, anxiety, and stress of the individual in the four weeks prior to completing the questionnire. DASS-21 is scored on Likert scale. Each subscale of this questionnaire includes seven questions and the final score of each is obtained from the total score for each question. Each question is scored between zero (does not apply at all in my case) to 3 (completely true in my case). Given that this questionnaire is the shortened form of the original scale (42 questions), the final score for each of the subscales should be doubled (28). Lovibond and Lovibond reported a correlation of 0.54 between the two scales of depression and anxiety (29). The reliability and validity of the questionnaire was evaluated by Samani and Jokar (30) in Iran. The retest reliability for depression, anxiety, and stress scales was 0.80, 0.76 and 0.77, respectively, and Cronbach's alpha for depression, anxiety, and stress was also reported as 0.81, 0.74 and 0.78, respectively (30).

After determining that the patients met the inclusion criteria, the demographic and the DASS-21 Questionnaire were completed by the participants during the first visit and the FSFI Questionnaire was completed during the second visit, when they were referred to clinics to know the culture results and drug prescription.

The participants included in the study in both groups were examined in the lithotomy position. By inserting a speculum, the researcher observed and assessed vaginal discharge in terms of color, odor, volume and other diagnostic features for Candida. Samples were collected from vaginal discharge and posterior fornix using a sterile cotton swab. Two swab samples were taken from each patient, one of which was mounted on a slide for microscopy. The second swab was sent for culture using Sabouraud's dextrose agar under sterile conditions. Slides were marked with identifying information and, at the end of each working day, the slides and culture swabs were sent to the mycology laboratory of Faqihi Hospital for viewing under a microscope and culturing. Examination of samples was carried out by an expert mycologist. The expert added a drop of potassium hydroxide to discharges of the first slide for viewing under a microscope. In the second sample for culture, a swab was placed on Sabouraud Dextrose Agar. The detection of yeasts in culture samples was initially made by observing yeast groups, with false hyphae, under a microscope. This was then confirmed by standard culturing in the laboratory. Finally, women with positive microscopic results and positive swab cultures for fungi were assigned to the case group, while women with negative microscopic results and negative swab cultures for fungi were assigned to the control group.

The research was approved by the Ethics Committee of the Deputy of Research and Technology Shiraz University of Medical Sciences (approval number: 7592). Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Data were analyzed using SPSS software, version 19 (IBM Inc., Armonk, NY, USA). The following statistical tests were used, as appropriate: Independent t-test, chi-square test, logistic regression, and Pearson correlation. The significance level for all tests was 5%.

Results

There was no significant relationship between demographic characteristics, method of contraception, or having specific dietary habits with recurrent Candida infection in both case and control groups. The history of infection in women with recurrent Candida infections (n=25/50) was significantly higher (χ^2=7.25, p=0.001) than healthy women (n=12/50). There were no significant differences regarding the use of vaginal douching between the two groups. However, the case group individuals (n=30/50) were significantly more inclined (χ^2=30.1, p<0.001) to wear tight clothes compared with the control group (n=4/50).

As shown in Table 1, the mean score of women's sexual function in domains of orgasm (p=0.042), and satisfaction (p=0.005) was higher in the control group and this difference was statistically significant. However, in other domains, there were no statistically significant differences between the two groups. The overall sexual function values in the control group on average were a score of two greater than in the case group, and this was significant (p=0.043). In all domains, the mean of sexual function score in the case group was lower than in the control group.

When aspects of sexual function were investigated it was found that less sexual satisfaction [odds ratio (OR): 0.608, 95% confidence interval (CI): 0.421-0.878] and less orgasm (OR: 0.741, 95% CI: 0.530-0.998) were reported by women with a history of RVVC in the preceding four weeks. There were no significant differences between the two groups in the domains of desire, mental stimulation, lubrication, and pain (Table 2).

Frequency distribution of depression score (p<0.001), anxiety (p<0.001), and stress (p=0.037) in the two groups were compared using Fisher's exact test or chi-square test. The results of this test showed the significance of the severity of these disorders in women with RVVC, such that the frequency distribution of these disorders in the case group compared to the control group showed a more severe situation.

Comparing mean scores for depression, anxiety, and stress in both groups showed that levels of these three measures of psychological function were significantly higher in the case group than the control group and the difference between the two groups was statistically significant (Table 3).

Self reported measures of depression, anxiety and stress in the past four weeks were associated with a history of RVVC

Table 1. Comparison of mean score of sexual function in both case and control groups

Sexual Function	Groups		Statistical index	p*
	Case (n=50) (mean ± SD)	Control (n=50) (mean ± SD)		
Desire	3.2±0.97	3.46±0.75	1.45	0.149
Mental stimulation	3.64±1.11	3.82±1.02	0.821	0.414
Lubrication	3.83±1.10	4.0±0.91	0.806	0.422
Orgasm	4.17±1.36	4.46±1.01	2.06	0.042
Satisfaction	3.86±1.28	4.83±0.86	2.86	0.005
Pain	3.78±1.38	4.18±1.17	1.31	0.193
Overall domains	22.73±5.73	24.77±4.03	2.04	0.043

*p<0.05 was considered statistically significant; t-test was used for all variables
SD: Standard deviation

Table 2. Association of sexual function with recurrent vulvovaginal candidiasis in both case and control groups

Sexual function	Beta	OR*	95% CI		p*
Desire	-0.306	0.736	1.143	0.474	0.173
Mental stimulation	-0.122	0.886	1.246	0.629	0.486
Lubrication	-0.126	0.882	1.248	0.623	0.478
Orgasm	-0.300	0.741	0.998	0.530	0.044
Satisfaction	-0.497	0.608	0.878	0.421	0.008
Pain	-0.180	0.835	1.125	0.620	0.237
General areas	-0.066	0.936	0.993	0.870	0.042

*p<0.05 was considered statistically significant; logistic regression analysis was used for all variables
OR: Odds ratio, CI: Confidence interval

Table 3. Comparison of mean scores of depression, anxiety and stress between the case and control groups

Variable	Groups		T-test index	p*
	Case (mean ± SD)	Control (mean ± SD)		
Depression	20.96±11.07	12.44±10.56	3.13	p<0.001
Anxiety	20.72±11.44	11.72±8.94	3.38	p<0.001
Stress	23.32 ±10.12	16.68 ±10.47	3.22	0.002

*p<0.05 was considered statistically significant; t-test was used for all variables
SD: Standard deviation

(Table 4). In addition, a significant and inverse correlation was found between the domains of overall sexual function and depression, anxiety, and stress (Table 5).

Discussion

The results showed that there were significant differences between the case and control groups regarding the overall sexual function score. Moreover, in the case group, sexual function score in all domains (desire, mental stimulation, lubrication, orgasm, satisfaction, and pain) was lower than the control group. However, in the domains of orgasm and satisfaction, this difference was statistically significant. This study showed that less sexual satisfaction was associated with a history of RVVC. However, the relationship of the other domains of sexual function with a history of RVVC was not significant.

In a previous study, the sexual function of 58 Brazilian women (11 patients with RVVC, 18 patients with localized vulvar vestibulitis and 29 healthy individuals) were investigated and it was found that both the individuals with RVVC and localized vestibulitis syndrome had significantly lower sexual function scores than the women in the control group. In addition, women with RVVC had significantly lower scores for satisfaction and orgasm domains (24). However, there was no significant difference found for other domains, which is consistent with the findings of the current research. Gungor et al. (31) in a study from Turkey, reported contrasting results. The study was conducted in 114 women in three groups. The first group included 58 women with no vaginal discharge, the second group included 29 women with abnormal vaginal discharge with itching and in the third group, 27 women had abnormal discharge without itching. Their results showed that women with abnormal vaginal discharge with or without itching had significantly higher overall score of sexual function compared to that of the control group. These differences may be attributed to subject selection bias, subjective reporting, possible cultural differences and differences in the diagnostic criteria for discharge culturing.

The results showed that there was a significant relationship between depression, anxiety, and stress and a history of RVVC. These findings suggest that levels of depression, anxiety, and stress in patients with RVVC are higher than healthy individuals. The result is consistent with another study which showed both chronic stress and reduced antioxidant capacity may be predisposing factors for RVVC. This implies that a dysregulation of immune function, which can be associated with poorer mental health parameters, may increase the risk of RVVC (16,20,32).

In a study the Short-Form Health Survey (SF-36) was used to measure health-related quality of life in 101 healthy women and 102 women with RVVC. The results showed that women with RVVC had lower physical and mental composite scores compared with controls (5). Although the scales used to measure stress and mental health in this and the current study were not similar, the results of both highlight that women with this infection report more stress. A further study showed that women with chronic vaginal symptoms such as RVVC, vestibulitis syndrome and inflammatory vulvovaginitis had high rates of mental disorders (33). Meyer et al. (34) suggested that psychosocial risk factors, particularly stress, were the main causes of RVVC.

The findings of the present study showed a significant and inverse correlation between the domains of sexual function and depression, anxiety, and stress. Mazinani et al. (35) showed that there was a significant relationship between psychiatric disorders, a history of psychiatric medicine and FSF. Although their study was not conducted on women suffering from RVVC, its findings regarding the significant relationship between mental disorders and sexual dysfunction are consistent with the present study. A study from Egypt showed that higher anxiety correlated with female sexual

Table 4. The association of depression, anxiety, and stress with recurrent vulvovaginal candidiasis in case and control groups

Variable	Beta	OR	95% CI		p*
Depression	0.070	1.073	1.116	1.032	p<0.001
Anxiety	0.082	1.086	1.132	1.041	p<0.001
Stress	0.62	1.064	1.109	1.022	0.003

*p<0.05 was considered statistically significant; Logistic regression analysis was used for all variables
OR: Odds ratio, CI: Confidence interval

Table 5. The correlation between the scores of different domains of sexual function and scores of depression, anxiety and stress in both case and control groups

Scores of sexual function	Depression		Anxiety		Stress	
	p*	r	p*	r	p*	r
Desire	p<0.001	-0.39	0.004	-0.28	0.006	-0.27
Mental stimulation	p<0.001	-0.42	0.002	-0.30	p<0.001	-0.33
Lubrication	p<0.001	-0.47	p<0.001	-0.33	0.004	-0.28
Orgasm	p<0.001	-0.36	p<0.001	-0.45	p<0.001	-0.56
Satisfaction	p<0.001	-0.32	p<0.001	-0.41	p<0.001	-0.52
Pain	p<0.001	-0.32	p<0.001	-0.34	p<0.001	-0.36
Overall domains	p<0.001	-0.39	p<0.001	-0.44	p<0.001	-0.56

*p<0.05 was considered statistically significant; Pearson correlation coefficient was used for all variables

dysfunction (22), which again is consistent with the present study. Another study showed that trait anxiety and anxiety sensitivity were related to greater self-reported female sexual arousal outside the laboratory (36). The etiology of anxiety, not the experience of anxiety *per se*, seems to interfere adversely with sexual function.

Studies have shown a high prevalence of female sexual dysfunction in depressed women, regardless of type and severity of depression (25,37). Sexual dysfunction occurs at any stage of the sexual response cycle and reduces the quality of life of many women. Multiple psychological distresses could be sufficient evidence to suspect associated sexual problems (38).

It may be that a reduction in sexual satisfaction and orgasm can affect the mental state of women leading to an increase in stress, anxiety and depression. As these problems increase, they can affect the immune system and the body becomes more susceptible to infections, and ultimately, they lead to an increase in RVVC. As demonstrated by the results of this study, sexual function status in these women had an inverse association with mental disorders (anxiety, stress, and depression). Thus, if the status of sexual function has a lower score, these parameters of mental health are likely to be worse.

The present study has attempted to bridge the research gap in the field of mental health and sexual function in women with RVVC. This study should be considered as a preliminary study for the planning of larger, prospective interventional studies in patients with RVVC. This study has some limitations. The study was conducted only in Fars province. Additionally, due to the case-control design of study, we could not assess causal connection between mental disorders and RVVC. Cohort studies or randomized control trials with psychological intervention would be necessary to establish if poor mental health leads to an increased likelihood of RVVC and whether psychological intervention can aid in the recovery from this chronic infection.

Conclusion

The results of the present study showed that the reduction in sexual satisfaction, orgasm and mental disturbances (anxiety, depression and stress) in the past month was associated with a history of RVVC. It has been suggested that poor mental health may be one of the causes of RVVC. In addition, this study showed an inverse relationship between sexual dysfunction and markers of mental health (stress, anxiety and depression) and has suggested that a reduction in sexual satisfaction and orgasm could increase anxiety, depression and stress, which may increase the likelihood of RVVC. Therefore, there may be a role for sexual counseling and psychotherapy techniques, such as relaxation, in order to enhance their mental performance, reduce stress and aid in the treatment of RVVC.

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Pregnancy of patients with idiopathic thrombocytopenic purpura: maternal and neonatal outcomes

Hakan Kalaycı, Gülşen Doğan Durdağ, Şafak Yılmaz Baran, Seda Yüksel Şimşek, Songül Alemdaroğlu, Serdinç Özdoğan, Esra Bulgan Kılıçdağ

Department of Obstetrics and Gynecology, Başkent University Faculty of Medicine, Adana Application and Research Hospital, Adana, Turkey

Abstract

Objective: Thrombocytopenia occurs in 7% of pregnant women. Along with other causes, idiopathic thrombocytopenic purpura (ITP), which is an autoimmune disease with autoantibodies causing platelet destruction, must be considered in the differential diagnosis. Antiplatelet antibodies can cross the placenta and cause thrombocytopenia in the newborn. The aim of our study was to assess the management of ITP in pregnancy, and to investigate neonatal outcomes.

Material and Methods: This retrospective study was conducted in a tertiary center including 89 pregnant patients with ITP followed between October 2011 and January 2018. Patients were evaluated in two groups according to diagnoses of ITP and chronic ITP. Age, obstetric history, ITP diagnosis, and follow-up period, presence of splenectomy, platelet count during pregnancy and after birth, treatment during pregnancy, route of delivery, weight and platelet count of newborn, sign of hemorrhage, and fetal congenital anomaly were assessed.

Results: Considering the ITP and chronic ITP groups, no significant difference was seen with respect to parity, timing of delivery, preoperative and postoperative platelet counts, and hemoglobin values. Route of delivery, birth weight, APGAR scores, newborn platelet count, and congenital anomaly rates were also similar. The timing of treatment was different because patients whose diagnoses were established during pregnancy were mostly treated for preparation of delivery. Treatment modalities were similar.

Conclusion: Probability of severe thrombocytopenia at delivery is higher in patients with ITP who are diagnosed during pregnancy when compared with patients who received prepregnancy diagnoses. ITP is an important disease for both the mother and newborn. Patients should be followed closely in cooperation with the hematology department. (J Turk Ger Gynecol Assoc 2020; 21: 97-101)

Keywords: Idiopathic thrombocytopenic purpura, neonatal thrombocytopenia, pregnancy, thrombocytopenia

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Introduction

Thrombocytopenia, which is defined as a platelet count being less than $150x10^3/\mu L$, occurs in approximately 7% of pregnant women (1). Various etiologies can cause thrombocytopenia during pregnancy. The most commonly seen, gestational thrombocytopenia and idiopathic thrombocytopenic purpura (ITP), are both diagnoses of exclusion of other pathologies necessitating different treatment strategies. These pathologies include preeclampsia; HELLP syndrome characterized by hemolysis, elevated liver enzymes and low platelet count; sepsis; disseminated intravascular coagulation; autoimmune diseases such as systemic lupus erythematosus, thrombotic thrombocytopenic purpura; microangiopathies such as hemolytic uremic syndrome; hematologic malignancies; and drug-induced thrombocytopenia (2-4).

Gestational thrombocytopenia, which usually occurs in the mid-second to third trimester and which is a mild form with platelet counts more than $70x10^3/\mu L$, constitutes 70-80% of cases (1,5).

Address for Correspondence: *Gülşen Doğan Durdağ*
e.mail: gulsendogan@hotmail.com ORCID: orcid.org/0000-0002-5064-5267

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ITP, which is an autoimmune disease with autoantibodies against the platelet membrane causing platelet destruction in the reticuloendothelial system, must be considered in the differential diagnosis. The incidence of ITP at pregnancy is 1-2/1000 and it forms 3-5% of thrombocytopenias encountered during pregnancy, though it is the most common cause of thrombocytopenias in early pregnancy and can cause severe thrombocytopenia (2,5,6). Patients may be asymptomatic or may have antenatal bleeding necessitating treatment. Thrombocytopenia may be first diagnosed during pregnancy or the diagnosis of ITP may have been established before pregnancy. ITP lasting more than 6 months is called chronic ITP (1). Splenectomy may be performed due to resistance to treatment. Time of diagnosis, severity, and accompanying factors must be considered for the differential diagnosis of thrombocytopenia. The onset time of ITP can affect pregnancy and delivery complications, and clinical conditions of the newborn such as thrombocytopenia, petechiae, and intracranial hemorrhage (1).

The aim of our study was to assess the follow-up and treatment of ITP and chronic ITP during pregnancy, along with neonatal outcomes. Proper diagnoses and management in the antenatal period will reduce complications.

Material and Methods

This retrospective study was conducted at a university hospital, including pregnant patients with ITP. A total of 89 patients followed between October 2011 and January 2018 in our center with ICD diagnose codes of pregnancy Z33, Z34.8, Z35.8, Z35.9 and concurrent D69.3 ITP or D69.6 thrombocytopenia codes were included. The records of patients were investigated, and phone calls with patients were used to collect missing data. Other causes of thrombocytopenia were excluded.

Age, obstetric and medical history, time of ITP diagnosis and duration of follow-up period, presence of splenectomy, platelet counts in early and late pregnancy and after birth, complete blood count and biochemistry parameters, treatment during pregnancy, route of delivery and anesthesia, need for thrombocyte or erythrocyte replacement, gestational week at time of birth, weight, APGAR scores and platelet count of newborn, signs of fetal hemorrhage, and fetal congenital anomalies were assessed.

This study was approved by Institutional Review Board and Başkent University Ethics Committee (approval number: KA 18/70). Informed consent was obtained.

Statistical analysis

The SPSS 23.0 program was used for statistical analysis. Categorical measurements were assessed as number and percentage, continuous measurements are summarized as mean and standard deviation. The chi-square or Fisher's exact test statistics were used to compare categorical variables. To compare continuous variables between the groups, ranges were assessed, ANOVA or Student's t-test were used in dual groups for variables in a parametric range. $P<0.05$ was considered significant for all tests.

Results

The mean age of the 89 patients included in the study was 30 years, and the mean age at ITP diagnosis was 28 years. The mean gestational week at birth was 37 weeks and 5 days, the mean birth weight was 3073 g, and the mean hemoglobin preoperatively and postoperatively was 11.7 g/dL and 10.4 g/dL, respectively. The mean platelet count of the patients was $98x10^3/\mu L$, ranging between $19x10^3/\mu L$ and $622x10^3/\mu L$. The mean platelet count of the newborns was $226x10^3/\mu L$. The mean parity of patients was 2. Chronic ITP was diagnosed in 36% of the patients. Time of diagnosis was in the first trimester in 11% of patients, the second trimester in 18% of patients, and in the third trimester in 34% of patients. The rate of women who smoked was 6.7%. Cesarean section was performed for 75% of patients due to previous cesarean or other obstetric indications, and 11% of these patients were underwent neuraxial anesthesia. Antenatal bleeding was not encountered in 84.3% of patients, 10.3% had vaginal bleeding, and 4.3% had bleeding of other sites not related to pregnancy. Of all the patients, 42.7% required treatment, 28.9% of which was for delivery preparation. Treatment was administered in the third trimester in 44.7% of cases, and 26.3% received treatment in first or second trimester.

The treatment modality was steroids for 12.4% of patients, platelet transfusion for 9.0%, steroid and platelet transfusion for 7.9%, and steroid and platelet transfusion and intravenous immunoglobulin (IVIG) for 13.5% of patients. No treatment was needed for 57.3% of the patients. Erythrocyte transfusion beyond other treatments was administered to 11 patients. Splenectomy was performed in five (5.6%) patients.

Of the 89 pregnancies, one resulted in missed abortus, one resulted in termination of pregnancy, one ended with intrauterine exitus at the 26^{th} week, and delivery data of five patients could not be obtained due to delivery at other centers. Data of 81 newborns were assessed. Neonatal intensive care unit (NICU) admission was needed for 19.7% of the newborns. Seven of the 81 (8.6%) newborn babies had thrombocytopenia. Babies without thrombocytopenia in the first examination were not checked again in terms of platelet count. Babies with a platelet count $<30x10^3/\mu L$ were hospitalized and their platelet counts were checked daily, and platelet counts $>50x10^3/\mu L$ were checked every 2-3 days.

When patients were classified into two groups as ITP and chronic ITP, 57 patients were in the ITP group and 32 patients

were in the chronic ITP group. No significant difference was seen between the two groups with respect to parity, timing of delivery, birth weight, preoperative and postoperative platelet counts and hemoglobin values, newborn platelet counts, 1st and 5th minute APGAR scores, and NICU admission. The times of diagnosis were significantly different between the two groups, the mean age being 30.3 years for patients with ITP and 23.8 years for patients with chronic ITP (p<0.001) (Table 1). The smoking rate was significantly higher in the chronic ITP group (p=0.001).

Table 1. Comparison of mean values of patients with idiopathic thrombocytopenic purpura (ITP) and chronic ITP

	Diagnosis	Mean ± SD	p
Age (years)	ITP	30.33±5.63	0.843
	Chronic ITP	30.09±5.10	
Age at diagnosis (years)	ITP	30.28±5.65	<0.001
	Chronic ITP	23.76±5.59	
Gestational week of birth (weeks)	ITP	37.44±2.42	0.607
	Chronic ITP	37.70±1.85	
Birth weight (grams)	ITP	3032.65±597.17	0.424
	Chronic ITP	3140.00±540.40	
Preoperative platelet count (1000/μL)	ITP	89.42±33.35	0.231
	Chronic ITP	115.01±113.90	
Postoperative platelet count (1000/μL)	ITP	87.10±27.58	0.175
	Chronic ITP	116.32±115.17	
Newborn platelet count (1000/μL)	ITP	237.43±101.66	0.266
	Chronic ITP	211.63±102.09	
Newborn APGAR 1st minute	ITP	8.55±0.81	0.97
	Chronic ITP	8.55±1.73	
Newborn APGAR 5th minute	ITP	9.48±0.76	0.96
	Chronic ITP	9.57±1.36	
ITP: Idiopathic thrombocytopenic purpura, SD: Standard deviation			

Route of delivery, antenatal bleeding, and congenital anomaly rates were similar. There were three congenital anomalies leading to neonatal death in the chronic ITP group; aortic coarctation - ventricular septal defect - patent ductus arteriosus - pulmonary hypertension in the first baby, transposition of the great arteries in the second baby, and patent ductus arteriosus in the third baby. The latter baby also had thrombocytopenia, and had intraventricular and subdural hemorrhage. None of the other babies had intracranial hemorrhage. In the ITP group, one pregnancy was terminated due to a severe skeleton deformity, one baby had hydroureteronephrosis, and two babies had hypospadias. Furthermore, one pregnancy resulted in intrauterine exitus at the 26th week in the ITP group, and there was one missed abortus in the chronic ITP group.

Of all the patients, low platelet counts were found in 7 of the newborn babies, 4 of whom were in the ITP group with platelet count between 51-66x10^3/μL, and 3 babies whose platelet counts were <30x10^3/μL were in the chronic ITP group. These babies underwent transfontanel and abdominal ultrasound imaging, and no hemorrhage was found except in the above-mentioned baby who had patent ductus arteriosus.

The timing of treatment was different between the groups (p=0.034) (Table 2). Patients whose diagnoses were established during pregnancy were mostly treated for preparation of delivery. Treatment modalities were similar (Table 3). Erythrocyte transfusion rates were also similar.

All patients who had splenectomy were in the chronic ITP group, and they underwent splenectomy surgery before or after pregnancy; therefore, none of our patients required such surgery for treatment during pregnancy.

Discussion

The differential diagnosis of thrombocytopenia in pregnancy may be difficult. The onset time of thrombocytopenia, and its

Table 2. Timing of treatment for the idiopathic thrombocytopenic purpura (ITP) and chronic ITP groups

Onset of treatment	1st trimester	2nd trimester	3rd trimester	Delivery	Total	p
ITP	0	6	8	7	21	
Chronic ITP	4	0	9	4	17	**0.034**
Total	4	6	17	11	38	
ITP: Idiopathic thrombocytopenic purpura						

Table 3. Treatment choice for idiopathic thrombocytopenic purpura (ITP) and chronic ITP groups

Treatment	None	Corticosteroid	Platelet transfusion	Corticosteroid + platelet transfusion	Corticosteroid + platelet transfusion + IVIG	Total	p
ITP	36	5	3	5	8	57	
Chronic ITP	15	6	5	2	4	32	**0.305**
Total	51	11	8	7	12	89	
ITP: Idiopathic thrombocytopenic purpura, IVIG: Intravenous immunglobulin							

severity and relationship with other abnormal clinical conditions direct the diagnosis. Gestational thrombocytopenia and ITP diagnosed after the second trimester of pregnancy may be especially difficult to differentiate. However, ITP causes more severe thrombocytopenia and it may necessitate treatment at the beginning of pregnancy or in the proceeding weeks.

Steroid and IVIG are the most commonly used treatments. However, timing of treatment may affect potential adverse effects. Steroids, which are used as the first step in treatment, may cause fetal anomalies when used in early pregnancy. Furthermore, it must be kept in mind that steroids may increase complications such as hypertension, gestational diabetes, and premature labor (2). When the thrombocyte response to steroids is insufficient or the adverse effects are intolerable, IVIG treatment can be used alone or in combination with low- dose steroids (4). Sun et al. (7), who compared the effectiveness of steroid and IVIG treatments in their retrospective study with 235 pregnant patients, found no significant difference between the groups with respect to maternal platelet count and newborn results. Wang et al. (3) also declared similar treatment efficacy. Other drugs such as mycophenolate mofetil, immunosuppressants such as azathioprine, and thrombopoietin receptor agonists can also be used for treatment (4,8). Treatment choice is determines based on efficacy, toxicity, and the cost of the drugs. In our study, 57.3% of the patients did not need treatment, 30.3% were given platelet transfusion alone or in combination with other treatments.

The ITP and chronic ITP groups were similar with respect to all treatment modalities used. Platelet transfusion is mostly effective in emergency cases when there is little time to wait for the results of other treatments. Gernsheimer et al. (4), reported 5-18.9% platelet transfusion rates before delivery in patients with ITP. Some of our patients were followed up in other hospitals and were canalized for delivery at our hospital as a tertiary center. This situation can explain the higher rates of platelet transfusion when compared with previous studies.

Resistance to treatment or severe toxicity may necessitate splenectomy for remission of the patient. This procedure can be performed in the second trimester; however, it is emphasized that transplacental crossing of maternal antibodies and the risk of neonatal thrombocytopenia is not affected by splenectomy (4). None of our patients necessitated splenectomy for treatment during pregnancy.

Wyszynski et al. (1) conducted a study with 446 pregnant patients with ITP, and they concluded that fetal demise, premature delivery, and congenital anomaly risk were higher in patients diagnosed as having ITP or chronic ITP before pregnancy when compared with patients diagnosed during pregnancy, and maternal ITP duration affected pregnancy significantly; however, other medical conditions of the mother and the medications used were not mentioned and their effects could not be evaluated. Subbaiah et al. (2), in their study with 30 pregnancies of 26 patients with ITP, found no increased rates of preterm delivery, low birth weight, still birth or neonatal death in pregnancies of patients with ITP. Moreover, they reported no significant difference between the platelet count in early pregnancy and before delivery. Of our patients, 64% were new diagnosed in pregnancy, and 36% had chronic ITP. When we compared these two groups, gestational week at delivery, birth weight, and congenital anomalies were similar. Also, in Subbaiah et al.'s (2) study, the probability of severe thrombocytopenia at delivery was shown to be higher in patients with ITP who were diagnosed during pregnancy when compared with patients who received their diagnosis before pregnancy. The difference in treatment time in our study is consistent with this result.

As stated previously, route of delivery as normal vaginal birth or cesarean section does not affect hemorrhagic complications in patients with ITP, and the decision must be led due to obstetric indications (5,6). Gernsheimer et al. (4) reported that treatment would usually not be necessary in the absence of bleeding symptoms or when the number of platelets was $>30x10^3/\mu L$ in pregnant women with ITP. Won et al. (6) also suggested that the number of platelets of mother should be $>30x10^3/\mu L$ during pregnancy and $>50x10^3/\mu L$ near delivery. Furthermore, more than $50x10^3/\mu L$ platelets for normal vaginal birth or cesarean section, and more than $80x10^3/\mu L$ platelets for neuraxial anesthesia was requested. It was emphasized that for asymptomatic patients, treatment might not be necessary until delivery if the platelet count was above $20x10^3/\mu L$; however, these patients should be followed closely. Lee et al. (9) also stated little risk of epidural hematoma related to neuraxial anesthesia for platelet counts $>70x10^3/\mu L$.

In our own clinical practice, neuraxial anesthesia is preferred for patients with platelet numbers above $100x10^3/\mu L$. Besides, in our center, the recommendation of the hematology department is mostly close monitoring of platelet count and follow-up without treatment as long as the platelet count is $>30x10^3/\mu L$ and the patient is asymptomatic. Steroid treatment is recommended in the event of decline in the platelet count and when the patient is symptomatic; $>70x10^3/\mu L$ platelets are suggested for delivery, and close follow-up of the newborn in terms of immune thrombocytopenia is recommended. Also, the platelet counts must be evaluated using peripheral blood smears before treatment.

Antiplatelet antibodies can cross the placenta and cause thrombocytopenia in the newborn. Wounds on the face and scalp; petechiae; cleft palate; intraventricular hemorrhage and hydrocephalus; and cardiac anomalies such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus

may be seen in the newborn. Preterm labor or low birth weight may be encountered both in patients with ITP and chronic ITP. Maternal ITP resistant to splenectomy was reported to be related to higher rates of intracranial hemorrhage in the newborn (1). Furthermore, it was shown in several studies that maternal platelet count at delivery was not related to the platelet count of the newborn and maternal treatment did not affect the newborn platelet count. It was emphasized that risk factors for neonatal thrombocytopenia were maternal history of splenectomy, maternal platelet count less than $50x10^3/\mu L$ in pregnancy, and neonatal thrombocytopenia in the previous pregnancies of the mother (3,5). Among our patients, there were seven newborns with thrombocytopenia, and platelet counts were $<50x10^3/\mu L$ in three of the mothers in this subgroup, besides, one of the mothers had splenectomy; therefore, these numbers may not be sufficient to draw a conclusion on the risk factors of neonatal thrombocytopenia.

Fujimura et al. (10) reported neonatal thrombocytopenia as 9-15%; however, they denoted that risk of fetal intracranial hemorrhage was very low. Loustau et al. (11), reported a rate of 8.3% severe thrombocytopenia without hemorrhagic complications in the newborn. The neonatal thrombocytopenia rate was 8.6% in our study, and we found no significant difference between the ITP and chronic ITP groups in this aspect. Gernsheimer et al. (4) reported that the neonatal platelet count was not needed to be repeated if it was normal in the first examination. However, for newborns with thrombocytopenia, the thrombocyte count should be checked daily and cranial ultrasound should be performed when the platelet count is <50.000. Our practice is consistent with these implementations.

Study Limitations

The limitations of our study are its retrospective nature and the missing data. The obstetric records of the referred patients were based on patient anamnesis. Also, some of the patients were admitted to other centers for delivery, which led to incomplete newborn data.

Conclusion

ITP diagnosed before or during pregnancy is important for both the mother and the newborn. The risk of severe thrombocytopenia at delivery is higher in ITP when compared with chronic ITP. Patients should be followed closely at a tertiary center in cooperation with a hematology department. The probability of hemorrhage during pregnancy, and preparation for either normal vaginal birth or cesarean section must all be considered and the platelet count must be kept stable. The newborn's platelet count must also be closely followed in terms of immune thrombocytopenia.

Ethics Committee Approval: *This study was approved by Institutional Review Board and Başkent University Ethics Committee (approval number: KA 18/70).*

Informed Consent: *It was obtained.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - H.K., G.D.D., Ş.Y.B.; Design - H.K., G.D.D., Ş.Y.B.; Data Collection or Processing - S.Y.Ş., S.A., S.Ö., E.B.K.; Analysis or Interpretation - S.Y.Ş., S.A., S.Ö., E.B.K.; Literature Search - S.Y.Ş., S.A., S.Ö., E.B.K.; Writing - H.K., G.D.D., Ş.Y.B., S.Y.Ş., S.A., S.Ö., E.B.K.*

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Clinicopathologic importance of atypical glandular cells in cervico-vaginal cytology

Seda Yüksel, Erhan Şimşek, Selçuk Yetkinel, Songül Alemdaroğlu, Filiz Aka Bolat, Hüsnü Çelik
Clinic of Obstetrics and Gynecology, Başkent University, Adana Dr. Turgut Noyan Practice and Research Center, Adana, Turkey

Abstract

Objective: To analyze the histopathologic outcomes of patients with atypical glandular cells (AGC) in cervicovaginal cytology examinations.

Material and Methods: Patients with AGC in cervicovaginal cytology were included in this study between March 2011 and March 2018 and patient data were collected retrospectively among all cytology results. AGC classification of cervicovaginal cytology were based on the Bethesda 2001 classification system.

Results: The total prevalence of cervical epithelial cell abnormality and AGC were found as 4.2% and 0.2%, respectively, in the study cohort. AGC-favor neoplasia (AGC-FN) was the subgroup of AGC with the highest malignancy rate with 62.5% (p=0.06). The incidence of malignancy in the postmenopausal group (33.3%) was detected higher than in the premenopausal group (8.3%) (p=0.07).

Conclusion: The probability of malignancy in AGC-FN cytology is more commonly associated with malignancy in the postmenopausal group. Therefore, histopathologic examination is strongly recommended in these patients with AGC smears because of the high risk for malignancy in this group. (J Turk Ger Gynecol Assoc 2020; 21: 102-6)

Keywords: Cervical cancer, neoplasms, pap smear

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Introduction

Preinvasive lesions of the cervix can be diagnosed with Papanicolaou smear tests and be treated long before overt carcinoma develops. Routine cervical cancer screening programs in many countries significantly reduced the incidence and mortality rate of cervical cancer (1). A thorough understanding of cervical cancer pathogenesis and the development of effective screening programs both with cervical cytology and human papilloma virus (HPV) typing and vaccination against high-risk HPV types have significantly altered the distribution of cervical cancer and premalignant lesions of the cervix in countries where screening programs cover the majority of the population. Although the incidence of squamous cell cancers of the cervix is decreasing, the rate of adenocarcinomas among cervical cancers is either unchanged or increasing (2). There are many reasons for this relative increase of cervical adenocarcinoma. First, the location of adenocarcinoma and its preinvasive lesion; adenocarcinoma in situ (AIS) is rather deep and with higher localization within the cervical crypts, which makes these lesions difficult to recognize, like their squamous counterpart lesions. Second, cytologic and colposcopic signs of AIS lesions are not easy to recognize, as with squamous pathologies. Thirdly, invasive adenocarcinomas may originate from a small foci of AIS areas of the cervix (3).

Glandular cell anomalies in cervical cytology are relatively rare compared to squamous cell anomalies. The incidence of atypical glandular cell (AGC) was reported as 0.17% in a recent large study on cervical cytologic screening (4). In

Address for Correspondence: *Seda Yüksel*
e.mail: dryukselseda@hotmail.com ORCID: orcid.org/0000-0003-3191-9776

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another study in a tertiary referral center, the incidence of squamous and glandular abnormalities were found as 1.5% and 0.4%, respectively (5). Another population-based study including patients with AGC cytology reported a 1.4% risk for developing invasive cervical carcinoma, whereas this risk was found as 2.5% and 0.2% in patients with high-grade intraepithelial lesion and low-grade squamous intraepithelial lesion cytology, respectively (1).

In the current literature, AGC is questioned to be associated with severe cervical pathologies. Atypical glandular cervicovaginal cytologic abnormalities are more frequently associated with cervical adenocancer, AIS and cervical squamous lesions than squamous cervicovaginal cytologic abnormalities.

In this study, we aimed to analyze the relationship between cervicovaginal cytologic glandular abnormalities with cervical malignant pathologies. For this purpose, cervicovaginal cytology reports were examined between March 2011 and March 2018, retrospectively, and histopathologic surveillance of patients who were diagnosed as having AGCs were analyzed and resultant cervical malignancies have been traced.

Material and Methods

Liquid-based (ThinPrep Pap Test, Hologic) cervicovaginal cytologic examinations that were performed between March 2011 and March 2018 within the context of an opportunistic cervical screening program were reviewed, and the patients reported as having AGCs were detected. The diagnostic and pathologic examinations following the cytologic examinations in these patients were obtained retrospectively by reviewing the patients' medical records. All cytology and pathology specimens were re-evaluated by the department of medical pathology as needed. The Bethesda 2001 classification system was used to classify the AGCs. The Bethesda 2001 system classifies AGCs as follows: AGC-not otherwise specified (AGC-NOS), AGC-endocervical cells (AGC-EC), AGC-endometrial cells (AGC-EM), and AGC-favor neoplasia (AGC-FN). Only cytologies obtained from cervix uteri were included in this study. AGC results of vaginal cuff cytologies were excluded. The results of these groups are explained separately.

This retrospective study was approved by the institutional ethical committee (approval number: KA18/230).

Statistical analysis

The SPSS 17.0 (IBM, USA) software was used for statistical analysis. All independent parameters were analyzed using the chi-square test and the Mann-Whitney U test. P values <0.05 were accepted as statistically significant.

Results

It was determined in the study that a total of 30,851 cervicovaginal cytologic examinations were performed between March 2011 and March 2018. Epithelial cell abnormality was encountered in 1299 patients (4.2%), and AGCs were detected in 69 patients (0.2%) (Figure 1). Cytology was obtained from the vaginal cuff in 17 of 69 patients. Fourteen of these 17 patients were diagnosed as having endometrial cancer and underwent surgery. During surveillance, AGCs were detected and further histopathologic examinations were performed. As a result, three cases of recurrence were found. There was one patient with cervical cancer and two patients underwent hysterectomy with benign indications. These 17 patients were excluded because the cytologic materials were obtained from the vaginal cuff, and majority of the patients were already diagnosed as having gynecologic malignancy.

The median age of the patients with AGCs was 47 (minimum: 25, maximum: 77) years, and 42.3% of patients (n=22) were postmenopausal. Sixty-five percent (n=34) of patients with AGCs were asymptomatic and were detected in routine cervicovaginal cytologic examinations, whereas symptoms of menometrorrhagia, menorrhagia, vaginal itching, urinary incontinence, postmenopausal bleeding, and leucorrhoea were reported in 6, 4, 1, 2, 2, and 3 patients, respectively. Further pathologic examinations were offered to all patients; 19% (n=10) were lost to follow-up and 80.7% (n=42) underwent histopathologic examinations with materials taken from the cervix, endocervical canal, and endometrial cavity as indicated. The evaluation based on subtypes of AGC revealed AGC-NOS, AGC-EC, AGC-EM, and AGC-FN in 17 (32.6%), 23 (44.2%), 2 (3.8%), and 10 (19.2%) of patients, respectively (Table 1). Menopausal status was shown to be associated with the subtype distribution of AGCs in our study. AGC-EC was predominantly found in the premenopausal group (63%), whereas AGC-NOS

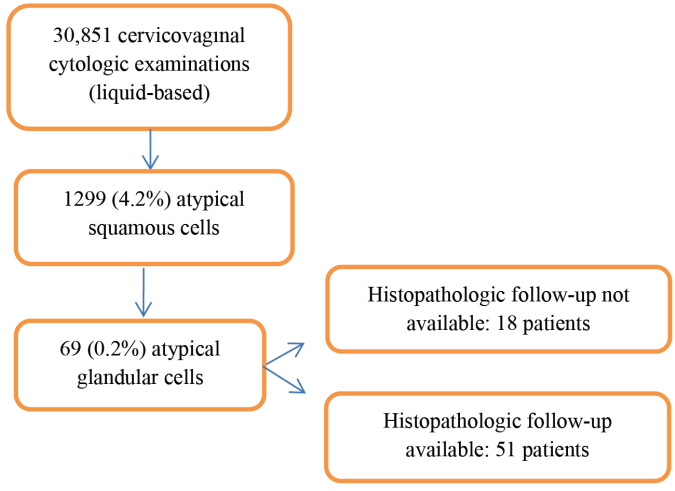

Figure 1. Flow diagram of the study

(50%) was higher in the postmenopausal group, and these differences were found to be statistically significant (p=0.01). HPV genotyping was possible after 2016 and HPV status was examined in only 10 out of 52 patients; all patients were HPV negative except for one patient with low-risk HPV positivity.

Twenty-eight percent (n=12) of the 42 patients with available pathologic follow-up data were normal, whereas active chronic inflammation, CIN1, CIN3, cervical squamous cell carcinoma, cervical adenocarcinoma, endometrial mixed carcinoma, endometrial polyp, endometrial hyperplasia, metastatic carcinoma, and ovarian serous carcinoma were encountered in 10 (23.8%), 6 (14.2%), 2 (4.7%), 3 (7.1%), 2 (4.7%), 1 (2.3%), 3 (7.1%), 1 (2.3%), 1 (2.3%), and 1 (2.3%) patient, respectively.

Regarding the patients with a malignant final diagnosis, AGC-FN (62.5%) was shown to be by far the most frequent AGC diagnosis (p=0.06). The subtypes of AGCs in the patient group with malignant lesions according to the pathologic follow-up examinations were found to account for 50% of the entire AGC-FN group (Table 2). On the other hand, 66% of all malignant cytologies in postmenopausal patients were AGC-FN initially (p=0.1) (Table 3). No statistically significant difference was found between the subtypes of AGCs in patients with malignant pathologies in the premenopausal group (p=0.3) (Table 4).

In terms of menopausal status, the incidence malignancy in the postmenopausal group (33.3%) was higher than in the premenopausal group (8.3%) (p=0.07).

Table 1. Subtype distribution of atypical glandular cells based on menopausal status

AGC subtypes	Postmenopausal	Premenopausal	Total
AGC-NOS	19 (43%)	6 (20%)	25
AGC-EC	4 (10.3%)	19 (63%)	23
AGC-EM	5 (12.8%)	1 (3.3%)	6
AGC-FN	11 (28.2%)	4 (13.3%)	15
Total	**39**	**30**	**69**

AGC: Atypical glandular cells, NOS: Not otherwise specified, EC: Endocervical cell, EM: Endometrial cell, FN: Favor neoplasia

Table 2. The distribution of histopathologic results according to subtype of atypical glandular cells

AGC Subtype	Benign	Premalignant	Malignant	Total
AGC-NOS	11 (34%)	3 (37.5%)	1 (9.1%)	15
AGC-EC	15 (46.9%)	3 (37.5%)	1 (9.1%)	19
AGC-EM	3 (9.4%)	0 (0%)	2 (18.2%)	5
AGC-FN	3 (9.4%)	2 (25%)	7 (63.6%)	12
Total	**32**	**8**	**11**	**51**

AGC: Atypical glandular cells, NOS: Not otherwise specified, EC: Endocervical cell, EM: Endometrial cell, FN: Favor neoplasia

Discussion

This study confirms that AGC is a rare cervico-vaginal cytologic abnormality with a prevalence of 0.2% out of 30,851 cytologic investigation. Similar prevalence rates of AGC have been reported in the literature (4,6-8). The prevalence of cervical malignant lesions within AGC cytology was 9.6%, whereas this rate reached 15.3% with the addition of all types of gynecologic malignancies, and 32.6% with the inclusion of premalignant lesions. The prevalence rates of the underlying neoplasia ranged between 9-50% according to AGC cytology reports, as in the literature (6,9). Tam et al. (10) reported that the risk for premalignant-malignant lesions in AGC-NOS cytology was 19%, whereas this risk rate was detected as 68% in the AGC-FN group (8). In our study, malignancy was encountered in 5 (50%) of the 10 patients with AGC-FN. When premalignant lesions were encountered, this rate was nearly 70% among patients with AGC-FN cytology. Among patients with a malignant final pathology, the leading prior AGC subtype was also AGC-FN in this cohort; nonetheless, the difference did not reach statistical significance (p=0.06).

AGC cytology may be due to cervical pathologies or endometrial pathologies. In one study on 41 patients with AGC cytology, endometrial cancer was detected in 13 patients, all of whom were aged over 40 years. It was reported in another

Table 3. The distribution of histopathologic results according to subtype of atypical glandular cells in the postmenopausal group

AGC Subtype	Benign	Premalignant	Malignant	Total
AGC-NOS	9 (64%)	3 (75%)	1 (11.1%)	13
AGC-EC	1 (7.1%)	1 (25%)	0 (0%)	2
AGC-EM	2 (14.3%)	0 (0%)	2 (22.2%)	4
AGC-FN	2 (14.3%)	0 (0%)	6 (66.7%)	8
Total	**14**	**4**	**9**	**27**

AGC: Atypical glandular cells, NOS: Not otherwise specified, EC: Endocervical cell, EM: Endometrial cell, FN: Favor neoplasia

Table 4. The distribution of histopathologic results according to subtype of atypical glandular cells in the premenopausal group

AGC subtypes	Benign	Premalignant	Malignant	Total
AGC-NOS	2 (11.1%)	0 (0%)	0 (0%)	2
AGC-EC	14 (78.8%)	2 (50%)	1 (50%)	17
AGC-EM	1 (5.6%)	0 (0%)	0 (0%)	1
AGC-FN	1 (5.6%)	2 (50%)	1 (50%)	4
Total	**18**	**4**	**2**	**24**

AGC: Atypical glandular cells, NOS: Not otherwise specified, EC: Endocervical cell, EM: Endometrial cell, FN: Favor neoplasia

study that endometrial pathology was especially found in patients aged over 45 years (11). It was suggested after the Bethesda 2014 revision that reporting age of patients with AGC-EM in cervical cytology should be adjusted as 45 years and over. This regulation was attributed to the presentation of endometrial pathologies, especially in the postmenopausal group (12). In this study, endometrial malignant pathology was encountered in one patient with endometrial mixed (serous + endometrioid) tumor; the age of this patient was 68 years. Benign pathologies of the endometrium included endometrial polyps and endometrial hyperplasia in three patients and one patient, respectively.

Our study showed that menopausal state was an important risk factor for AGC smears resulting with a final diagnosis of malignancy. Only two premenopausal patients (6.6%) were diagnosed as having malignancy, both of whom had cervical adenocarcinoma. The ages of these patients were 36 and 40 years. On the other hand, postmenopausal patients' pathologic follow-up examinations showed that considerably more patients in the postmenopausal group were diagnosed as having malignancies (33.3%) as final diagnoses (p=0.07). Although this difference seems insignificant statistically, this may result from the limited number of patients. Therefore, AGC diagnoses in menopause must be evaluated cautiously because of the increased risk of a malignant tumors.

HPV co-testing with cervical cytology has an important role in the triage of cervical squamous lesions; however, its importance is not as clear in glandular pathologies and cervical adenocancer. In a Swedish population-based study, it was reported that the HPV reflex test had a very positive predictive value in the prediction of high-grade cervical lesions in patients with AGCs, and that the planning of a follow-up schedule based on HPV status would be reasonable (13). A systematic review that analyzed the importance of HPV in AGC cytology noted that the hr-HPV test had a sensitivity of 90% in the prediction of CIN-2 and higher lesions in patients with AGC (14). In our study, only a minority of the patients diagnosed as having AGCs had co-testing with HPV because we perform colposcopy to all patients with AGCs; the absence of HPV co-testing was not a concern other than for selecting patients who could be followed up less often if their HPV test were found as negative. HPV status was analyzed in only 10 patients in our study group and 9 patients were found as HPV-negative, whereas one patient had low-risk HPV positivity. No interpretation could be made about the importance of HPV in the triage of AGC because HPV status was unknown for all 52 patients with AGCs in our study.

The guideline of the American Society for Colposcopy and Cervical Pathology has recommended colposcopy and endocervical sampling in the management of AGC (15). In accordance with this guideline, we also perform colposcopic examinations, and cervical and endocervical sampling in patients.

There is more debate as to which patients should undergo endometrial biopsy. Endometrial sampling can be recommended according to the age and symptoms of the patient. Although AGC subtype with AGC-EM constitutes only a minority of AGC cytologies, this sub-group carries higher risk for endometrial pathologies and malignancies. The small number of patients and also the retrospective nature of our cohort precludes us from drawing firm conclusions.

Conclusion

The detection of AGCs on cervicovaginal cytology carries a potential risk of various malignancies, particularly in postmenopausal patients. It can be stated from our study that among all AGC subtypes, AGC-FN cytologies are more commonly correlated with malignancy and this risk was particularly high for postmenopausal patients. Any result with AGCs necessitates further investigation with histopathologic examination. Future studies with large patient series on AGCs at cervicovaginal cytology may help to delineate patients at risk for malignancies.

There is no conflict interest between the authors of the manuscript.

Ethics Committee Approval: *This retrospective study was approved by the institutional ethical committee (approval number: KA18/230).*

Informed Consent: *Informed consent was not obtained because it was a retrospective study.*

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Analysis of cystic hygroma diagnosed in the first trimester: Single-center experience

Betül Yakıştıran[1], Orhan Altınboğa[1], Emre Canpolat[2], Esra Şükran Çakar[3], Şevki Çelen[1], Ali Turhan Çağlar[1], Yaprak Engin Üstün[4]

[1]Department of Obstetrics and Gynecology, University of Health Sciences, Ankara Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey

[2]Department of Pediatrics, University of Health Sciences, Ankara Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey

[3]Department of Genetic, University of Health Sciences, Ankara Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey

[4]Department of Obstetrics and Gynecology, University of Health Sciences Turkey, Ankara Etlik Zubeyde Hanım Women`s Health and Research Center, Ankara, Turkey

Abstract

Objective: To evaluate the obstetric outcomes of fetuses with cystic hygroma other than karyotype abnormalities and structural malformations.

Material and Methods: We conducted a retrospective study based on the review of medical records of pregnant women in whom ultrasonographic diagnosis of fetal cystic hygroma was established in the first trimester from January 2014 to October 2018. All patients were offered genetic counselling and prenatal invasive diagnostic procedures to obtain fetal karyotype. For ongoing pregnancies fetal echocardiography and detailed second trimester sonographic anomaly screening was performed by a perinatologist/pediatric cardiologist. The demographic characteristics of the women and the results of the karyotype analysis were obtained from the database of our hospital and correlated with the obstetric outcomes.

Results: Within a five-year period, there were 106 cases of fetal cystic hygroma. Of those, fetal cardiac malformations were detected in four and micrognathia in one fetus. Eighty-five women underwent fetal invasive procedures and karyotype abnormalities were detected in 52 of the cases. Fetal outcomes of 33 cases with normal karyotype and 21 cases in whom karyotyping analysis were not performed due to patient refusal were enrolled into the study. Obstetric outcomes of 21 women who refused karyotyping consisted of 13 livebirths, seven missed abortions, and one fetal death, whereas those of 33 women with normal karyotype were; 12 livebirths, 12 missed abortions, two hydrops fetalis, and five fetal deaths. Nineteen of 33 fetuses with a normal karyotype and eight of 21 fetuses in whom karyotyping was not performed were terminated.

Conclusion: The presence of cystic hygroma carries a high risk for fetal karyotype abnormalities and cardiac malformations. The postnatal outcomes of the fetuses with cystic hygroma appeared to be correlated with the absence of structural malformations and karyotype abnormalities. (J Turk Ger Gynecol Assoc 2020; 21: 107-10)

Keywords: Cystic hygroma, perinatal outcomes, prenatal diagnosis

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Introduction

Cystic hygroma is a congenital malformation characterized by the presence of abnormal fluid collection at sites of lymphatic-venous collection within the neck, mediastinum, abdomen, and axillary region (1). It is also defined as a subgroup of lymphangiomas with the cystic variety, filled with protein-rich fluid (2). Cystic hygroma is classified as septated and non-septated. The overall incidence of cystic hygroma is approximately 1/1000-6000 births and 1/750 spontaneous abortions (3).

Address for Correspondence: *Betül Yakıştıran*
e.mail: btlengin@gmail.com ORCID: orcid.org/0000-0002-3993-4017

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Cystic hygromas of nuchal origin are reported to be associated with fetal aneuploidy and structural anomalies in 50-80% of cases (1). Association with aneuploidy and/or fetal structural abnormalities worsens the prognosis. This condition can be diagnosed with sonography during fetal nuchal translucency measurement in the mid-sagittal plane in the first or early second trimester. When a cystic hygroma is diagnosed, the fetus should undergo thorough anatomic scanning for other system anomalies. In the next step, the parents should be offered invasive procedures for fetal karyotype analyses in order to detect any chromosomal abnormalities (4). If they accept karyotype analyses, chorion villus sampling or amniocentesis should be performed by a perinatologist.

Previous studies reported poorer perinatal outcomes in pregnancies with fetal cystic hygroma and associated aneuploidy (5,6). We conducted this retrospective study to evaluate the pregnancy outcomes of fetuses with cystic hygroma either with normal karyotype or with no karyotype analysis in the prenatal period.

Material and Methods

All procedures involved performed in studies involving animals and humans were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

A retrospective cohort based on a review of medical records of patients with fetal cystic hygroma, diagnosed and/or referred to our hospital, between January 2014 and October 2018 was conducted. All scans were performed using a Voluson™ 730 Pro (GE Healthcare, USA) multifrequency convex transducer at 2.0-7.0 MHz. Cystic hygroma was defined as an enlarged sonolucency with clearly visible septations extending along the fetal body axis, in contrast to nuchal translucency, which was described as a non-septated sonolucent area confined to the fetal neck. They were differentiated from nuchal edema by the presence of the nuchal ligament. Upon diagnosis of cystic hygroma, all patients were provided genetic counselling. Prenatal invasive diagnostic procedures were offered for fetal karyotyping. A complete fetal anomaly scanning was then performed for the detection of other associated structural anomalies. Women who wanted to continue their pregnancies with cystic hygroma with normal karyotype and undetermined karyotype/due to the fact that parents did not accept the invasive procedures were enrolled into the study. For those women, fetal echocardiography and second trimester detailed sonographic evaluation were performed by a perinatologist.

The demographic characteristics of the patients, and results of the fetal karyotypes were recorded from the electronic database of the hospital. Pregnancy outcomes were tabulated from electronic records of the hospitals, and for women who did not deliver at our hospitals, telephone interviews for the pregnancy outcomes were made. Moreover, physical examination findings of the infants were also performed by inviting them to the hospital.

Statistical analysis

Data were calculated using the SPSS 11.5 software package for Windows (SPSS Inc., USA). Descriptive statistics are presented as mean ± standard deviation and median (minimum-maximum) and percentages.

Results

Within this five-year period, there were 106 cases of fetal cystic hygroma; 85 women underwent karyotype analysis, whereas 21 refused karyotype analysis.

The demographic characteristics of the women are depicted in Table 1. The median maternal age was 35 (range, 22-40) years. Among them, a normal karyotype was revealed in 33 (38.8%) cases. In the remaining 52 (61.2%), fetal karyotype abnormalities were detected and they were excluded from the study. Thus the study population included the outcomes of 54 fetuses with cystic hygroma in whom invasive diagnostic procedures were either not performed (n=21) or normal (n=33).

The flow chart of the evaluation of the women with hydrops fetalis together with the details of the karyotype abnormalities, fetal structural abnormalities, and pregnancy outcome are summarized in Figure 1. Associated structural anomalies were present in 7 (12.9%) cases, including hydrops fetalis (n=2; 28.6%), transposition of the great arteries (TGA) (n=2; 28.6%), perimembranous ventricular septal defect (VSD) (n=1; 14.3%), atrioventricular septal defect (AVSD) (n=1; 14.3%), and micrognathia (n=1; 14.3%).

In the group that refused karyotype analysis (n=21), pregnancy outcomes were as follows: 13 live births (n=11 vaginal births; n=2 cesarean deliveries), seven missed abortions, and one intrauterine death. In the other group with normal fetal karyotype (n=33),

Table 1. Demographic characteristics of study group

	Pregnants underwent invasive sampling (n=85)		Pregnants refused invasive sampling (n=21)	
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)
Age, years	32.00±7.21	35 (22-40)	31.00±5.22	32 (24-38)
Gravida	2.00±0.80	2 (1-3)	2.00±0.62	2 (1-3)
Parity	1.86±0.69	2 (1-3)	1.80±1.00	2 (1-3)
Abortus	0.43±0.53	0 (0-1)	0.20±0.35	0 (0-1)
Live birth	1.71±0.76	2 (1-3)	0.81±0.42	1 (1-2)

SD: Standard deviation, Min: Minimum, Max: Maximum

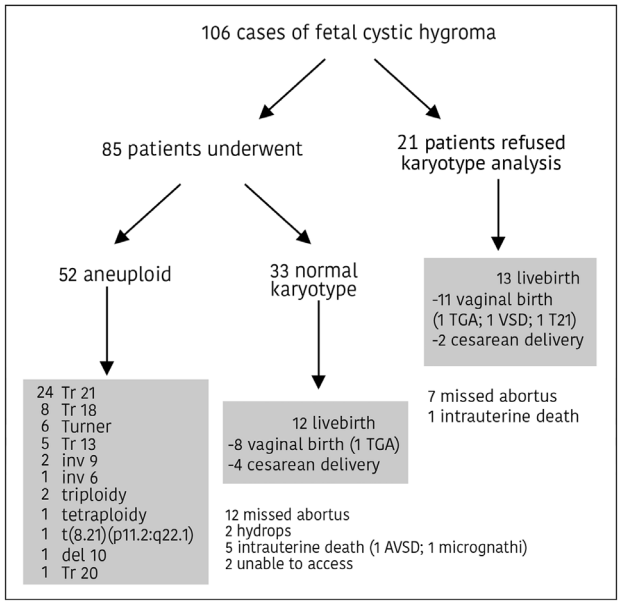

Figure 1. Overall outcomes from the prenatally diagnosed cases of cystic hygroma

pregnancy outcomes included 12 live births (n=8 vaginal births; n=4 cesarean deliveries), 12 missed abortions, two hydrops, and five fetal deaths. We were unable to obtain the results about pregnancy outcomes in two fetuses with cystic hygroma with normal karyotype. Second trimester pregnancy termination was performed on 19 women with fetal cystic hygroma with normal karyotype and eight of 21 women who refused karyotyping. Two newborns with cardiac malformation died within the first week of delivery. Both of these cases were TGA. Follow-up of the 23 infants continued for nearly 36 months. Only one infant underwent surgery due to congenital hip dislocation. Regarding the 13 live births that refused karyotyping in utero, and were karyotyped postnatally; one infant was trisomy 21 and the remaining 12 infants were euploid. No neurologic developmental disorders were detected in any infants excluding the infant with trisomy 21.

Discussion

This study once again confirms the fact that increased nuchal translucency in first trimester screening is associated with chromosomal abnormalities, structural malformations, and fetal demise. The overall probability of live births for both groups was 23.5%, and after the exclusion of aneuploid fetuses, it was 46.3%. Bilardo et al. (7) reported these rates as 43.2% and 68.1%, respectively, for increased nuchal translucency groups. On the other hand, the live birth rates of women who refused karyotyping prenatally was 61.9% (n=13/21), and the overall chance of live birth in the total group was 12.3% (n=13/106).

Nuchal translucency is an essential part of the screening for chromosomal anomalies on routine or indicated first trimester fetal sonographic assessment. During fetal nuchal translucency measurement in the mid-sagittal plane, we should keep in mind the association between increased nuchal translucency and chromosomal abnormalities, congenital malformations or several genetic syndromes (8). When a cystic hygroma is diagnosed, detailed ultrasound examination and fetal chromosomal analyses are indicated due to the high rates of fetal aneuploidy and coexisting structural malformations (9). Despite invasive prenatal diagnostic procedures for fetal karyotyping and parental counseling about poor fetal prognosis, parents sometimes refuse these procedures due to religious beliefs, and the increased risk of abortion with invasive fetal procedures. Even if normal karyotype is reported due to the limited treatment modalities and possibility of unfavorable consequences, the parents can opt for elective termination.

Previous studies indicated that cystic hygroma with fetal structural abnormalities is associated with poor fetal outcomes (1-6). The most frequent fetal structural malformation is cardiac defects within euploid groups. TGA has the highest incidence (90%) in this group. Septal or valvular defects are present in 43% and aortic valve/isthmus stenosis is present in 86% of cardiac abnormalities (7). We found that the overall frequency of cardiovascular anomalies in our study group was 7.4%. Among the cardiac defects, TGA, perimembranous VSD, and AVSD were detected with a frequency of 28.6%, 14.3%, and 14.3%, respectively, emphasizing the fact that in the second trimester, targeted fetal echocardiographic examinations are important and an essential diagnostic tool in euploid fetuses with cystic hygroma (1,7).

Hydrops fetalis is another important prognostic marker. Bernard et al. (10), reported a mortality rate of 96.5% in hydropic fetuses. Our findings showed that the incidence of fetal death with coexisting hydrops was 100%. Generalized edema and hydrops may be the cause of left atrium dysfunction and aorta due to a compression effect leading to fetal death. In the literature, only a few studies have reported the resolution of hydrops and healthy newborns (11); the majority of the studies demonstrate that hydrops is associated with poor fetal outcomes (6,10,12,13). On the other hand, the resolution of nuchal edema with a normal karyotype is a good prognostic marker in the absence of any coexisting malformation. Two fetuses with hydrops fetalis were present in our study. Cardiac malformations were detected more frequently than hydrops fetalis. Cardiac malformations, arrhythmia, aneuploidy, and fetal structural malformations may lead to non-immune hydrops fetalis (14). Our findings showed 25 live births in all groups, two of which with TGA died postnatally; one of the newborns was trisomy 21. Of the remaining newborns, 22 (88%) had normal postnatal neurologic development. Similarly, Sanhal et al. (5) reported that 90% of fetuses (euploid

and structurally normal) with septated cystic hygroma had normal neurologic outcomes.

Other than fetal karyotyping, chromosomal microarray analysis (CMA) is an advanced technology with the ability to survey the entire genome and to identify chromosomal abnormalities, submicroscopic genomic alterations. Increased nuchal translucency and cystic hygroma are associated with different conditions, aneuploidy and structural abnormalities. Shaffer et al. (15) reported that the detection rate of CMA for fetuses with cystic hygroma was 17.1%. CMA should be offered for any patient undergoing invasive sampling to identify all clinically significant alterations.

Though previous studies focused on cases with karyotyping, our study also investigated cystic hygroma with unknown karyotype in the prenatal period. The refusal rate of karyotyping was higher (19.8%) than in the published data from European countries; this condition might be due to lower sociocultural levels and religious beliefs. We think our findings may be helpful to physicians providing parental counseling for women who refuse karyotype analysis. In fetuses with cystic hygroma with normal karyotype and in whom no structural malformations are present, pregnancy outcomes may be favorable as reported in the literature (5).

The small number of cases with cystic hygroma and unknown karyotype in 21 cases are the main limitations of this study.

Conclusion

The presence of cystic hygroma carries a high risk for aneuploidy and major structural malformations. Invasive prenatal karyotyping procedures, fetal echocardiographic examination, and parental counselling are necessary for the prediction of the prognosis. Until multicenter and large-sample sized studies have been published, these results might be helpful in providing parental counselling for those with fetal cystic hygroma.

Ethics Committee Approval: *All procedures involved performed in studies involving animals and humans were in accordance with the ethical standards of the institution or practice at which the studies were conducted.*

Informed Consent: *It was retrospective- designed. We didn't have the informed consent forms signed.*

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Analysis of community-based studies related with knowledge, awareness, attitude, and behaviors towards HPV and HPV vaccine published in Turkey: A systematic review

Serpil Özdemir[1], Rabia Akkaya[1], Kazım Emre Karaşahin[2]

[1]Department of Public Health Nursing, University of Health Sciences Turkey, Gülhane Faculty of Nursing, Ankara, Turkey

[2]Department of Obstetrics and Gynecology, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Ankara, Turkey

Abstract

Human papilloma virus (HPV) vaccine is a proven method for preventing HPV-related cancers and genital warts, especially preventing cervical cancer. It is aimed to systematically review and synthesize conclusions in detail from community-based studies published in Turkey between 2009 and 2019, which evaluate the knowledge, awareness, attitude, and behaviors of individuals towards HPV and HPV vaccination. This systematic review is conducted based on the PRISMA reporting method and includes community-based, descriptive cross-sectional and cross-sectional studies published between 2009 and 2019. In this systematic review, 5132 studies from six databases were scanned in total. It was determined that there were 23 studies that met the eligibility criteria for this systematic review. In the reviewed studies, it was determined that the rate of "Hearing of HPV before" was 3.8% at the lowest and 57.0% at the highest, and the rate of "Hearing of HPV vaccine before" was 2.2% at the lowest and 74.7% at the highest. In the reviewed studies, it was reported that although parents' willingness to have their daughters vaccinated with HPV vaccine varied between 14.4% and 68.0%, their willingness to have their sons vaccinated with HPV vaccine varied between 11.0% and 62.0%. In addition, it was reported that the lowest rate of vaccination with HPV vaccine among participants was 0.3% at the lowest and 6.0% at the highest. Consequently, it is considered that conducting common, systematic, and continuous health education programs aimed at both sexes and including both parents, which will increase the knowledge and awareness on HPV and its vaccine, would provide positive attitudes, and will be effective in protecting against HPV-related cancers. (J Turk Ger Gynecol Assoc 2020; 21: 111-23)

Keywords: Human papilloma virus, HPV vaccine; knowledge, awareness, attitude, public health

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Introduction

Human papilloma virus (HPV) infection, which is sexually transmitted to both males and females, is a global epidemic (1-3). Approximately 75% of sexually active individuals encounter HPV at some time in their lives (4). Thirteen known carcinogenic types of HPV, which have approximately 200 diagnosed types, may become cancerous by causing chronic and progressive infection (5). HPV-related cancers are listed as cervical, vulvar, vaginal, anal, rectal, penile, and oropharyngeal cancers (5,6). According to data from the surveillance program conducted by the Centers for Disease Control and Prevention in the United States of America between 2008-2012, it is reported that 38,793 people on average were diagnosed as having HPV-related cancer and 59% of whom were females and 41% were males (6). In the last five years in Turkey, the reported prevalences of cervical cancer, vulvar cancer, anal cancer and penile cancer were 16.09%, 1.82%, 1.09%, and 0.16%, respectively (7).

HPV vaccine is a proven method for preventing HPV-related cancers and genital warts, especially preventing cervical cancer

Address for Correspondence: *Serpil Özdemir*
e.mail: serpilozdemir327@gmail.com ORCID: orcid.org/0000-0003-0952-3337

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(8,9). It is reported that vaccines containing HPV16-18 types prevent 63% of all HPV-related cancers; vaccines containing nine types of HPV (HPV6-11-16-18-31-33-45-52-58) provide protection against cervical, vulvar, vaginal, and anal cancers by 90% (6,10). Throughout the world and in Turkey, HPV vaccines are recommended to individuals from both sexes between the ages of 9 and 26 years and before the first sexual experience (11,12). The HPV vaccine, the safety of which has been verified by the European Medicines Agency (13), is included in national vaccination program in many countries, but it is not included in Turkey's national vaccination schedule (13-15).

Objectives

The literature reported that negative attitude and behaviors of individuals and parents such as lack of knowledge and low awareness about mode of transmission, protection, and early diagnosis methods of HPV infection, cost of HPV vaccine, potential adverse effects, and suspecting vaccine safety, and negative news on all vaccines prevented the generalization of the HPV vaccination (16-18). In the current study, the aim was to systematically review community-based studies that evaluated the knowledge, awareness, attitude, and behaviors of individuals towards HPV and HPV vaccine published in Turkey between 2009 and 2019, and the available conclusions were synthesized in detail.

Protocol and registration

This systematic review was registered on the International Prospective Register of Systematic Reviews system (approval number: 128435). This systematic review was conducted based on PRISMA reporting method and includes community-based, descriptive cross-sectional and cross-sectional studies published between 2009 and 2019.

Eligibility criteria

The investigated studies, which were about protection methods against cervical cancer in Turkey published in the last 10 years, were focused on individuals' knowledge, awareness, attitude, and behaviors on HPV and HPV vaccine. In the literature, no systematical national research report was found on individuals' knowledge, awareness, attitude, and behaviors on HPV and the HPV vaccine (2). In this systematic review, it was decided that synthesizing community-based studies would be appropriate by anticipating that they would reflect the current status of the community at risk in terms of HPV infection in Turkey. In this respect, eligibility criteria were based on the literature as follows: (1) descriptive cross-sectional and cross-sectional research design published in a national or international peer-reviewed journal; (2) conducted within the borders of the Republic of Turkey; (3) published between 2009 and 2019; (4) sample consisting of healthy/sick individuals. Review articles, letters to the editor, qualitative studies, case-control studies, congress proceedings, and theses were excluded from the systematic review.

Information sources

Studies included in the systematic review were obtained as a result of comprehensive review of EBSCO, Google Scholar, Proquest, PubMed, Springer, and TR index databases between March 1st and 4th, 2019.

Search

Keywords in English used in the review were "Turkey", "HPV", "Human Papilloma Virus", "HPV vaccine", "knowledge", "awareness", "attitudes", "behavior"; and "Türkiye", "İnsan Papilloma Virüsü", "Human Papilloma Virüsü", "HPV aşısı", "bilgi", "farkındalık", "tutum" and "davranış" words were used in the Turkish database.

Study selection

In this systematic review, as a result of comprehensive scanning of the databases, 118 research reports were identified according to the titles and abstracts that met the eligibility criteria. It was observed that there were 43 recurring studies among this research. In the assessment according to title and abstract after the recurring researches were identified, studies conducted by healthcare professionals/students (n=47), intervention studies (n=3), scale validity reliability studies (n=2), and studies conducted on immigrant Turks (n=1) were eliminated because they did not fit the purpose of the systematic review. After this stage, the full texts of the studies were reviewed (n=25). Studies for which the full text was not available were excluded from the systematic review (n=2). Following the assessments, it was determined that there were 23 studies that met the eligibility criteria for this systematic review (Figure 1).

Data collection process

Evidence centers such as the Cochrane Library and Joanna Briggs Institute (JBI) recommend that the studies addressed in systematic reviews are assessed using standardized critical instruments to determine their scientific value and bias risk according to their objectives, design, and method properties (19). It is reported that valid and reliable instruments for determining the reporting quality of cross-sectional studies are limited (20). To assess the reporting quality and properties of the 23 studies included in this systematic review, the 8-question

JBI-Critical Appraisal Checklist for Analytical Cross-sectional Studies, which was developed by JBI, was used (21). In the check list, the quality of the studies was assessed in each question as "1=yes", "2=no", "3=unclear", "4=not applicable" (Table 1).

A data collection form developed by the researchers based on the literature was used to collect the data of the scanned studies included in the systematic review. The data collection form includes the author, year, subject, location, sample size and properties, method, main findings, conclusion, and suggestion titles of the study. Researchers reviewed the full texts of 23 studies in detail and recorded in the data collection form under titles independently from each other. Data collection forms of each study were reviewed by all researchers and the data of the systematic review were established.

Data items

The collected data was merged under the titles of "Author", "Year", "Location of the Research", "Age Range", "Health

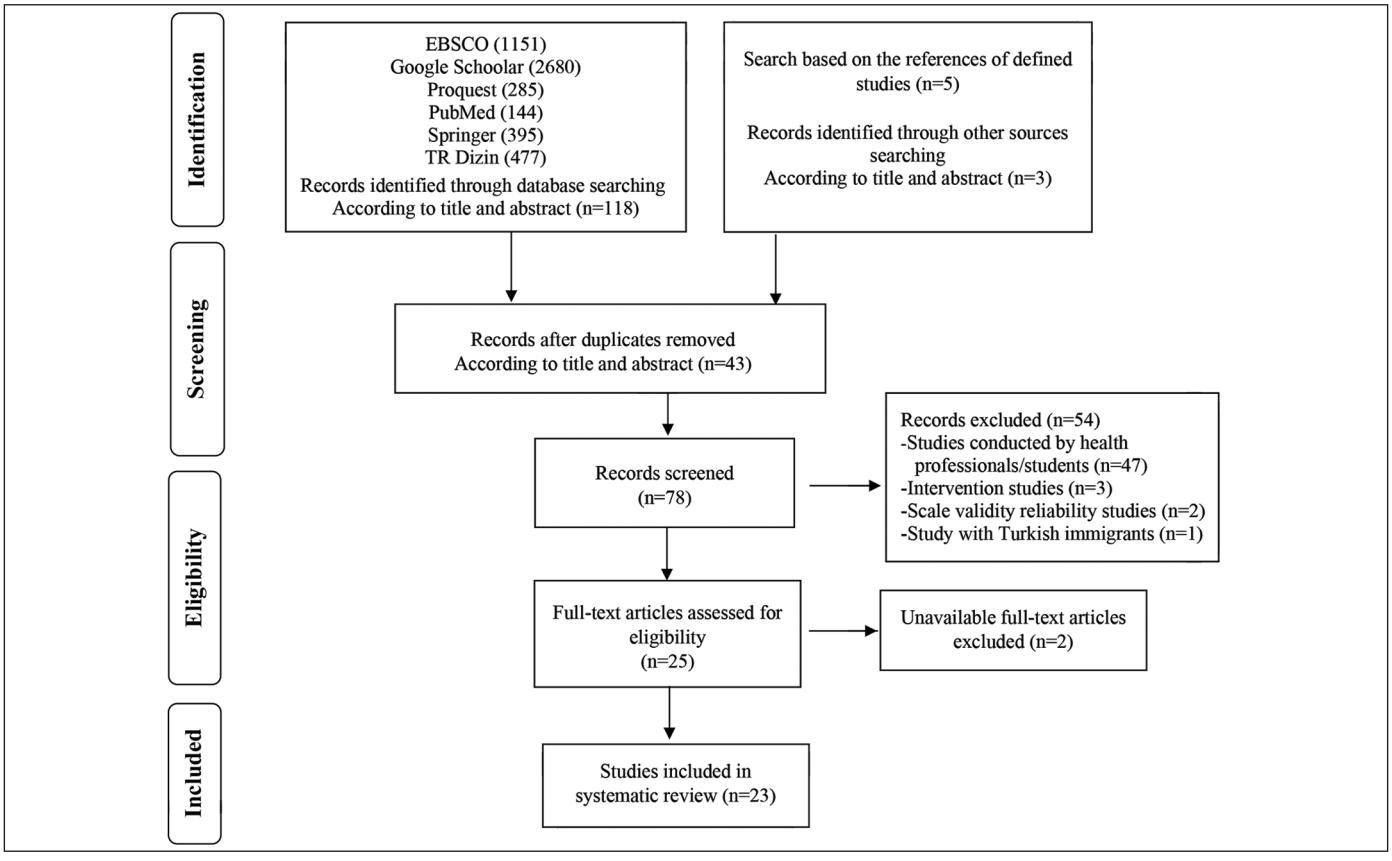

Figure 1. PRISMA flow diagram of the systematic review

Table 1. Joanna Briggs Institute-critical appraisal checklist for analytical cross-sectional studies (n=23)

	Yes		No		Unclear		Not applicable	
	n	%	n	%	n	%	n	%
1. Were the criteria for inclusion in the sample clearly defined?	22	95.6	1	4.3	-	-	-	-
2. Were the study subjects and the setting described in detail?	13	56.5	9	39.1	1	4.3	-	-
3. Was the exposure measured in a valid and reliable way?	1	4.3	22	95.6	-	-	-	-
4. Were objective, standard criteria used for the measurement of the condition?	23	100	-	-	-	-	-	-
5. Were confounding factors identified?	4	17.3	19	82.6	-	-	-	-
6. Were strategies for dealing with confounding factors stated?	4	17.6	19	82.6	-	-	-	-
7. Were the outcomes measured in a valid and reliable way?	23	100	-	-	-	-	-	-
8. Was appropriate statistical analysis used?	23	100	-	-	-	-	-	-

Center", "Number of Participants", "Properties of Sample", "Hearing of HPV", "Hearing of HPV vaccine", "Vaccination Rate", "Willingness to Vaccination for Own Self", "Willingness to Vaccination for Daughter", "Willingness to Vaccination for Son", "Barriers of HPV Vaccine", "Source of HPV Knowledge", "Willingness to have Education about HPV", "Factors in relation to HPV and Vaccine Knowledge" and "Suggestions" (Table 2, 3).

Study selection

In this systematic review, 5132 studies from six databases were scanned in total. It was determined that there were 43 recurring studies out of 118 studies identified according to the titles and abstracts. Number of identified studies was determined as 78. Fifty-four studies that were determined to be beyond the purpose of the systematic review based on the title and abstract were eliminated. Out of the 25 studies whose full texts were to be assessed for eligibility, two studies were excluded because their full texts were not available. The full texts of 23 studies that met the eligibility criteria were included in the scope of the systematic review (Figure 1).

Reporting characteristics of studies

In the assessment of the studies according to the JBI-Critical Appraisal Checklist for Analytical Cross-sectional Studies, it was determined that eligibility criteria were defined clearly in the sample in 95.6% (n=22) of the studies, and the study subject and methods were explained in detail in 56.5% (n=13) of the studies. It was observed that the researched case was measured in a valid and reliable manner in only 4.3% (n=1) of the studies included in the systematic review, but all of the studies (n=23) used objective criteria for measuring the researched case. It was determined that confounding factors were not identified in 82.6% (n=19) of the studies, and also strategies for coping with confounding factors were not specified. It was determined that the results of all studies (n=23) were assessed using objective criteria and suitable statistical analyses were conducted (Table 1).

Study characteristics

It was determined that 56.5% (n=13) of the studies included in the systematic review were published between 2009 and 2013 and 56.5% (n=13) were published in international indexed journals. In the studies that were assessed, the age range of the participants varied between 13 and 87 years. The number of participants in the studies was between 229 and 1808. Sixty-five percent (n=15) of the studies addressed only adult women; 21.7% (n=5) addressed adult men and women; 8.6% (n=2) addressed female adolescents and young females; 4.3% (n=1) addressed only males, and 4.3% (n=1) addressed female adolescents and their mothers. In terms of the location of the studies, it was observed that 65.2% (n=15) of the studies were conducted at tertiary healthcare institutions. Studies were conducted in 13 different provinces in total (Table 2).

In the studies, it was determined that the rate of "Hearing of HPV before" was 3.8% at the lowest and 57.0% at the highest, and the rate of "Hearing of HPV vaccine before" was 2.2% at the lowest and 74.7% at the highest. In the assessed studies, it was reported that the parents' willingness to have their daughters vaccinated with HPV vaccine varied between 14.4% and 68.0%, whereas their willingness to have their sons vaccinated with HPV vaccine varied between 11.0% and 62.0%. In addition, it was reported that the lowest rate of vaccination with HPV vaccine among the participants was 0.3% at the lowest and 6.0% at the highest (Table 2). Two of the reviewed studies investigated the willingness to have education about HPV and its vaccine and it was reported that 69.2% and 95% of the participants were willing to receive health education (Table 3).

In nine studies conducted on in HPV vaccine barriers (43.4%), it was reported that the first three barriers identified were lack of knowledge about HPV and vaccine (40.9% to 76.6%), adverse effects concern (0.9% to 64.5%), and the price of HPV vaccine (0.2% to 49.5%), respectively. According to data obtained from the studies, it was observed that the information source of the participants about HPV and vaccine was healthcare personnel at the rate of 12.3% to 72.2%, and media (e.g. TV, internet, newspapers) at a rate of 23.5% to 88.8% (Table 3). In the studies included in the systematic review, it was reported that awareness, knowledge, and positive attitudes on HPV and vaccine increased as the woman's/mother's education level increased in studies that investigated factors in relation to knowledge on HPV and vaccine (60.8%, n=14). In addition, in 17.3% of the studies (n=4), it was reported that awareness, knowledge, and positive attitudes on HPV and vaccine increased in the woman/mother who worked and have high economic level. In this review, it was stated that 82.6% of the studies (n=19) recommended health education, 21.7% (n=5) recommended that more comprehensive and in-depth research should be conducted, and 26.0% (n=6) recommended that policies should be made about vaccine prices and strengthening of primary healthcare services (PHCS) (Table 3).

Summary of evidence

When the reporting properties of 23 cross-sectional studies included in this systematic review were assessed, it was observed that most of them explained the eligibility criteria

in the sample (95.6%) and objective measurements were performed with appropriate statistical analyses and results were reported objectively in all of them. Taking confounding factors under control is quite important in terms of the reliability of the results in cross-sectional studies (22,23). In most of the addressed studies (82.6%), not taking confounding factors under control was considered as a significant limitation in the cross-sectional research design. In addition, using standardized measurement instruments is important in increasing the quality of results obtained in cross-sectional studies (24). In most of the studies reviewed in this study (95.6%), it was determined that standardized valid and reliable measurement instruments were not used. Two valid and reliable scales that assess knowledge, attitude, and beliefs on HPV and vaccine, and which were adapted to Turkish were published in 2016 (25,26). It takes time to publish and announce measurement instruments that are adapted to the culture of a society and use them commonly (27). It was considered that there was a limitation in the studies in terms of using standardized measurement instruments because there were no available standardized measurement instruments until the publication date of valid and reliable HPV and vaccine scales in Turkish, and the measurement instruments were published relatively recently.

In information and awareness studies on HPV and the HPV vaccine that were conducted in developed countries, it was reported that HPV knowledge and awareness were at low-to-moderate levels, and vaccination rates (26%-55%) were not at desired levels, although the willingness for vaccination was high (17,28-34). In studies conducted in developing countries, it was reported that HPV knowledge and awareness and willingness for vaccination were at low-to-moderate levels, and HPV vaccination rates were quite low (13.3%-16.1%) (35-41). In line with the literature, it is considered that the awareness and knowledge level on HPV and the HPV vaccine (3.8%-57.0%) and willingness for vaccination (6.3%-69.0%) and vaccination rates (0.3%-0.6%) are quite low in this systematic review, which addresses community-based studies in Turkey. It was reported that offering consultancy services on HPV performed by healthcare professionals promoted positive attitudes in these countries by increasing awareness and knowledge on HPV (38,42,43). In Turkey, it is anticipated that the fact that HPV has limited coverage in education programs conducted by healthcare professionals is the cause for the awareness and knowledge on HPV and HPV vaccine and therefore vaccination rates not being at desired levels.

Although HPV immunization willingness was high, various barriers made it difficult to raise vaccination rates to the desired level. HPV vaccination barriers in developed countries were listed as doubts about vaccine safety and efficiency, adverse effect concerns, lack or inconsistency of information about HPV and the HPV vaccine, and the price of the HPV vaccine (29,32,34). In developing countries, HPV vaccine barriers were the lack of awareness of the vaccine, doubting the safety and efficiency of the vaccine, finding it embarrassing to buy the vaccine for sexually transmitted infections, and people thinking that they were not at risk for HPV (35,37,41). In parallel with this, it was determined that the most frequently reported HPV vaccine barriers in studies included in the systematic review were lack of information (40.9% to 76.6%), concerns about the potential adverse effects of the vaccine (0.9% to 64.5%), and the price of the vaccine (0.2% to 49.5%). It was reported that the fact that HPV vaccine was included in the national vaccination schedule in many countries contributed to HPV vaccination in those countries (42). The low HPV vaccination rate obtained in this systematic review could be explained by the fact that HPV vaccine is not included in the national vaccination schedule in Turkey and that vaccine prices are not affordable for the majority of society. In addition, it is anticipated that the fact that healthcare professionals' level of knowledge and awareness is low, common and continuous health education on HPV is not conducted because of the lack of information about HPV vaccination, therefore resulting in the quite low vaccination levels in Turkey.

The most frequent source of healthcare information in developed countries was healthcare professionals, and media (television, internet, newspaper) at a lower rate (17). In developing countries, it was reported that the most frequent source of healthcare information was media, and healthcare professionals at a lower level (36,38). Similarly, in this review, the most frequently preferred source of healthcare information was the media, and healthcare professionals were preferred at a lower rate. In the studies addressed in this review, it was determined that society was willing and ready at a high rate to obtain information on HPV and the HPV vaccine (69.2%, 95%). Correct and reliable healthcare information should be transferred to society only by specialized healthcare professionals (29,44,45). The misinformation sources and broadcasts against vaccination in the media could prevent society from obtaining correct and reliable information about the HPV vaccine (46). For that reason, it is anticipated that healthcare professionals, who are the reliable sources of information on HPV vaccine, can form positive attitudes and behaviors and encourage the society towards vaccination with continuous and common health educations.

In the literature, it was reported that level of knowledge on HPV vaccine increases as people's education levels and income levels increase (28,30,35,39,40,47). In parallel with the literature, it was determined that level of knowledge on HPV vaccine increased as the education level and income level increased in the studies addressed in this systematic review.

In that respect, it was suggested that groups with lower education and income levels should be addressed primarily in programs in relation to HPV and the HPV vaccine. Consistent with the literature, it was determined that most of the studies addressed in this review recommended health education for increasing knowledge, awareness, and positive behaviors towards HPV and the HPV vaccine (48). Systematic, common, and continuous health education programs conducted by professionals in accordance with the culture of the society are the most effective method for creating healthy behaviors (48).

The systematic review was limited to the studies published in EBSCO, Google Scholar, Proquest, PubMed, Springer, and TR index databases for which full texts could be accessed. There full text of two studies were not accessible.

Conclusions

It is considered that conducting common, systematic, and continuous health education programs aimed at both sexes and including both parents, which would increase knowledge and awareness on HPV and the HPV vaccine, and provide positive attitudes, will be effective in protecting people against HPV-related cancers (17,31,33,34,36,38). In addition, it will be an important initiative for the protection of public health that healthcare authorities include HPV vaccines in their immunization programs and that policies encourage acceptance of the vaccine in society in countries where the HPV vaccine is not included in national vaccination schedules. In addition, there is a need for studies with methodologically strong designs that test the methods that will provide positive attitudes towards HPV vaccination in society (30,36,38).

Table 2. Distribution of the community-based cross-sectional studies (n=23)

Author	Year	Location of the research	Rage of age	Health institutions	Sample size	Properties of sample	Hearing of HPV (%)	Hearing of HPV vaccine (%)	Vaccination rate (%)	Willingness to vaccination for		
										Self (%)	Daughter (%)	Son (%)
Adıguzel et al. (49)	2016	Adana	18-65	Tertiary	426	Females	39.4	33.1	-*	42.7	43.7	
Akyuz et al. (43)	2011	Ankara	20-59	Tertiary	229	HPV negative (-) and HPV positive (+) females	HPV (-): 14.7 HPV (+): 43.0	HPV (–): 70.7 HPV (+): 74.7	-*	-*	-*	-*
Bebis et al. (50)	2013	Ankara	20-36	Military based	787	Young adult men	29.2	-*	-*	-*	-*	-*
Bülbül et al. (51)	2013	Ankara, Kırıkkale, Gaziantep	16-60	Tertiary	1405	Mothers with children of ≤15 years old	-*	46.3	-*	-*	If free of charge: 23.4 Even if paid: 76.6	
Çetin et al. (16)	2014	İstanbul	13-18	Tertiary	501	Female adolescents	22.2	11.7	0.9	6.3	-*	-*
Dursun et al. (52)	2009a	Ankara, Adana, Alanya, Konya	17-80	Tertiary	1427	Females	45.0	-*	-*	70.0	64.0	54.0
Dursun et al. (53)	2009b	Ankara, Adana, Alanya, Konya	21-56	Tertiary	618	Mothers with 10-15 year olds children	45.0	-*	-*	69.0	68.0	62.0
Ersan et al. (54)	2012	İzmir	≥18	Sex business	239	Sex workers	33.0	19.2	-*	-*	-*	-*
Kose et al. (55)	2014	Sakarya	18-55	Tertiary	799	Mothers with children of ≤18 years old	11.9	16.5	0.7	-*	-*	-*

Table 2. Continued

Author	Year	Location of the research	Rage of age	Health institutions	Sample size	Properties of sample	Hearing of HPV (%)	Hearing of HPV vaccine (%)	Vaccination rate (%)	Willingness to vaccination for		
										Self (%)	Daughter (%)	Son (%)
Kürtüncü et al. (12)	2018	Zonguldak	≥25	Tertiary	100	Mothers with 10-15 years old daughters	57.0	67.0	-*	-*	59.0	11.0
Onan et al. (56)	2009	Ankara	15-87	Primary	1808	Females	24.8	24.3	-	17.0	51.1	43.6
Ozan et al. (57)	2011	Bursa	≥18	Tertiary	336	Females	33.6	44.6	-*	-*	42.2	22.4
Ozyer et al. (58)	2013	Ankara	9-24	Tertiary	408	Female adolescents and young Females	41.6	-*	-*	11.2	-*	-*
Önder et al. (59)	2015	Ankara	15-49	Primary	294	Females	24.5	28.2	-*	-*	-*	-*
Pınar et al. (60)	2010	Ankara	19-65	Tertiary	471	Females	53.5	57.7	-*	-*	-*	-*
Saylam et al. (61)	2016	Konya	≥18	Tertiary	500	Females	16.6	32.0	2.6	-*	32.0	-*
Seven et al. (62)	2015	Ankara	24-58	School-based	368	Parents with 10- years old children	Mother: 26.9 Father: 25.0	- *	-*	-*	Mother: 14.4 Father: 15.5	Mother: 21.6 Father: 22.4
Tas et al. (63)	2016	İstanbul	18-≥65	Tertiary	273	Males and females with anogenital wart lesions	Females: 8.9 Males: 3.8	Females: 2.2 Males: 2.2	-*	Females: 66.7 Males: 48.1	-*	-*
Tonguc et al. (64)	2012	Elazığ	18-66	Tertiary	945	Females	26.0	21.6	6.0	40.6	36.3	26.0
Turhan et al. (65)	2017	Hatay	≥18	Tertiary	1087	Females and males	27.0	23.2	2.7	-*	23.5	
Turkol et al. (66)	2009	Malatya	15-49	Primary	417	Females	-*	46.5	-*	52.4	47.0	-*
Uzuner et al. (67)	2018	İstanbul	≥18	Primary	318	Females and males	-*	49.6	0.3	-*	-*	-*
Oz et al. (68)	2018	Ankara	18-30	School-based	1160	Females and males	43.7	26.6	1.0	45.1	-*	-*

*Data on the relevant area were not found
HPV: Human papilloma virus

Table 3. Distribution of community-based cross-sectional studies (n=23)

Author, publication year	Barriers of HPV vaccine			Source of HPV knowledge		Willingness to have education about HPV (%)	Factors in relation to HPV and vaccine knowledge		Suggestions		
	Lack of knowledge (%)	Adverse effect (%)	Price (%)	Healthcare personnel (%)	Media (TV, internet, newspaper) (%)		Education level	Working/ economic level	Education	Research	Policy
Adıguzel et al. (49) 2016	-*	-*	-*	40.4	39.1	-*	As the level of education increases, knowledge and awareness level increase (p<0.001)	-*	Health education	-*	-*
Akyuz et al. (43) 2011	-*	-*	-*	HPV (-): 12.3 HPV (+): 32.2	HPV (-): 86.8 HPV (+): 62.7	-*	-*	-*	Health education	-*	-*
Bebis et al. (50) 2013	-*	-*	-*	-*	-*	-*	As the level of education increases, knowledge level increases (p<0.001)	-*	-*	Comprehensive research	-*
Bülbül et al. (51) 2013	-*	-*	44.4	-*	-*	-*	As the level of education increases, knowledge level increases (p<0.001)	-*	Health education	Comprehensive research	Wages policy
Çetin et al. (16) 2014	40.9	16.4	26.4	17.1	59.4	-*	As mothers' education level increases, knowledge level increases (p<0.001)	-*	Health education	Comprehensive research	-*
Dursun et al. (52) 2009	-*	-*	-*	-*	-*	-*	As mothers' education level increases, knowledge level increases (p<0.001)	-*	Health education	Comprehensive research	Vaccination policy
Dursun et al. (53) 2009	-*	-*	-*	-*	-*	-*	-*	-*	-*	Comprehensive research	-*

Table 3. Continued

Author, publication year	Barriers of HPV vaccine			Source of HPV knowledge		Willingness to have education about HPV (%)	Factors in relation to HPV and vaccine knowledge		Suggestions		
	Lack of knowledge (%)	Adverse effect (%)	Price (%)	Healthcare personnel (%)	Media (TV, internet, newspaper) (%)		Education level	Working/ economic level	Education	Research	Policy
Ersan et al. (54), 2012	-*	-*	-*	-*	-*	-*	There is no relation between HPV knowledge and education level (p>0.001)	-*	Health education	-*	-*
Kose et al. (55), 2014	-*	-*	-*	27.1	61.2	-*	As mothers' education level increases, knowledge level increases (p<0.001)	As the level of economic status increases, awareness level increase (p<0.001)	Health education	-*	-*
Kürtüncü et al. (12), 2018	66.0	-*	26.0	-*	-*	95.0	As the level of education increases, knowledge level increases (p<0.001)	There is relation to work status and level of knowledge (p<0.001)	Health education	-*	Strengthening of PHCS+
Onan et al. (56), 2009	-*	1.5	-*	-*	-*	-*	-*	-*	Health education	-*	-*
Oz et al. (68) 2018	76.6	32.3	-*	14.0	61.0	-*	-*	-*	Health education	-*	-*
Ozan et al. (57), 2011	-*	-*	-*	-*	-*	-*	As the level of education increases, knowledge level increases (p<0.001)	There is relation to work status and level of knowledge (p<0.001)	Health education	-*	-*
Ozyer et al. (58), 2013	-*	0.9	0.2	25.9	23.5	-*	-*	-*	Health education	-*	-*

Table 3. Continued

Author, publication year	Barriers of HPV vaccine			Source of HPV knowledge		Willingness to have education about HPV (%)	Factors in relation to HPV and vaccine knowledge		Suggestions		
	Lack of knowledge (%)	Adverse effect (%)	Price (%)	Healthcare personnel (%)	Media (TV, internet, newspaper) (%)		Education level	Working/ economic level	Education	Research	Policy
Önder et al. (59), 2015	-*	-*	-*	72.2	88.8	-*	As the level of education increases, knowledge level increases (p<0.001)	-*	-*	-*	Strengthening of PHCS+
Pınar et al. (60), 2010	-*	-*	-*	25.7	42.9	-*	As the level of education increases, knowledge level increases (p<0.001)	-*	Health education	-*	-*
Saylam et al. (61), 2016	-*	-*	-*	50	25.6	69.2	-*	-*	Health education	-*	-*
Seven et al. (62), 2015	67.2	64.5	6.4	-*	-*	-*	-*	-*	Health education	-*	-*
Tas et al. (63) 2016	-*	-*	-*	-*	-*	-*	-*	-*	-*	-*	-*
Tonguc et al. (64), 2012	-*	-*	49.5	-*	-*	-*	As the level of education increases, knowledge level increases (p<0.001)	-*	Health education	-*	Wages policy
Turhan et al. (65), 2017	-*	5.9	-*	-*	-*	-*	As the level of education increases, knowledge level increases (p<0.001)	-*	Health education	-*	-*
Turkol et al. (66), 2009	-*	-*	-*	-*	63.6	-*	As the level of education increases, knowledge level increases (p<0.001)	As the level of economic status increases, awareness level increase (p<0.001)	Health education	-*	-*

Table 3. Continued

Author, publication year	Barriers of HPV vaccine			Source of HPV knowledge		Willingness to have education about HPV (%)	Factors in relation to HPV and vaccine knowledge		Suggestions		
	Lack of knowledge (%)	Adverse effect (%)	Price (%)	Healthcare personnel (%)	Media (TV, internet, newspaper) (%)		Education level	Working/ economic level	Education	Research	Policy
Uzuner et al. (67), 2018	47.1	3.1	-*	55.0	64.0	-*	As the level of education increases, knowledge level increases ($p<0.001$)	-*	Health education	-*	Strengthening of PHCS+

*Data on the relevant area were not found.
+PHCS: Primary healthcare services, HPV: Human papilloma virus

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Endometrial "Scratching" An update and overview of current research

Veronika Günther[1,2], Sören von Otte[2], Nicolai Maass[1], Ibrahim Alkatout[1]

[1]Clinic for Obstetrics and Gynecology, UKSH Campus Kiel, Kiel, Germany

[2]University Fertility Center, Ambulanzzentrum des UKSH gGmbH, Kiel, Germany

Abstract

About one in every six couples is affected by sterility. Assisted reproduction procedures are currently the treatment of choice for a number of patients who desire children. Many causes of sterility can be overcome with the aid of in vitro fertilization, but successful implantation of the embryos is the major limiting factor. Failure of implantation may occur repetitively. In the treatment of sterility, many approaches have been used to overcome the barrier of implantation failure and improve the chances of successful nidation. Scratching the endometrium prior to embryo transfer has been suggested as one means of enhancing the likelihood of implantation. The current literature was examined to investigate if there was any possible benefit from endometrial scratching. The studies were divided according to whether the women suffered from recurrent implantation failure or not. In summary, it was found that unselected subfertile women generally benefit less from endometrial scratching, but scratching appears to be successful in women who have experienced repeated implantation failure. Although the heterogeneous body of data on the subject deserves further clarification. The latest data presented at "European Society of Human Reproduction and Embryology" 2018 in Barcelona suggested that the method should be abandoned. (J Turk Ger Gynecol Assoc 2020; 21: 124-9)

Keywords: Infertility, reproductive immunology, perinatal immunology and inflammation

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Introduction

Approximately one in every six couples is affected by sterility. Procedures of assisted reproduction are currently the method of choice for a number of patients desiring children (1). Many causes of sterility can be overcome by the aid of in vitro fertilization (IVF), but successful implantation of the embryo is still the major limiting factor. Implantation, also known as nidation, starts on day 5 and ends on day 10, post conception (p.c.). The zona pellucida surrounding the blastocyst ruptures (on day 4 p.c.) due to growth of the blastocyst and enzymatic lysis; this phenomenon is also known as hatching. This is followed by apposition and adhesion of the blastocyst to the endometrium. In this process the microvilli on the surface of the external trophoblast cells interact with the epithelial cells of the uterus and form junctional complexes with the aid of surface glycoproteins (2). An essential element of implantation is the estrogen- and progesterone-induced reconstruction of the endometrium during the luteal phase, which is responsible for the receptivity of the endometrium. This episode, which is limited to a period of a few days, is referred to as the implantation window (3).

Recurrent implantation failure

Implantation failure may occur repeatedly. Recurrent implantation failure has been variously defined. One assumes a failure of pregnancy after two to six IVF cycles, following the transfer of at least 10 embryos of good quality (4). Other authors refer to repeated implantation failure when no clinical pregnancy has occurred after the transfer of at least four embryos in at least three fresh embryo transfers (ET) or cryo-thawed ETs; it is assumed that the patient is below 40 years of age (5). There are many possible causes that may be responsible for the infertility of the couple. Uterine factors such

Address for Correspondence: *Ibrahim Alkatout*
e.mail: ibrahim.alkatout@uksh.de ORCID: orcid.org/0000-0002-7194-6034

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as polyps or uterine abnormalities, infections, thrombophilia, immunological factors or genetic factors are just a few examples. In this context, endometriosis, which is particularly frequently associated with an increased sterility rate, deserves special mention. The prevalence of endometriosis in female infertility patients, at 25-50%, is significantly higher than in fertile women. It is assumed that 30-50% of endometriosis patients are confronted with sterility (6). Endometriosis remediation is associated with an increased pregnancy rate and should be performed prior to planned fertility treatment (7,8).

Endometrial "scratching"

Several approaches have been used to overcome the problem of implantation failure in the treatment of sterility, or improve the chances of successful nidation. Scratching of the endometrium prior to ET is one method of enhancing the likelihood of implantation. Usually, in the luteal phase of the cycle preceding IVF, the endometrium is "scratched" with a small catheter, 3 mm in width, known as the Pipelle®. Usually without hooking on the cervix, the catheter is pushed forward through the cervix to the fundus, and then retracted in circular movements in order to stimulate the endometrium (Figure 1). In case further diagnostic investigation is desired, such as the investigation of chronic endometritis or the presence of plasma cells or uterine killer cells, the Pipelle® can be used simultaneously to obtain a biopsy specimen of the endometrium. This is regarded as a low-risk procedure with a low rate of complications. Scratching can be performed on an outpatient basis without anesthesia and is associated with minor pain for the majority of patients.

As an alternative to the use of the Pipelle®, scratching can also be performed in the course of a diagnostic hysteroscopy. In order to evaluate the uterine cavity and detect or rule out potential barriers to implantation, such as a septum, a polyp, or a myoma, it is usually sufficient to perform a mini-hysteroscopy.

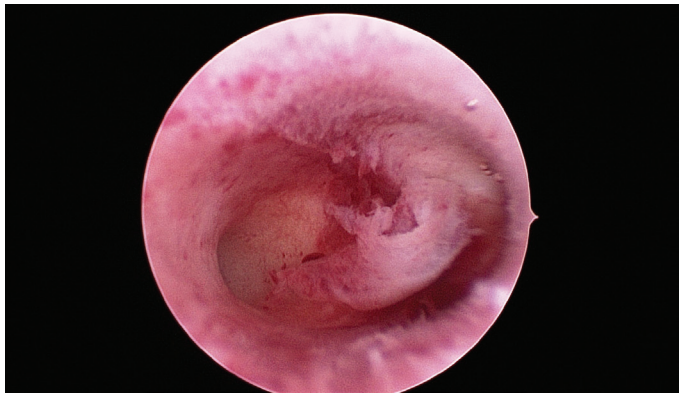

Figure 1. Hysteroscopy
Hysteroscopic view of an inconspicuous cavum uteri. In the middle of the picture the thrown-up endometrium is shown and in the rear part the exit of the right tube can be seen

Figure 1 shows the hysteroscopic view of an inconspicuous cavum. In this intervention the gynecologist may perform an endoscopy of the uterine cavity without anesthesia, and usually even without hooking the cervix. The small optical instrument, measuring just 3 mm in diameter, serves the purpose of inspection as well as "scratching" or endometrial stimulation. After inspection and photographic documentation, when the instrument is withdrawn, a mucosal lesion is created usually on the posterior wall (Figure 2 a, b, c).

The first observations about scratching were made in 1907 by Loeb (9), who described the rapid proliferation of decidual cells after injury to the endometrium in the uterus of guinea pigs. In 2003 Barash et al. (10) first reported injury to the

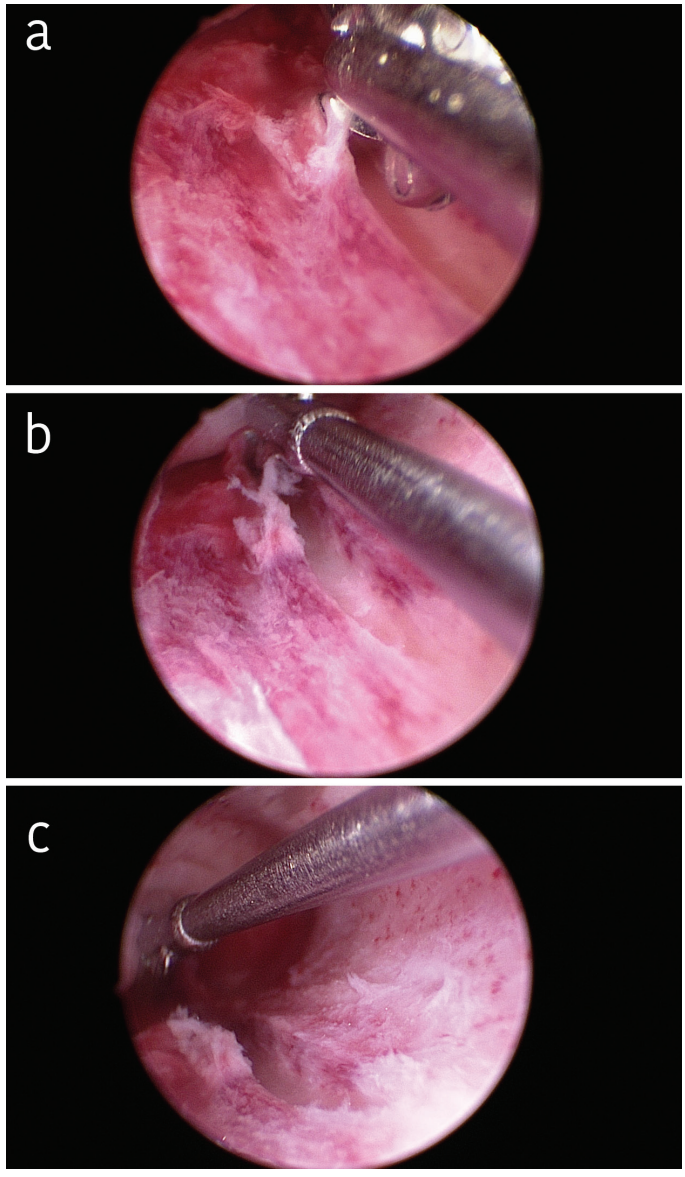

Figure 2. a, b, c) Endometrial scratching
For immunomodulatory stimulation, a mucosal lesion is created usually on the posterior wall with the hysteroscope

endometrium and its positive effect on implantation rates. They showed that a biopsy of the endometrium on day 8, 12, 21, and 26 of the menstrual cycle was associated with a higher pregnancy rate after IVF. Endometrial injury resulted in the secretion of growth factors and cytokines during the healing process, which, according to the authors, exerted a positive effect on endometrial receptivity (10).

Three approaches have been used to enhance uterine receptivity by endometrial scratching and thus enhance pregnancy rates after IVF-ET:

1. Local stimulation of the endometrium which induced decidualization, which in turn increases the likelihood of implantation of the transferred embryo (11).

2. The healing and repair process after successful scratching caused a significant increase in macrophages, dendritic cells, and proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), growth-regulated oncogene-α, and macrophage-inflammatory protein-1B (MIP-1B), which exert a positive effect on implantation (11,12). Especially TNF-α and MIP-1B were found in high concentrations during the implantation window, which underlined the inflammatory effect on the receptive endometrium (13).

3. Ovarian stimulation during IVF treatment has been associated with high levels of estrogen, which causes an early increase in progesterone levels. Compared to the embryonic stage, the endometrium is already in an advanced stage of differentiation, which makes it difficult for implantation to take place (14-16). Scratching during the preceding cycle may suppress proliferation and thus optimize synchronicity between the endometrium and the embryo to be transferred (11).

Current data

A number of studies and overview articles have focused on scratching and success rates of subsequent pregnancies.

Studies on recurrent implantation failure

A meta-analysis and review in 2012 comprised 2062 women from four randomized and three non-randomized controlled studies; one to six IVF attempts had been made prior to the study. A hysteroscopy in the early proliferative phase as well as endometrial scratching in the preceding cycle, interpreted as endometrial injury, were regarded as inclusion criteria. The evaluation revealed a 70% higher rate of clinical pregnancies in the intervention group compared to the control group (17). Karimzadeh et al. (18), and Narvekar et al. (2), who were also included in the above mentioned meta-analysis, noted higher pregnancy rates after successful screening in their respective randomized controlled studies.

Karimzadeh et al. (18) included 58 patients in the treatment group and 57 patients in the control group. Implantation rates were 10.9% in women who underwent scratching and 3.4% in controls ($p=0.039$); pregnancy rates were 27.1% and 8.9%, respectively ($p=0.023$). No difference was noted in miscarriage rates ($p>0.05$). Narvekar et al. (2) included 49 patients in the treatment group and 51 women in the control group, both after recurrent implantation failure. Scratching was performed once in the follicular phase and a second time in the luteal phase, both in the cycle preceding IVF. It should be noted that, in the control group, a hysteroscopy was performed on day 7-10 of the preceding cycle; the hysteroscopy might have caused mild mechanical stimulation and also effected an alteration of the endometrium (19). Implantation, clinical pregnancy, and live birth rates were significantly higher in the intervention group than in controls (implantation rates 13.07% vs 7.1%; clinical pregnancy rates 32.7% vs 13.7%, $p=0.01$; live birth rates 22.4% vs 9.8%; $p=0.04$) (2).

Shohayeb and El-Khayat (20) showed that scratching performed during hysteroscopy resulted in significantly higher implantation, pregnancy, and live birth rates compared to hysteroscopy without scratching. Two hundred patients with recurrent implantation failure were included in the study, and were assigned to the treatment and control groups in equal numbers. Group A received a hysteroscopy in the early follicular phase (day 4-7), with endometrial scratching of the fundus and the posterior wall, whereas group B only underwent a diagnostic hysteroscopy (21). Implantation rates were 12% in group A, and just 7% in group B ($p=0.015$). Clinical pregnancy rates were 32% in group A and 18% in group B ($p=0.034$). Live birth rates were 28% in group A and 14% in group B ($p=0.024$). Miscarriage rates did not differ significantly (12.5% in group A and 22% in group B; $p=0.618$) (20).

In a randomized controlled study, Kumbak et al. (22) investigated the outcome of IVF after hysteroscopy and endometrial biopsy on day 21 of the cycle during the luteal phase. A sample was obtained with a small biopsy catheter and sent for histological investigation. Seventy patients in the treatment group were compared with 58 patients in the control group; the latter had received no intervention. Pregnancy rates were significantly higher in the treatment group (82% vs 73%; $p=0.009$) than in controls. Given the same number of transferred embryos of category A, the implantation rates (38% vs 25%, $p=0.04$) and pregnancy rates per embryo (67% vs 45%; $p=0.01$) were significantly higher in the scratching group than in controls (22).

In two further randomized controlled studies, the authors registered no benefit from scratching (23,24). Baum et al. (23) performed a randomized double-blind study comprising 36 patients who had undergone at least three previous IVF

attempts. The intervention group (n=18) underwent scratching twice (day 9-12 and day 21-24), followed by IVF treatment. The special feature of the control group (n=18) was that the patients underwent a placebo investigation during which the biopsy catheter was inserted into the cervix without contacting the endometrium. The study revealed lower implantation rates (2.08% vs 11.1%, p=0.1), clinical pregnancy rates (0% vs 31.25%, p<0.05), and live birth rates (0% vs 25%, p=0.1) in the treatment group compared to controls.

A more recent randomized controlled study performed in 2015 by Gibreel et al. (24) also revealed no statistically significant improvement in live birth rates after scratching compared to controls. A subgroup analysis, on the other hand, showed a higher live birth rate in women who had undergone two or more failed IVF attempts after scratching, compared to those who had undergone only one IVF attempt (24).

A Cochrane analysis performed by Nastri et al. (25) in 2015 comprised 14 studies with a total of 1063 patients in the treatment group and 1065 patients in the control group. Endometrial scratching was performed between day 7 of the preceding cycle and day 7 of the ET cycle. The control group underwent no manipulation of the endometrium. A prerequisite was at least two previous ETs. Higher rates of pregnancies and live births were noted in the intervention group (relative risk: 1.42; 95% confidence interval: 1.08-1.85, p=0.01). A subgroup analysis, which excluded all studies with a potential bias, yielded an equally significant result. If 30% of women who underwent no scratching had become pregnant, the intervention group would have achieved a pregnancy rate of 33-48% (25). Scratching, according to the authors, had no impact on miscarriage rates, potential bleeding, or multiple pregnancies (25).

In contrast to the above mentioned studies, the following authors investigated the impact of scratching in women without recurrent implantation failure.

Studies on women without recurrent implantation failure

In a prospective randomized study comprising 121 women who had undergone IVF treatment, Zhou et al. (26) performed endometrial scratching in the intervention group (n=60) when they noted irregular endometrial patterns in the vaginal ultrasound investigation (atypical, absence of trilaminar pattern, echogenic lesions). Scratching was performed during ovarian stimulation in all cases, with the purpose of enhancing endometrial receptivity. The control group underwent no scratching. The treatment group revealed higher implantation rates (33.33% vs 17.78%), clinical pregnancy rates (48.33 vs 27.86%) and live birth rates per ET (41.67% vs 22.96%) after scratching (26).

Nastri et al. (27) performed scratching with a Pipelle® 7 to 14 days prior to scheduled hormonal stimulation for an IVF cycle, while the women were taking an oral contraceptive. The authors registered higher pregnancy and live birth rates (p=0.01) in the treatment group compared to the control group, with no impact on miscarriage rates (p=0.53) (27).

Guven et al. (28) achieved similar results, although they performed scratching on day 3 of the transfer cycle rather than the preceding cycle. The authors registered higher pregnancy (48.2% vs 29%, p=0.025) and live birth rates (33.9% vs 17.7%, p=0.035) in the treatment group compared to controls (28).

In contrast to the majority of authors, who investigated the effect of scratching by local manipulation in the preceding cycle, Karimzade et al. (29) investigated the effect of scratching with the Novak curette on the day of follicle aspiration. One hundred fifty-six patients were included in this prospective controlled study. However, this study revealed negative effects on implantation rates (7.9% vs 22.9%, p=0.002) and the outcome of IVF (9.6% vs 29.1%, p=0.004) after scratching compared to controls. It may be assumed that, since manipulation was performed shortly before ET, pro-inflammatory cytokines, macrophages and dendritic cells could not be formed rapidly enough in adequate numbers. The receptivity of the endometrium was damaged rather than enhanced as a result thereof (29).

In their treatment group (n=50) Safdarian et al. (30) performed scratching with a biopsy catheter on day 21 of the preceding cycle, and registered no statistically significant difference compared to controls (n=50) in regard of implantation and pregnancy rates (30).

Yeung et al. (31) achieved similar results. In their randomized controlled study the authors included 300 subfertile women, selected randomly, who were scheduled to undergo or had undergone IVF cycles. In the treatment group the authors performed scratching with a Pipelle® in the mid-luteal phase of the preceding cycle. Compared to controls, the authors registered no differences in regard of implantation, pregnancy, multiple pregnancy, or miscarriage rates. In a subgroup analysis of women who had undergone repeated IVF attempts, the pregnancy rate after scratching was lower than that in controls (31).

In a recent but retrospective case control study performed in May 2017 in Israel (32), 238 patients were included in the treatment group and 238 in the control group. Women in the treatment group underwent scratching for the first time. Scratching was performed once or twice in the proliferation phase as well as the luteal phase. The results in the scratching and control groups were similar in regard of implantation (28.06% vs 30.08%, p=0.8), pregnancy (34.03% vs 40.33%, p=0.18), and continued pregnancy rates (18.48% vs 28.99%, p=0.33) (32).

At the European Society of Human Reproduction and Embryology meeting, which was held from 1 to 4 July 2018 in Barcelona, Dr. Sarah Lensen from New Zealand presented the recent results of her work on the subject of scratching (33). Her contribution received the Clinical Science Award for oral presentation. Meanwhile her work has been published in the New England Journal of Medicine (34). Data from this randomized multicenter study were collected between June 2014 and June 2017 at 13 centers in five countries. 1364 women (690 in the scratching arm vs 674 in the control group) who had undergone ET after IVF during the fresh embryo or cryo-thawed cycle were included in the study, with no recent exposure to disruptive intrauterine instrumentation (e.g., hysteroscopy). Participants were randomly assigned in a 1:1 ratio to either endometrial scratching (by pipelle biopsy between day 3 of the cycle preceding the embryo-transfer cycle and day 3 of the embryo-transfer cycle) or no intervention. The primary outcome was live birth. The results revealed no increase in live birth rates after endometrial scratching: 26.1% (180/ 690) vs 26.1% (176/674) in controls, odds ratio 1.00 (0.78-1.27). Even a subgroup analysis in regard of recurrent implantation failure, fresh or cryo-thawed cycles, and the interval between scratching and ET yielded no specific group that would benefit from scratching. The authors concluded that endometrial scratching should not be offered or performed in the course of fertility treatment.

Conclusion

Practical significance

To estimate the final value or benefit of scratching in regard of implantation, pregnancy, and live birth rates, it is important to precisely define the respective patient population that would benefit from this intervention. Scratching is able to enhance the receptivity of the endometrium, but a number of other pathologies may be responsible for implantation failure. The present overview of studies shows that unselected, sub-fertile women generally benefit less from endometrial scratching. In contrast, scratching appears to be a successful measure for enhancing the chances of implantation in women with recurrent implantation failure. However, recent data from Lensen et al. (34) contradict this thesis. Rather, these data have shown that endometrial scratching is not associated with a higher live birth rate even in women with recurrent implantation failure. Patients should be informed of these recent data.

Scratching is convenient, easy to perform, and associated with very little pain. Based on the existing body of data, as mentioned above, scratching could be offered to patients with recurrent implantation failure in order to try to enhance pregnancy and live birth rates, after the women have been informed in detail about the procedure. The patients should definitely be informed of the heterogeneous data on the subject including the most recent work from Lensen et al. (34) Taking these latest data into account, endometrial scratching did not show any advantage in pregnancy and live birth rate and the conclusion of this work was that this method should not now be offered, which patients should be made aware of.

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Considerations on a new, frameless copper-releasing intrauterine system for intracesarean insertion and its future clinical significance: A review

Hazal Kutlucan[1], Recep Onur Karabacak[1], Dirk Wildemeersch[2]
[1]Department of Gynecology and Obstetrics, Gazi University Faculty of Medicine, Ankara, Turkey
[2]Control Research ICC Technologiepark Zwijnaarde, Belgium

Abstract

Family planning is a system for attaining the desired number of children and enabling a desired spacing between pregnancies. Family planning can be achieved through both the use of contraceptive methods and the treatment of infertility. A woman's ability to limit her pregnancy has a significant effect on her health.While family planning reduces the rate of unintented pregnancies, it also reduces the number of unsafe abortions.

Contraception is an important component of family planning and reproductive health. Among various contraceptive methods, intrauterine devices (IUDs) are very popular because of some of the features of IUDs including being affordable, simplicity of insertion, long duration of action and reversibility. Modern, frameless, copper IUDs contain more copper and their copper content is contained in the solid tubular sleeves rather than in the wire which increases efficacy and lifespan. Immediate postpartum intrauterine device insertion (IPPI) during cesarean section can be considered in women who desire long acting, reversible contraception. Fertility returns instantly after removal of the device and pregnancy rate is not affected. IPPI is a very attractive method, especially for women who have undergone cesarean and require an interval of contraception before getting pregnant again. However, IPPI needs more clinical attention due to many aspects. The advantages remain including the prevention of unintended short interval pregnancies and, by providing an optimal timeframe for post-cesarean uterine recover, can reduce the incidence of the next cesarean delivery. With the publication of international IPPI studies, it will take a place in the range of globally available contraceptive methods, which in this author's opinion, it deserves. (J Turk Ger Gynecol Assoc 2020; 21: 130-3)

Keywords: Intrauterine device, intraoperative contraception, preventing expulsions, frameless IUD, insertion technique

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Introduction

Family planning provides individuals and couples to get desired number of children and interval between pregnancies. The allowing can be achieved with contraceptive methods (1).

Over three decades ago, an article appeared in the journal Contraception titled: "Immediate postplacental intrauterine devices (IUD) insertion (IPPI): the expulsion problem" (2). The authors had extensive experience with vaginal or cesarean section delivery insertion of several IUDs, having inserted 2646 copper or plain plastic IUDS from June 1, 1974 up to July 1, 1983. IPPI insertion satisfies the basic requirements of any contraceptive method: Ease of insertion, safety of insertion, and high contraceptive effectiveness, but more importantly allows family planning discussions and contraception choices at a time when patient awareness is highest. Postpartum IUD insertion does not enhance the risk of infection or the rate of uterine perforation, has no effect on uterine involution and/or resumption of menstrual activity and does not adversely affect lactation. The authors identified a persisting problem with IPPI, namely poor device retention when compared to conventional interval insertion. Numerous international multicenter clinical trials conducted over the intervening years have repeatedly confirmed the problem. Expulsion rates of up to 70% for the Lippes Loop were reported (2) while a comparative IUD

Address for Correspondence: *Hazal Kutlucan*
e.mail: hazalkutlucan@gmail.com ORCID: orcid.org/0000-0003-4698-7624

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trial conducted by the World Health Organization had to be terminated early precisely because "the predetermined termination indices for expulsions were exceeded at six months"; at one year, the expulsion rates amounted to 41, 44, and 35% for the TCu220C-PP, the Lippes Loop D, and the 7 Cu 200, respectively (3). Finally, a trial conducted by Family Health International in the US reported six-month expulsion rates of 22% and 12% for the Lippes Loop D and the TCu220C, respectively (4).

The American College of Obstetricians and Gynecologists refers to expulsion rates between 10 and 27% (5-8) but a great variety of expulsion rates are seen in different studies (9), and even higher expulsion rates were found in more recent studies, using copper or levonorgestrel (LNG)-releasing IUDs (10). High expulsion rates may also affect the cost-effectiveness of the method (10).

The clinical and societal benefits of IPPI are clearly evident. However, current methods are viewed by many experts as unacceptable for general use (8). Over the years, numerous attempts have been made to solve the problem of expulsion and IUD displacement primarily focused on establishing a maximal insertion window of 10 minutes post-placenta expulsion. Although these efforts tended to result in more favorable expulsion rates, they remain significantly higher after IPPI than after interval insertion of the same IUD.

In addition to the expulsion problem, there are the high rates of IUD displacement and/or partial expulsion, which result in patient discomfort and early removal of the IUD. Displacement rates are typically not routinely reported in studies or included in expulsion rate determinations. Many IUDs when proper retention and placement is not optimal and, if not completely expelled, will be displaced by uterine contraction and lochia, and can become embedded in the lower uterine segment causing discomfort, cramping and abnormal bleeding. Swati et al. (11) found displacement of the TCu380 IUD in up to 50% of women; many were removed because of abnormal bleeding and pain. For all IUD models, virtually all expulsions are clustered in the first three months after IPPI (2,10).

The GYN-CS IUD

A new surgery-focused approach was devised which eliminates the timing, uterine compatibility issues and clinical complexities associated with IPPI use. The frameless copper-releasing IUD is placed onto the fundal uterine surface via an inserter specifically designed for immediate post-placental delivery after cesarean section (Figure 1). An additional benefit of this new device is that 100% of the copper surface area is available for copper release, the procedure takes advantage of the surgeon's full view and access to the uterus that is achieved during cesarean delivery and removal of the placenta. The technique consists of the precise placement and fixation of a tiny anchoring knot in the fundus of the uterus immediately following delivery (Figure 2). The entire procedure can be performed in less than four minutes with no discomfort to the patient and minimal surgical risk. Following a series of "proof of concept" studies designed at optimization of the inserter design, the first randomized controlled trial (RCT) was conducted at a tertiary center in gynecology and obstetrics in Turkey. The comparative study, with a follow-up period of three months, compared the frameless, anchored, copper GYN-CS® with the TCu380A IUD in 140 women; 70 in each arm of the study. The approach and insertion procedure of the GYN-CS® is completely novel with respect to IUD placement; the anchor is first pushed through the fundus; then a biodegradable suture is inserted through the noose of the knot after which the knot is withdrawn one millimeter below the serosa and fixed to the serosa using the biodegradable suture. When the suture

Figure 1. Detail of the tip of the applicator with anchoring knot fixed to the insertion stylet

Figure 2. Following puncturing of the fundus, a biodegradable suture is put though the noose of the anchoring knot. Then the anchoring knot is pulled 1 mm below the serosa and fixed to the serosa using the biodegradable suture. (http://www.wildemeersch.com/products/gynefix-cs/video/)

dissolves after approximately one month, the uterus will have involuted and the knot behaves similarly as after interval insertion. Removal of the GYN-CS®, if deemed necessary, has shown to be possible as soon as 30 days post-insertion with no discomfort to the patient or clinical complications. In the study, the TCu380 IUD was inserted using the conventional sponge forceps technique. The RCT results demonstrated the distinct superiority of the anchoring technique as there was only one expulsion (1.4%) in the GYN-CS group while eight total expulsions (11.4%) were observed with TCu380A at the 3-month conclusion of the study (12).

The second study, conducted at the same institution, in 100 women, with follow-up of up to three months, confirmed the validity of the anchoring technique. Only one expulsion was reported (13). The two expulsions, one in each study, were thought to be caused by incorrect physician insertion or by inadvertent or excessive pulling at the tail when setting the anchor or during trimming. Inadvertent traction on the tail could be prevented by trimming the IUD tail in the lower uterine segment at the time of insertion, as opposed to follow-up examination during patient discharge. In the two studies, the single tail of the GYN-CS® could be visualized by subsequent speculum examination in 50-60% of the cases. In the RCT, approximately 25% of the TCu380A IUD strings were visible in the vagina, probably because the single tail of the GYN-CS® is stiffer than the tails of conventional IUDs. If the tail is not visible, the IUD can easily be located in the uterus by abdominal or transvaginal ultrasound examination. The precise positioning of the anchor can be verified in the fundus of the uterus, as the anchor is provided with a tiny stainless-steel marker, highly visible on ultrasound examination.

Advantages of frameless devices

Frameless devices have an advantage over conventional, framed, t-shape IUDs as they fit uterine cavities irrespective of size or shape. Numerous studies have confirmed that maximal uterine widths are substantially smaller in the majority of women than the width of most conventional IUDs (14). Due to their small size and segmented design, resulting in flexibility and the absence of cross arms, frameless devices have high long-term patient acceptance rates and lack the structure to become embedded. Framed IUDs may be discrepant with the uterine cavity, may displace and embed during involution of the uterus, particularly during prolonged lactation when the uterus becomes extremely small (15).

The most commonly used frameless IUD is active for five years but a frameless device for immediate postpartum insertion, lasting 10 years, has recently been approved and granted CE-marking. A significant advantage of the frameless devices, as they occupy a limited space in the uterus, is that the device can be loaded with a sufficient amount of copper to last up to 25 years. Similarly, a small diameter, high capacity LNG device, loaded with 100 mg of LNG will likely release a sufficient amount of hormone per day to guarantee contraceptive safety for a full 20-year period (16). Both approaches can easily be adapted for use with IPPI procedures. These new, non-hormonal and hormonal, postpartum intrauterine contraceptives will be highly beneficial for women, their clinicals and the general medical community and society in general. They should be welcomed and supported by regulatory authorities for fast-track approval, especially since the long-term efficacy and safety of copper and of LNG is well-established.

The successful implementation of a postpartum program, in addition to solving the expulsion problem, will also depend on taking cost price into consideration. In the USA promotion of the practice of IPPI by the American College of Obstetricians and Gynecologists has been followed by the insurance companies agreeing to reimburse immediate IUD insertion. Currently, 38 states have adopted Medicaid policies to allow the reimbursement of IUDs inserted immediately post-delivery, an extremely welcome initiative. The method will be highly cost-effective if women continue to use the method and thus patient acceptance and comfort are critical factors (10). As the method shows promise, international trials are now planned.

Implications

In addition to the huge advantages for women, preventing unintended pregnancy, the economic advantages of a highly effective and well-tolerated immediate postpartum method is significant. Therefore, the contraceptive method should be totally reimbursed.

Conclusion

The development of frameless IUDs has been driven by the growing need to develop high-performing, long-acting, reversible and acceptable contraceptives with a high continuation of use (17). IPPI deserves greater clinical attention as it can provide immediate contraception, prevents repeat unintended pregnancies, and may serve to reduce the incidence or need for secondary cesarean delivery by allowing the uterus to recover optimally post-surgery. Of all the available postpartum birth control methods, IUDs represent the near ideal form, being recommended by physicians and gynecological organizations worldwide. They have the advantage of high effectiveness as well as having an extremely low failure rate, in part because of the lack of concerns of recipient women because these IUDs are well tolerated and are not expelled.

In our department, we have started inserting this useful contraceptive method and will report on the results later.

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What is your diagnosis?

A 27-year-old, gravida 3 para 1 woman who had pelvic pain was admitted to hospital. In her obstetric history, she had delivered a 1100 g female baby by cesarean section (C-section) one year ago because of acute fetal distress. A single fetus consistent with 11 weeks 5 days with no cardiac activity was detected in the uterus using ultrasonography. In addition, an arcuate uterus was observed. The patient was hospitalized for medical termination. The patient received a single dose of misoprostol 400 μg vaginally. Six hours later, she had severe abdominal pain. Her blood pressure was 100/60 mmHg, and the pulse rate was 96 beats per minute. Her abdomen was distended with guarding and rebound tenderness. The patient also had chest pain. Transvaginal ultrasonography was performed and an intrauterine gestational sac was seen. A prior cesarean scar was intact and a 9 cm deep free fluid collection was observed in the perisplenic and perihepatic spaces. Her hemoglobin concentrations decreased from 9.4 g/dL to 7.8 g/dL within two hours. Emergency laparotomy was performed.

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Answer

Intraoperatively, uterine fundus rupture 4 cm in length was seen (Figure 1). The ruptured area was occupied by a clot and the gestational sac was still in the uterus and was successfully suctioned. Approximately 1000 mL blood collection was drained during the operation. The site of rupture was repaired using continuous 1-0 absorbable sutures. A single unit of packed red blood cells and one unit of fresh frozen plasma were transfused during laparotomy. An additional unit of red blood cells was given postoperatively. The patient was stable after the surgery and was discharged five days later.

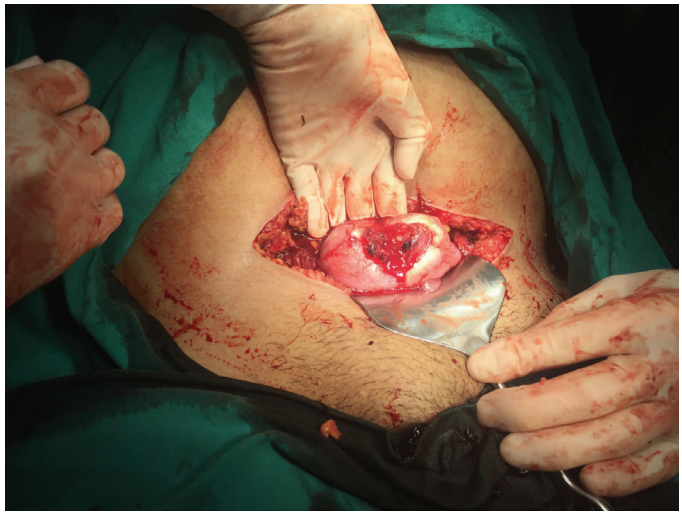

Figure 1. Intraoperative view of the uterine fundus rupture

There are guidelines for termination of pregnancy with misoprostol; however, there is no certain management on the route or dosage of misoprostol in patients with prior cesarean. The International Federation of Gynecologists and Obstetricians recommends misoprostol use for missed abortion with a dose of 800 μg vaginally every 3 hours before the 13th week of gestation (1). Despite the lack of data about the safety of misoprostol, uterine rupture is one the major concerns for administration of the drug for termination of pregnancy especially for the second and third trimester. The incidence of rupture varies from about 1:1000 to 1:20,000 labors, and most of them were associated with a prior C-section (2). Management of uterine rupture is not certain because data on the management of uterine rupture in early pregnancy are limited and differ due to patient status. In general, hysterectomy is performed by reason of clinical condition. In the literature, there are some reports about conservative surgical repair of uterine rupture. An article by O'Connor and Gaughan (3) described pregnancies in patients in whom repair of a ruptured uterus had been performed previously. Seventeen of 18 pregnancies had a successful outcome and no cases of recurrent rupture were observed.

Address for Correspondence: *Fatih Aktoz*
e.mail: fatihaktoz@gmail.com ORCID: orcid.org/0000-0003-3210-849X

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Cases of uterine rupture have been reported in early gestation even if small doses of misoprostol were given. For example, Jwarah and Greenhalf (4) and Kim et al. (2) reported two cases in 2000 and 2005, respectively. In both cases, uterine rupture was observed in first trimester of pregnancy following misoprostol use in women with prior C-sections. The case reported by Kim et al. (2) was interestingly similar to our case because uterine rupture existed in a horn and not the previous cesarean scar. In that case, it was said that the reason of uterine rupture could be misoprostol administration and local thin myometrium, not the previous caesarean scar. In 2006, Hidar wrote a letter to the editor about this case report and speculated about the possibility of ectopic pregnancy in the tubal interstitium (5). In view of the eccentric location of the gestational sac, the thin myometrium observed retrospectively by the authors, and the timing of pain after drug administration, this assessment seems reasonable.

This case seems to be the first report of a uterine fundus rupture occurring in the first trimester of gestation in a patient who was given a single vaginal dose of misoprostol.

Sultan Can, Fatih Aktoz

Clinic of Obstetrics and Gynecology, Ağrı State Hospital, Ağrı, Turkey

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Pregnancy and immune thrombocytopenia: New trends

To the Editor,

I've read the article written by Kalaycı et al. (1) with interest. I'd like to emphasize a few points. The term "idiopathic thrombocytopenic purpura" has been abandoned and replaced with "immune thrombocytopenia" following the Vicenza Concensus of 2009. This was as a result of new understanding concerning the pathophysiology of the disease, although the abbreviation "Immune thrombocytopenic purpura (ITP)" remained the same. Also from the diagnosis, up to the first three months, between 3-12 months and after 12 months is now defined as acute, persistent and chronic ITP respectively. The term "primary ITP" should be used unless another condition, such as autoimmune disorders, co-exist. To diagnose ITP, the thrombocyte count should be below $100x10^9$/L (2). ITP is diagnosed in between one and 10 of every 10,000 pregnancies and 30% of cases need therapy. If no other hemostatic abnormality exists, thrombocyte count at delivery should be between 75 to $80x10^9$/L and this view is supported by most guidelines. The "safe" platelet level to prevent post-partum bleeding has been suggested to be $50x10^9$/L in one study similar to yours (3). The American Society of Hematology and International Working group guidelines support intravenous immunoglobulin or corticosteroids as the first line treatment, and they seem to be equally potent in enhancing thrombocyte counts. Intravenous immunoglobulin can achieve a fast but temporary increase in trombocyte counts and is a very useful option for conditions such as delivery or bleeding. Both agents can be given in combination refractory to single agents alone (4). Thrombocyte concentrates should not be used unless there's a potential life threating bleed. Fetal malformation risk restricts the choice for second-line treatment. Azathioprine may be considered to spare steroids. Anti-RhD immunoglobulin, cyclosporine, and rituximab could be good alternatives, as this has been previously reported although they are not routinely used (4). In an experimental study, it was reported that recombinant human thrombopoietin may be a safe and effective option for the treatment of pregnant ITP patients. Recombinant human thrombopoietin (rhTPO) treatment in ITP at pregnancy is reported in murine models. Significant higher platelet counts were noted in rhTPO-treated groups with no teratogenic effects; supporting that it could be a safe and effective option for refractory cases (5). Although all there is much data, the pregnancy-ITP relationship remains to be illuminated with further prospective studies.

İrfan Yavaşoğlu, Atakan Turgutkaya

Department of Hematology, Adnan Menderes University Medical Faculty, Aydın, Turkey

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Address for Correspondence: *Atakan Turgutkaya*
e.mail: atakanturgutkaya@yahoo.com.tr ORCID: orcid.org/0000-0001-8428-4730

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Author's Response

Dear Editor,

Thank you for precious evaluation and suggestions. The terms and abbreviations which we preferred are consistent with the references included in our manuscript. However, this is a kind reminder of the changes in terms, as well as of some innovations in management. We certainly will consider these comments.

Yours sincerely,

Hakan Kalaycı, Gülşen Doğan Durdağ, Şafak Yılmaz Baran, Seda Yüksel Şimşek, Songül Alemdaroğlu, Serdinç Özdoğan, Esra Bulgan Kılıçdağ

Department of Obstetrics and Gynecology, Başkent University Faculty of Medicine, Adana Application and Research Hospital, Adana, Turkey

Ethical and scientific issues of gene-edited twin by clustered regularly interspaced short palindromic repeats Cas9 technology

To the Editor,

In November 2018, He Jiankui, a Chinese biophysicist at Southern University of Science and Technology, announced through an online video that the first gene-edited twin girls were born without chemokine receptor type 5 (CCR5). This had been achieved by using clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 technique and was undertaken because the father was infected with human immunodeficiency virus (HIV). The aim was to create HIV resistant offspring. Although the goal of creating humans with HIV resistant genes seems very reasonable and needs to be appreciated, he did not receive any plaudits but the contrary. This was because he had acted against a number of the fundamental principles of medical practice including "First do no harm", the Nuremberg Code which states that one must not conduct research on humans without animal experiment, and the Helsinki Declaration (HD) concerning human enhancement and intervention in the human embryo (1). The HD is the main ethical document of the World Medical Association, which regulates the ethical norms of all clinical research in all fields globally (1).

This endeavour was criticized by the authorities around the World because gene-edited human embryos using CRISPR-Cas9 has never been approved to reach birth because of the unpredictable side effects, and also because the technique is still imperfect (2). The first question that should be answered by he is how he managed to start and complete this "experiment" on human embryos without any form of ethical committee approval. The weakness of institutional board control and national legal regulations regarding the use of gene-editing technologies in humans might have enabled him to perform this "experiment". However, he acted against basic international rules of scientific research, especially those involving humans. Although he is not a medical doctor, the team must have included a gynecologist to perform oocyte pick-up and this doctor should have informed the authorities and also prevented he from contacting the couple claiming to be the parents of the twins. It remains unclear whether the team obtained informed consent by fully explaining the consequences and possible unpredictable side effects of using CRISPR-Cas9.

There are also major scientific limitations to CRISPR-Cas9 technology. It is not 100% effective for inserting new gene(s) or deleting gene(s) and also might lead to unwanted mutations that are potentially harmful to humans (3). More specifically some scientists have reported concerns about neurological deficits after knockdown of CCR5 by CRISPR-Cas9 (4). The twin girls were claimed to be free of the *CCR5* gene; however, it is known that CCR5 is not the only route that HIV enters cells. Since HIV is not only physically and psychologically debilitating, but culturally and socially devastating too, this case can be considered as a promising option for people infected with HIV (5). They have the right to reproduce and have healthy offspring. Nevertheless, this should be achieved by well-established methods, not by experimental and possibly harmful technologies.

There is an urgent need for legal regulations to control the usage of CRISPR-Cas9 in humans, that both international and national authorities should prepare and adhere to. In Turkey all regulations are based on the HD. We believe that it is very important that all innovative clinical research fields should first be harmonized according to the ethical standards of the HD.

Esra Bilir[1], Emine Elif Vatanoğlu Lutz[2], Mustafa Levent Özgönül[3]

[1]Koç University Faculty of Medicine, İstanbul, Turkey
[2]Department of Medical History and Ethics, Koç University Faculty of Medicine, İstanbul, Turkey

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Address for Correspondence: *Emine Elif Vatanoğlu Lutz,*
e.mail: drvatanoglu@yahoo.com ORCID: orcid.org/0000-0003-3156-4733

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[3]Department of Medical History and Ethics, Akdeniz University Faculty of Medicine, Antalya, Turkey

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Hysteroscopic treatment of symptomatic adenomyoma

Jin Yu[1,2,3], Duo Zhang[1,2,3], Wei Xia[1,2,3], Jian Zhang[1,2,3]

[1]Department of Obstetrics and Gynecology, International Peace Maternity and Child Health Hospital School of Medicine, Shanghai Jiaotong University, Shanghai, China

[2]Institute of Embryo-Fetal Original Adult Disease Affiliated to School of Medicine, Shanghai Jiaotong University, Shanghai, China

[3]Shanghai Key Laboratory of Embryo Original Diseases, Shanghai, China

Abstract

Hysterectomy has been the definitive treatment option for symptomatic adenomyosis and/or adenomyoma when medical or other conservative treatments fail to control the symptoms. Conservative surgery has already developed as an alternative treatment because of patients' increasing desire to preserve their uterus. This video demonstrates a novel hysteroscopic treatment of symptomatic adenomyoma for patients with no desire for fertility. (J Turk Ger Gynecol Assoc 2020; 21: 140-2)

Keywords: Adenomyoma, adenomyosis, hysteroscopy, hysteroscopic surgical procedures

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Introduction

Adenomyosis is a kind of benign gynecologic disorder with the invasion of endometrial glands and stroma in the uterine myometrium, which results in pelvic pain, dysmenorrhea, and menorrhagia (1). The disease may be diffuse or focal with adenomyoma. Hysterectomy has been known as the primary treatment for adenomyosis and/or adenomyoma (2).

Traditionally, adenomyosis would be found incidentally in specimens obtained from uterine biopsies or hysterectomy and/or percutaneous ultrasound-based biopsies. Modern diagnostic imaging techniques, such as magnetic resonance imaging (MRI), which have high accuracy in identifying this kind of pathology, have led to conservative uterine-sparing treatments of adenomyosis and/or adenomyoma becoming efficacious and feasible (3,4).

This video shows the hysteroscopic surgical procedures of two women with adenomyoma (Figure 1) requesting surgical management for the relief of symptoms and the preservation of the uterus, but with no desire for future fertility. These two patients both had heavy menstrual bleeding and severe dysmenorrhea. We used saline solution to dilate the uterine cavity and set the intrauterine pressure at 120 mmHg. The operation was performed with a transcervical resection resectoscope equipped with a 3 mm and 5 mm wide loop. The surgeon dilated the cervix to 9 mm, then used a cutting loop to resect the lesions repeatedly and progressively. With color Doppler ultrasound guidance, the first step was to evaluate the features of the uterine cavity. Then, the surgeon used a cutting loop to progressively resect the lesions (Figure 2). The operation was completed with the appearance of the pink fasciculate structure of the myometrium. Tissue fragments were removed at intervals using ovum forceps. The specimens were sent for histologic analysis (Figure 3).

Follow-up was performed twice at 3-month intervals. The patient menstruated regularly. The postoperative visual analogue scale scores of menstrual blood volume and dysmenorrhea appeared to decline substantially. The uterine volume was evaluated using MRI 6 months later and was reduced by approximately 33%.

Address for Correspondence: *Jian Zhang*
e.mail: zhangjian_ipmch@sjtu.edu.cn ORCID: orcid.org/0000-0003-0365-9022

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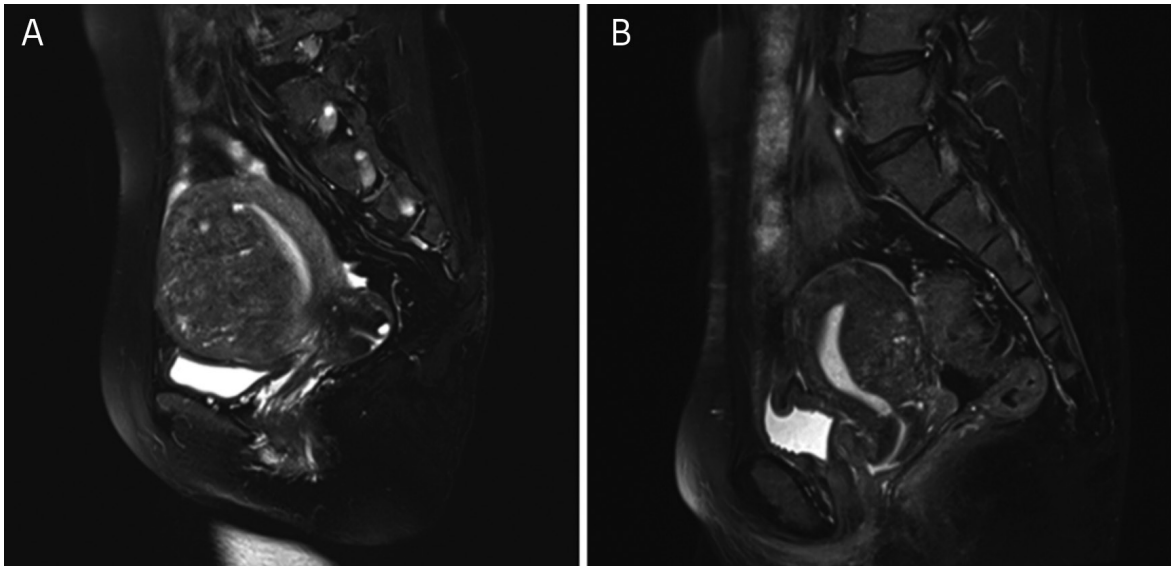

Figure 1. Magnetic resonance imaging imaging of adenomyosis
The adenomyotic lesions in case one were located in the anterior uterine wall (A), and the lesions in case two were located in the posterior wall (B)

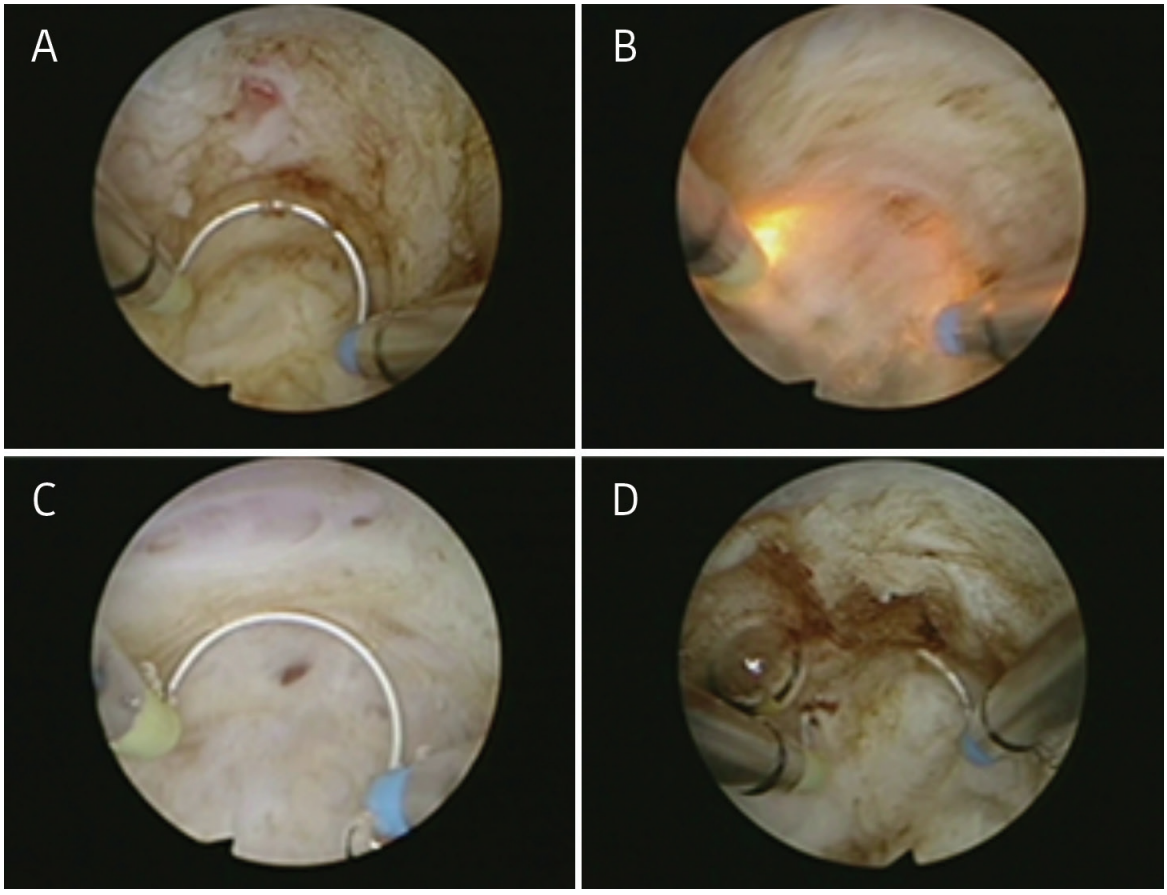

Figure 2. Surgical procedure
In case one, upon cutting the endometrium covering the adenomyotic lesions (A), pink ectopic endometrial lesions in the myometrium were exposed. (B) The ectopic endometrium and adenomyotic lesions were gradually excised from the myometrium. (C) During the resection of lesions, several intramural microcysts with a wide base were revealed. (D) Opening the microcyst resulted in the outflow composed mostly of old blood

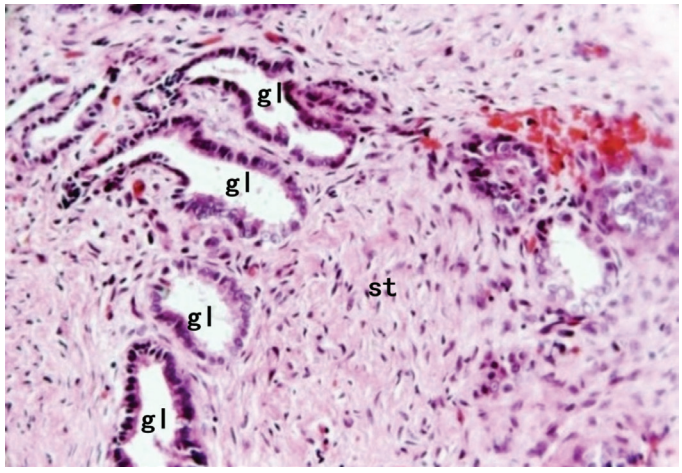

Figure 3. HE staining of adenomyosis
St: Stromal cells, gl: Glands

Uterine perforation is the greatest risk associated with hysteroscopic resection surgery. For the duration of the procedure, the surgeon should pay particular attention to fluid management and prepare with solutions when fluid overload or hyponatremia is suspected. Hysteroscopic excision of uterine adenomyoma has the following benefits: The uterus is preserved and the symptoms of adenomyoma are improved; the minimally invasive operation takes a short time and patients recover quickly. Therefore, hysteroscopic excision can become an effective conservative treatment option for adenomyoma.

Video 1: https://www.doi.org/10.4274/jtgga.galenos.2019.2019.0062.video1

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

September 11-13, 2020	**International Gynecologic Cancer Society (IGCS) 2020 Meeting, Rome, Italy**
October 1-4, 2020	**IFCPC – 2020 – 17th World Congress for Cervical Pathology and Colposcopy, Hyderabad, India**
October 11-14, 2020	**ESGE 29th Annual Congress, Lisbon, Portugal**
October 17-21, 2020	**American Society for Reproductive Medicine (ASRM) 76th Annual Meeting, Portland, United States**
October 17-21, 2020	**30th World Congress on Ultrasound in Obstetrics and Gynecology, Glasgow, United Kingdom**
November 15-19, 2020	**49th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Colorado, United States**
November 19-21, 2020	**World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Berlin, Germany**

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2020.com)

November 4-8, 2020 **9. Üreme Sağlığı ve İnfertilite Kongresi – TSRM, Antalya, Turkey**

Göründüğünden *daha fazlası*[1]

dienille

- *Orta dereceli akne tedavi endikasyonu*[1]
- *Yüksek kontraseptif etkinlik*[2]
- *İyi siklus kontrolü*[2]
- *Dismenorede azalma*[2]

Referanslar: 1. Dienille Kısa Ürün Bilgisi. **2.** Bartsch V. J Med Drug Rev. 2015;5:1-31.

DİENİLLE KÜB ÖZETİ: ÜRÜN ADI: DİENİLLE 2 mg/0.03 mg Film Kaplı Tablet. **FORMÜL:** Her bir film kaplı tablet 2 mg dienogest ve 0,03 mg etinilestradiol içerir. **FARMAKOLOJİ:** ATC kodu: G03FA15. DİENİLLE dienogest (progestojen) ve etinilestradiol (östrojen) içeren, antiandrojenik etkili bir kombine oral kontraseptif (KOK)'tir. **ENDİKASYONLAR:** Oral kontrasepsiyon, orta dereceli akne tedavisi (uygun topikal tedavilerin ve oral antibiyotik tedavilerinin başarısız olması durumunda oral kontraseptif kullanması seçen kadınlarda). **KULLANIM ŞEKLİ VE DOZU:** Tabletler her gün aynı zamanda ve birbirini izleyen 21 gün boyunca alınır. **UYGULAMA ŞEKLİ:** Oral. **KONTRENDİKASYONLAR:** İçeriğindeki maddelerden herhangi birine karşı aşırı duyarlılık; venöz tromboz veya pozitif hasta öyküsü; arteriyel tromboz veya pozitif hasta öyküsü veya prodromal olayların varlığı; arteriyel tromboz için ciddi ya da birçok risk faktörünün varlığı, damarların da tutulduğu diyabet hastalığı, şiddetli hipertansiyon, şiddetli dislipoproteinemi, venöz veya arteriyel trombozun kalıtsal veya edinilen yatkınlığının göstergesi olabilecek biyokimyasal faktörler, sigara kullanımı, ağır karaciğer hastalığı veya pozitif hasta öyküsü (karaciğer fonksiyon değerleri normale dönmemişse), karaciğer tümörü veya pozitif hasta öyküsü; bilinen veya şüphelenilen steroid bağımlı tümörler; tanı konulmamış vajinal kanama; fokal nörolojik belirtili migren öyküsü; geçmişte yaşanan pankreatit veya ağır hipertrigliseridemi; ağır veya akut böbrek yetmezliği, uzun süreli immobilizasyon gerektiren önemli ameliyat. **ÖZEL KULLANIM UYARILARI VE ÖNLEMLERİ:** DİENİLLE kullanımından önce olası dolaşım bozukluğu risklerine karşı KOK tedavisi dikkatlice tartışılmalıdır. Herhangi bir KOK kullanımı, kullanılmadığı durum ile karşılaştırıldığında venöz tromboemboli riski artar. Bazı epidemiyolojik çalışmalarda uzun süre KOK kullanımının servikal kanser riskinde artışa neden olabileceği bildirilmiştir, ancak bu bulguların KOK kullanımının hangi etkilerine bağlı olabileceği halen tartışılmaktadır. Kendisinde ya da aile öyküsünde hipertrigliseridemi olan kadınlarda, KOK kullanımı sonucu pankreatit riski artabilir. Hormonal kontraseptif kullanımında depresif duygudurumu ve depresyon sık görülen yan etkilerdir. Depresyon ciddi olabilir ve intihar için iyi bilinen bir risk faktörüdür. Duygudurum dalgalanmaları ve depresif semptomlar olması halinde, bu semptomlar tedavinin başlamasından kısa bir süre sonra ortaya çıksa dahi hastalara doktorlarına başvurmaları önerilmelidir. **İLAÇ ETKİLEŞİMLERİ VE GEÇİMSİZLİKLER:** Herhangi bir geçimsizlik yoktur. Diğer ilaçlar ile arasındaki etkileşmeler ara kanamaya ve/veya kontraseptif potansiyel kaybına yol açabilirler. Bu etkiler karaciğer enzim indüksiyonunu arttıran hidantoin, barbitüratlar, primidon, karbamazepin ve rifampisin durumunda gösterilmiş olup; rifabutin, efavirenz, nevirapin, okskarbazepin, topiramat, felbamat, ritonavir, nelvinafir, griseofulvin ve St. John's wort içeren bitkisel ilaçlar için geçerlidir. Antibiyotik tedavisi (rifampisin ve griseofulvin dışında) alan kadınlar, ilacın sonlanmasını takiben 7 gün boyunca bariyer yöntemi kullanmalıdırlar. **GEBELİK VE EMZİRME:** Gebelik kategorisi: X. Gebelik döneminde kontrendikedir. Kullanımı sırasında gebelik meydana gelirse kullanım durdurulmalıdır. Emzirme döneminde kullanılmaması tavsiye edilir. **ARAÇ VE MAKİNE KULLANIMI:** Herhangi bir etkisi bulunmamaktadır. **İSTENMEYEN ETKİLER:** KOK kullanan kadınlarda venöz ve arteriyel tromboemboli (örn. Venöz tromboz, pulmoner emboli, inme, kalp krizi) riski vardır. Sigara, hipertansiyon, kan pıhtılaşması ve lipid metabolizması bozuklukları, ağır obezite, varis, gelişmiş flebit ile tromboz gibi faktörler venöz ve arteriyel tromboemboli riskini artırabilir. Yaygın: Baş ağrısı, karın bölgesinde ağrı, göğüslerde hassasiyet veya ağrı. **DOZ AŞIMI VE TEDAVİSİ:** Dienogest ve etinilestradiolün akut oral toksisitesi düşüktür. DİENİLLE küçük bir çocuk tarafından önemli miktarda alındığı zaman, toksik semptomların gelişiminin olasılığı düşüktür. Doz aşımı mide bulantısı ve kusma ile genç kızlarda çekilme kanamasına neden olabilir. Özel tedaviye gerek yoktur. Gerekirse semptomatik tedavi uygulanmalıdır. **RAF ÖMRÜ VE SAKLAMA KOŞULLARI:** 36 ay-25°C'nin altındaki oda sıcaklığında saklayınız. **TİCARİ TAKDİM ŞEKLİ:** PVC/PVDC-Alu blisterde, 21 film kaplı tablet. **FİYATI:** 62,23 TL (Şubat 2020 itibariyle). **ÜRETİM YERİ:** Laboratorios Leon Farma S.A.La Vallina s/n. Polígono Industrial Navatejera 24008, Leon İSPANYA. **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:** 16.02.2015-2015/136. **Güncel KÜB Tarihi:** 23.05.2019 **REÇETE İLE SATILIR. Kısaltılmış KÜB güncellenme tarihi:** 25.02.2020 **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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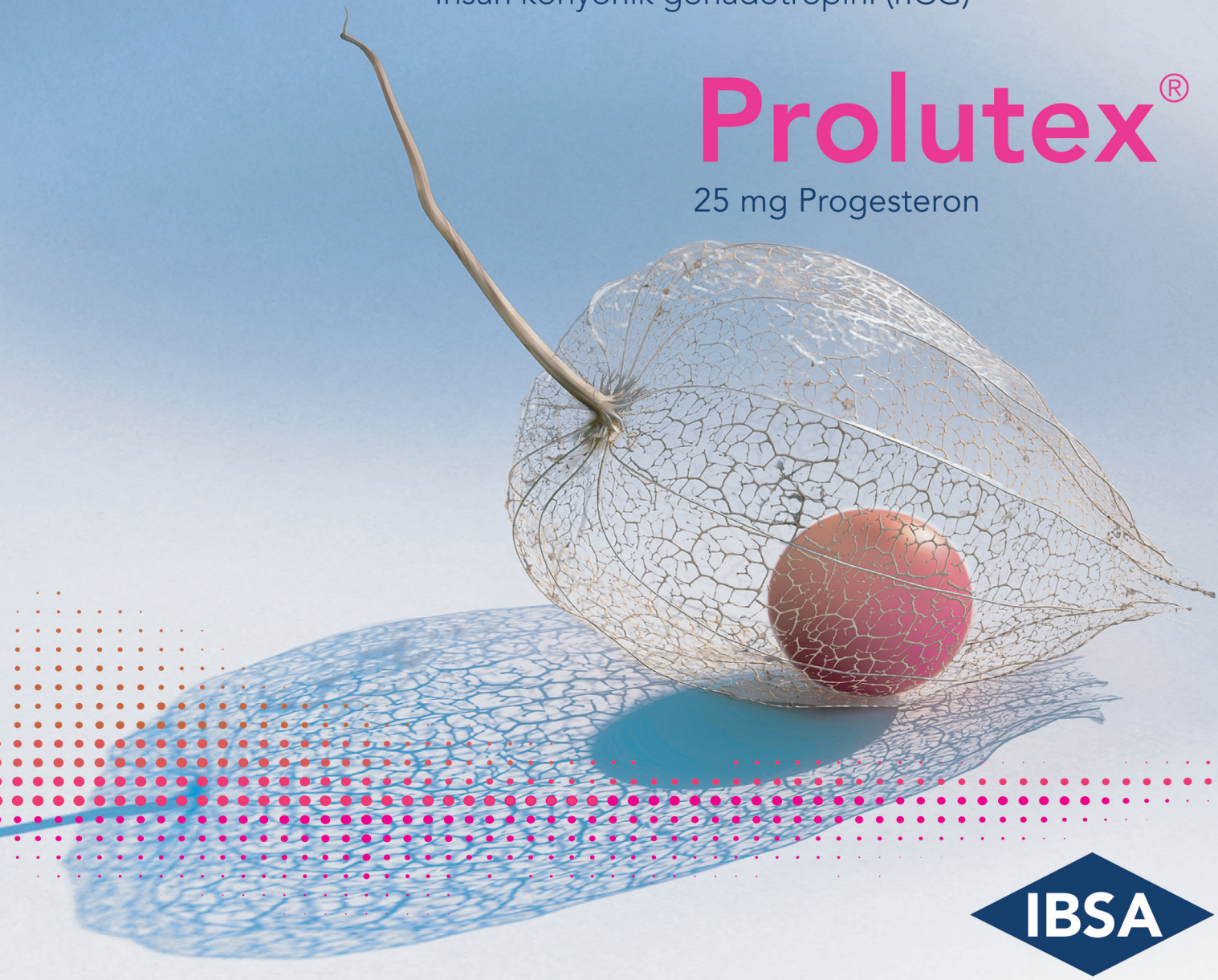

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