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ARVELES®

DEKSKETOPROFEN TROMETAMOL

ARVELES® TABLET

- Hafif ve orta şiddetteki ağrıların semptomatik tedavisinde,

ARVELES® AMPUL IM/IV

- Postoperatif ağrı
- Renal Kolik
- Bel ağrısı

gibi orta ve ağır şiddetteki akut ağrıların semptomatik tedavisinde kullanılan

bir ağrı kesicidir...



REFERANSLAR 1- ARVELES® Tablet / ARVELES® Ampul Ürün Bilgi

ARVELES®
FORMÜL: Her bir tablet 25 mg deksketoprofenü (INN) tekabül eden 36,9 mg deksketoprofen trometamol ve titanyum dioksit (E 171) içerir. Her bir 2 ml'lik ampul 50 mg deksketoprofen'e eşdeğer 73,8 mg deksketoprofen trometamol, 200 mg etanol (%96), 8 mg sodyum klorür, sodyum hidroksit çözücü, enjeksiyonluk su 0,4, 2 ml iğne, **FARMAKOLOJİK ÖZELLİKLER:** Deksketoprofen trometamol, steroid olmayan antiinflamatuar ilaç grubuna dahil analjezik, antiinflamatuar ve antipiretik bir ilaçtır. **ENDİKASYONLAR:** ARVELES® 25 mg Tablet: Muskül-skeletal ağrı, diş ağrısı, postoperatif ağrı gibi hafif ve orta şiddetteki ağrıların semptomatik tedavisinde kullanılır. ARVELES® 50 mg Ampul: Oral kullanımı uygun olmadığı postoperatif ağrı, renal kolik ve bel ağrısı gibi orta ve ağır şiddetteki akut ağrıların semptomatik tedavisinde kullanılır. **KONTRENDİKASYONLAR:** ARVELES® Tablet ve Ampul aşağıdaki durumlarda uygulanmazlar: Deksketoprofene, diğer NSAİİ'leri veya ürünlere herhangi bir yardımcı maddesine karşı daha önce duyulan alerjik hastalıklar • Menstrüel ağrı (Oral, Aspirin veya diğer NSAİİ'leri bileşimlerini içeren, trombosetazam, akut miokardiyal infarktüsü veya nazal polipoid, ürtiker veya anjiyödem). Ödem neden olduğu hastalar • Akut veya şiddetli gastrointestinal ülseri olan veya gastrointestinal ülser veya kronik dispeziye eğilimli olan hastalar • Gastrointestinal kanama veya diğer ağız kanamaları veya kanama bozukluğu olan hastalar • Crohn hastalığı veya ülseratif kolit olan hastalar • Şiddetli kalp yetersizliği olan hastalar • Orta veya şiddetli böbrek fonksiyon bozukluğu olan hastalar • Şiddetli karaciğer fonksiyon bozukluğu olan hastalar • Hemorajik diatezi veya diğer pıhtılaşma bozukluğu olan veya antikoagulan tedavisi gören hastalar • Bronşiyal astım geçmişi olan hastalar • Gebelik ve laktasyon dönemlerinde ARVELES® Ampulün, etanol içeriğinden dolayı nörolojik (nötralek veya epürasi) veya epürasiyi önlemek için kortikosteroidler, ÖZEL UYARILAR ve ÖZEL KULLANIM TEDBİRLERİ: Çocuklarda kullanılmaya uygun değildir. Alerji hikayesi olan hastalarda kullanılmaya dikkatli olunmalıdır. Deksketoprofen trometamol ilacı hastalarda enjeksiyonlu olarak gastrointestinal kanama veya ürtikeri tetikleyebilir, tedaviye hemen son verilmelidir. NSAİİ'ler, trombozisi ağırlaştırabilir, kanama süresi uzatabilirler. Numaralı tedavi alan hastalar dikkatli izlenmelidir. Tüm NSAİİ'ler plazma üre azaltıcı ve kreatinin artırabilir. Bu hastalarda renal fonksiyonlar izlenebilir ve sıvı retansiyonu ile sonuçlanabilir. Nefrotoksik riskinde artma olması nedeniyle diüretik tedavi gören hastalar ile hipovolemik olabilecek hastalarda da dikkat gerektirir. Kalp yetersizliği tedavileri ne artılabileceğinden, kalp hastalığı hikayesi bulunan hastalarda özel dikkat gösterilmelidir. Tüm NSAİİ'ler infarkiyoz hastalarını semptomlarını maskelenebilir. Yaşlı hastalar, istemeyen etkilere daha fazla duyarlıdır ve sonuçlar daha ciddi olabilir. Yaşlı hastalarda hepatic ve renal fonksiyonlar izlenmelidir. Hemopoetik bozukluklar, sistemik lupus eritematozus veya karışık bağ dokusu hastalığı olan hastalarda dikkatli kullanılmalıdır. **Gebelik ve Laktasyonda Kullanım:** Gebelik Kategorisi: C. ARVELES® Tablet ve Ampul hamilelik ve laktasyonda kullanılmamalıdır. **ARAC ve MAKİNE KULLANMAYA ETKİSİ:** Baş dönmesi ve uykulama olasılığı nedeniyle makine veya araç kullanma yeteneği üzerinde hafif veya orta şiddette etkiler oluşturabilir. **YAN ETKİLER/ADVERS ETKİLER:** ARVELES® Tablet ile 1%-10% sıklıkta görülen istemeyen etkiler, bulantı ve veya kusma, abdominal ağrı, diyare, dispepsi ve Ampul için bulantı, kusma, enjeksiyon yeri ağrısıdır. Sık olmayan (%0,1-1%) yan etkiler: uykusuzluk, anksiyete, baş ağrısı, baş dönmesi, vertigo, palpasyonlar, gastrit, konstipasyon, ağız kuruluğu, göz çirkinliği, saç çıkarma, cilt döküntüleri, yorgunluk, acık basması, akciğer, asteni, rigörler, hasta hissetmeçdir. Ayrıca ender olarak (%0,01-0,1) parestizi, hipertansiyon, periferik ödem, bradipnisi, pektik ürtikerasyon, hemorajik veya perforasyon, anoreksi, hepatic enzimlerde artma, ürtiker, alerji, terleme, artma, polidüri, diside menstruel bozukluklar; erkeklerde prostatik bozukluklar, sırt ağrısı, senkop ve çok ender-izole olarak da (%0,01) nöbetleri, trombotisitemi, görme bulanıklığı, tinnitus, taşikardi, hipotansiyon, bronkopnözis, dispezi, pankreas hasarı, karaciğer hasarı, şiddetli mükoskitisizoz cilt reaksiyonları (Stevens-Johnson, Lyell sendromları), anjiydem, dermatolitik reaksiyonlar, fotosensibilite reaksiyonları, pruriti, böbrek hasarı (nefrin veya nefrotik sendrom), anafilaksi, feşyal ödem bildirimleri bulunmaktadır. Belirgin olarak sistemik lupus eritematozus veya karışık bağ dokusu hastalığı olan hastalarda olası bir aseptik menenjit ve hematolojik reaksiyonlar (purpura, aplastik ve hemolitik anemi, ve ender olarak agranülozite ve medullar hiperplazi), BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. **İLAC ETKİLEŞİMLERİ ve DİĞER ETKİLEŞİMLER:** Aşağıdaki etkileşimler genellikle tüm steroid olmayan antiinflamatuar ilaçlar (NSAİİ) için geçerlidir. Önerilmeyen kombinasyonlar: • Salisilatlar, diğer NSAİİ'ler • Oral antikoagulanlar, parenteral heparin ve lidopidin • Litium • Metotreksat • Hidantoinler ve sulfonamidler. **KULLANIM ŞEKLİ ve DOZU:** ARVELES® Tablet: Genel Popülasyon: Ağrıdan önce ve şiddetine göre önerilen doz genellikle her 4-6 saatte bir 12,5 mg veya 8 saatte bir 25 mg'dir. Postoperatif ağrı tedavisinde önerilen doz her 8 saatte bir 25 mg'dir. Günlük toplam doz 75 mg'yi geçmemelidir. ARVELES® Ampul: Yetişkinlerde: Tavsiye edilen doz her 8-12 saatte bir 50 mg'dir. Günlük maksimum doz olan 150 mg'yi aşmamak şartıyla, 6 saat aralığı uygulanabilir. ARVELES® Tablet ve 50 mg/2 ml Enjektabl Çözelti İçeren Ampul, kısa süreli kullanımı için ve tedavi akut semptomatik dönem ile sınırlanmalıdır (Ampul için maksimum 2 gün). **Uygulama Yöntemi:** IM uygulaması 1 adet ampul iğne ile iğne derisi ve yavaş bir enjeksiyon ile verilmelidir. IV uygulaması: IV infüzyon bir ampul 2 ml iğne ile normal NaCl, glukoz veya ringier laktil solüsyonu ile 30 ila 100 ml hacim dışı katmanca şekilde seyreltilmelidir. 10 ila 30 dakika arası bir sürede yavaş bir şekilde damar içine infüzyon ile verilmelidir. Solüsyon damar direkt püresi uygulanmaz. **IV/DOZ:** Genel ilacı, bir ARVELES® 50 mg/2 ml Enjektabl Çözelti İçeren Ampul iğne 15 saniyeden uzun bir sürede veya IV bolus ile verilmelidir. **DOZ ASIMI:** Kazara veya fazla alınmış, acilen semptomatik tedavi uygulanmalı ve gerekirse mide yıkanmalıdır. Deksketoprofen trometamolü diyalize uzaklaştırılmaz. **SAKLAMA KOŞULLARI:** 30°C'nin altında ve oda sıcaklığında, ısktan korunacak şekilde saklayınız. Çocukların ulaşamayacağı yerlerde ve ambalajında saklayınız. **TICARI TAKDİM ŞEKLİ ve AMBALAJ İÇERİĞİ:** 20 film kaplı enjektabl tablet, 2 ml Enjektabl çözelti içeren cam ampuller (6 ampul), **RUNSAT SAHİBİNİN İSİMİ ve ADRESİ:** ÜRSA İlaç Sanayi Tic. A.Ş., Davutpaşa Cad. No: 12, 34472 Topkapı-İSTANBUL, Tel: (0212) 467 11 11, Faks: (0212) 467 12 12, **RUNSAT TARİHİ ve NUMARASI:** ARVELES® Tablet: 30/12/2003-116/18. ARVELES® Ampul: 29/12/2006-121/57, **KDV DAHİL PERAKENDE SATIŞ FİYATI:** ARVELES® Tablet: 12,56 TL, ARVELES® 6 Ampul: 17,17 TL, **ÜRETİM YERİ ve ADRESİ:** ARVELES® Tablet A, Menarini Industrie Sud S.r.l., Via Campo di Pile - 61100 L'Aquila-ITALYA, / Laboratorios Menarini SA Alfonso XII, 587 0918 Barcelona - İspanya, ARVELES® Ampul A, Menarini Manufacturing Logistics And Services S.r.l., Via Sette Santi, 3, Fioransa-ITALYA, Reçete ile satılır. Ayrıntılı bilgi için prospektüse bakınız. Daha geniş bilgi için firmamıza başvurunuz, **PROSPEKTÜS**

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Hayata Kesintisiz Devam...



Günde 2 Tablett



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Cover Picture: Picture of a Didelphic uterus as seen during laparoscopy". With Permission of Assoc. Prof. Cemil Yaman, Austria.

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A-I

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FERLOS®

Demir (III) Hidroksit Polimaltoz Kompleksi

Anemi
tedavisini keyfe
dönüştürür!



Santa  Farma

İlacın ticari adı: Ferlos® Oral Solüsyon
Etkin maddenin onaylanmış jenetik adı: 100 mg elementer demire eşdeğer demir (III) hidroksit polimaltoz kompleksi. Bileşimindeki etkin maddelerini birim dozdaki miktarları: Her bir oral flakon (5 ml); etkin madde olarak 100 mg elementer demire eşdeğer demir (III) hidroksit polimaltoz kompleksi, tatlandırıcı olarak şeker ve sorbitol, koruyucu olarak sodyum metilhidroksibenzoat, sodyum propilhidroksibenzoat ve ayrıca krema esansı ile karamel esansı içerir. Güncelleştirilmiş KÜB'e uygun ruhsatlandırılmış endikasyonu: Özellikle demir eksikliği anemisi başta olmak üzere tüm latent ve belirgin demir eksikliğinin tedavisinde kullanılır. Kullanış şekli ve dozu: Ferlos® Oral Solüsyon, yemekler sırasında veya hemen yemekten sonra alınmalıdır. Çocuklar (1-12 yaş), erişkin ve yaşlılar: Latent demir eksikliği: Günde 1/2-1 flakon (50-100 mg) Ciddi demir eksikliği: Günde 2-3 defa 1 flakon (200-300 mg) Tedavi süresi, demir metabolizmasının durumuna (azalmış akm, arkan ihtiyacı, patofizyolojik kayıp ve eritrosit sayısının normalleşmesine bağlıdır. Belirgin demir eksikliğinde normal kan değerlerine ulaşmak ortalama 3-5 aylık tedavi ile olur. Latent demir eksikliğinde tedavi süresi 1-2 aydır. Hb konsantrasyonunun normale döndürülmesinden sonra depoların dolması için 2-3 aylık süre boyunca her gün 1 flakon içilmesi gereklidir. Uygulanması: Oral yolla uygulanır. Başlıca yan etkiler ve alınması gereken önlemler: Demir (III) hidroksit polimaltoz kompleksindeki demir (III) esasen non-iyonik olduğundan Ferlos® Oral Solüsyon ile iyonize demir tuz preparatlarında görülen gastrointestinal irritasyona, epigastrik ağrıya, bulantı, diare, kabızlık gibi istenmeyen etkiler nadirdir. Başlıca etkileşimleri: Demir (III) hidroksit polimaltoz kompleksindeki demir (III), kompleks yapmış olduğundan yiyeceklerdeki bileşenlerle (tali, oksalat, tanen) ve birlikte uygulanan ilaçlarla (tetrasiklin, antiasidler) iyonik etkileşime girmez. Buna karşın demir iyonları (ferroz iyonları), yukarıda sayılan maddelerle çözünmeyen keller oluşturarak demir emilimini azaltır. Dişlerde diş kan araması sırasında yanığa neden olmaz. Bu nedenle, bu ilaçlama sırasında tedavinin kesilmesini gerek yoktur. Kontraindikasyonları, uyarılar ve dikkat edilmesi gereken durumlar: Kontraindikasyonları: Demir yüklenmesi bulgularında veya demirin kullanımında bir bozukluğun söz konusu olduğu durumlarda (örneğin hemokromatoz, hemosideroz, kurşun anemisi, sidere akrestik anemi, talasemi), demir eksikliğinin nedeni otoimmün anemiler (örneğin hemolitik anemi), Uyarılar/Önemli: İnfeksiyöz veya kansere bağlı oluşan anemilerde demir, retiküloendotelial sistemde depolanmakta ve ancak primer hastalığın tedavisine mobilize olmakta ve kullanılmaktadır. Oral demir preparatlarının kullanımı sırasında dişlerin rengi koyulaşabilir; bu durum, normal olup herhangi bir önlem gerektirmez. İmalatçının ismi ve adresi: SANTA FARMA İLAÇ SANAYİ A.Ş. 34382 Şişli - İSTANBUL. Ruhsat tarihi ve numarası: 31.01.2006 - 207/15. "Diğer genetik bilgi için firmamıza başvurunuz." Reçete ile satılır. Prospektüsün son güncellenme tarihi: 04.12.2007. Perakende satış fiyatı (K.D.V. dahil) ve onay tarihi: 16,93 TL (20 Nisan 2009).

İlacın ticari adı: Ferlos® Çiğneme Tableti
Etkin maddenin onaylanmış jenetik adı: 100 mg elementer demire eşdeğer demir (III) hidroksit polimaltoz kompleksi ve 0,35 mg folik asit Bileşimindeki etkin maddenin birim dozdaki miktarları: Her bir çiğneme tableti, etkin madde olarak 100 mg elementer demire eşdeğer demir (III) hidroksit polimaltoz kompleksi ve 0,35 mg folik asit; tatlandırıcı olarak aspartam ve dekstral ile çikolata aroması ve karamel aroması içerir. Güncelleştirilmiş KÜB'e uygun ruhsatlandırılmış endikasyonu: Latent ve manifest demir eksikliğinin tedavisinde, ayrıca gebelik boyunca, gebelik öncesinde ve sonrasında (laktasyon döneminde) görülen demir ve folik asit eksikliği engellenmede etkilidir. Kullanış şekli ve dozu: Manifest demir eksikliği: Hemoglobin değerleri normal değerlere ulaşana kadar günde 2-3 kez birer tablet, daha sonra demir depolarının doldurulması amaçlı ile gebelik boyunca günde 1 tablet. Latent demir eksikliği ve demir/folik asit eksikliğinin engellenmesi: Günde 1 tablet. Ferlos® Çiğneme Tableti'nin yemek sırasında veya yemekten sonra çiğnenmesi ve üzerine bir yudum sıvı alınması önerilir. Röntgenimleri SÜTÜYLE biraz sıvı ile yutmak mümkündür. Demir depolarını doldurmak için, kan parametrelerinin (Hb, Hct, eritrosit) normale dönüştürülmesi yaklaşık bir ay zamanına kadar tedavi sürdürülmelidir. Uygulanması: Oral yolla uygulanır. Başlıca yan etkiler ve alınması gereken önlemler: Çok ender olarak tokluk hissi, epigastrik ağrı, kabızlık, bulantı, kabızlık ve ishal gibi yan etkiler görülebilir. İlacın kesilmesiyse bu şikayetler kaybolur. Dişlerde görülebilecek koyu rengin klinik olarak hiçbir önemi yoktur. Başlıca etkileşimleri: Demir (III) hidroksit polimaltoz kompleksi, kompleks halinde ve iyonik olmayan demir içerdiğinden besinlerde bulunan unsurlarla (tali, oksalat, tanenler gibi) veya aynı zamanda verilen ilaçlarla (tetrasiklinler, antiasitler gibi) etkileşime girmez. Ferlos® Çiğneme Tableti, dişlerde boyanmaya sebep olmaz. Dişlerde diş kan araması sırasında yanığa neden olmaz. Bu nedenle bu inceleme sırasında tedavinin kesilmesini gerek yoktur. Kontraindikasyonları, uyarılar ve dikkat edilmesi gereken durumlar: Kontraindikasyonları: Organizmaya aşırı doza demir yüklenmesi Hemokromatoz, hemosideroz, demir kullanımı bozuklukları (kurşun anemisi, sidere akrestik anemi, talasemi) B12 vitamini eksikliğine bağlı megaloblastik anemi ve hemolitik anemilerde kullanılmamalıdır. Uyarılar/Önemli: Çocuklar tarafından yanlışlıkla fazla miktarda ilacın alınması akut demir zehirlenmesine neden olabileceğinden, ilaç, çocukların erişemeyeceği yerlerde saklanmalıdır. Enfeksiyöz ya da kansere bağlı anemilerde yerine konulan demir, retiküloendotelial sistemde depolanır ve ancak primer hastalığın tedavisi dışında kullanılabılır. Her bir tabletin 0,04 dilim şeklinde eşdeğer olduğu diyabetiklerde dikkate alınmalıdır. İmalatçının ismi ve adresi: SANTA FARMA İLAÇ SANAYİ A.Ş. 34382 Şişli - İSTANBUL. Ruhsat tarihi ve numarası: 14.01.2006 - 201/15. "Diğer genetik bilgi için firmamıza başvurunuz." Reçete ile satılır. Prospektüsün son güncellenme tarihi: 16.08.2006. Perakende satış fiyatı (K.D.V. dahil) ve onay tarihi: 12,59 TL (20 Nisan 2009).

Journal of the Turkish-German Gynecological Association

Aims and Scope

Journal of the Turkish-German Gynecological Association is an official journal of the Turkish-German Gynecological Education and Research Foundation, Turkish-German Gynecological Association and the Turkish Society of Reproductive Medicine and is published quarterly on March, June, September and November.

The target audience of Journal of the Turkish-German Gynecological Association includes gynaecologists and primary care physicians interested in gynecology practice. It publishes original work on all aspects of gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor and case presentations are also published.

It is an independent peer-reviewed international journal printed in English language. Manuscripts are refereed in accordance with "double-blind peer reviewed" process for both referees and authors.

Papers written in English language are particularly supported and encouraged.

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FORMÜLÜ: Triptorelin asetat ENDİKASYONLARI: IVF, Endometriyozis, uterus miyomu KONTRENDİKASYONLARI: Klinik olarak belirgin osteoproz ya da osteoproz riski (örn. Azalmış kemik yoğunluğu), Hamilelik , Laktasyon Yardımlı üreme tekniklerinde kullanımında; özellikle polistik overli hastalarda, ultrasonografi ile tespit edilen folliküller 10' dan fazla olduğunda Decapeptyl kullanımında önlemlerin sayısı artırmaktadır. Triptorelin, poli (DL-laktid-ko-glükolid), dekstran veya diğer herhangi bir bileşene duyarlılık gösteren kişilerde kontrendikedir. UYARILAR/ ÖNLEMLER: Tedavi seks steroidlerinin serum düzeylerine göre ayarlanmalıdır. Özellikle polistik overli olanlarda aşırı uyanımlı olmak için folliküler büyüme ve luteal faz dikkate izlenmelidir. Tedavinin önce gebelik durumu kontrol edilmelidir. Tedavinin ilk ayında kadınlar hormonal olmayan kontraseptifler kullanmamalıdır. Decapeptyl® tedavisi sırasında kadınlar östrojen preparatı kullanmamalıdır. Uterus miyomu tedavisi sırasında uterusun ve miyomun boyutları, örneğin ultrasonografi ile düzenli olarak ölçülerek takip edilmelidir. Az sayıdaki vakada, miyom dokusuna göre orantısız olarak uterus hacminin hızla küçülmesi, kanamaya ve sepsise neden olmuştur. Gebelik ve laktasyon: Gebelikte kullanım kategorisi X. Gebelik ve laktasyon döneminde kesinlikle kullanılmaz. ARAÇ VE MAKİNA KULLANIMINA ETKİSİ: Araç ve makina kullanımına hiçbir etkisi yoktur. YAN ETKİLER/ ADVERS ETKİLER: Hormon üretiminin baskılanması sonucu en çok sıcak basması olmak üzere %75-100 hastada yan etkiler görülebilir. Kanama veya deride lekelenme, terleme, vajinal kuruma ve veya disparoni, libido azalması ve ruh hali değişiklikleri kadınların %10'unda görülür. Depresif ruh hali, bulantı, miyali, artirajli, yorgunluk; uyku bozuklukları; aşırı duyarlılık reaksiyonları (kasıntı; cilt döküntüsü; ateş), uygulama noktasında geçici ağrı ve nadir olarak serum kolesterol düzeyinde hafif artış görme bozuklukları; parestezi , sırt ağrısı, yükselmiş enzim seviyeleri (LDH ,GT, SGOT, SGPT), anafiksisi, uygulama noktasında yabancı vücut reaksiyonu gözlenmiştir. Hafif trabekül kemik kaybı görülebilir. Bu durum, tedavinin kesilmesinin takiben 6-9 ay içinde genellikle geçer. Triptorelin kullanımında iki epifizyolizis capitis femoris vakası bildirilmiştir. Nedenleşmiş bir ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. İLAÇ ETKİLEŞİMLERİ ve DİĞER ETKİLEŞİMLER: Östrojen içeren hiçbir ilaçta birlikte kullanılmamaktadır. KULLANIM ŞEKLİ ve DOZU: Mutad doz, 7 gün süreyle 0.5 mg' dir ve deri altına zerkedilir. Daha sonra idame dozu, 0.1 mg uygulanır. IVF'te dozaj uygulanan protokole göre değişir. Genellikle, siklusluk folliküler fazı ilk gündünden itibaren hCG uygulamasına kadar günde 0.1mg (kisa protokol) siklusluk folliküler fazı ilk gününden itibaren hCG uygulamasına kadar üç gün 0.1mg'dir (çok kısa protokol). SAKLAMA KOŞULLARI: Decapeptyl® 0.1mg buzdolabında (2-8°C) saklanmalıdır. Tek kullanımlık enjektörler ambalajı içinde ve ışıkta korunarak saklanmalıdır. TİCARİ TAKDİM ŞEKLİ ve AMBALAJ MUHTEVASI: Decapeptyl® 0.1 mg; 1 ml solüsyon içeren, kullanıma hazır 7 sıringalık kutularda RUHSAT SAHİBİ: FERRING İlaç San. Tic. Ltd. Şti. Büyükdere Cad. Nuru Plaza, No: 71 A Blok Kat 13, Maslak / İstanbul RUHSAT TARİHİ ve NO: 02.11.2006 ve 121/7 KDV DAHİL PERAKENDE SATIŞ FİYATI: 127,27 TL (Nisan 2009 itibarıyla). ÜRETİM YERİ: Ferring GmbH Kiel, Almanya REÇETE İLE SATILIR. Ayırtılı bilgi için lütfen firmamıza başvurunuz.

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FORMÜLÜ: Triptorelin asetat (3.75 mg triptorelin'e eşdeğer) ENDİKASYONLARI: Uterus miyomları ve endometriyozis, overyen hormon yapımının baskılanması gereken durumlarda. Yardımlı üreme teknikleri: Luteal fazda premature LH piderinin önlenmesi; folliküler fazda ise flare-up etkisinden yararlanmak amacıyla. KONTRENDİKASYONLARI: Klinik olarak belirgin osteoproz ya da osteoproz riski (örn. Azalmış kemik yoğunluğu), Hamilelik , Laktasyon Yardımlı üreme teknikleri: Özellikle polistik overli hastalarda, ultrasonografi ile tespit edilen folliküller 10' dan fazla olduğunda Decapeptyl® Depot kullanımında önlemlerin sayısı artırmaktadır. Triptorelin, poli (DL-laktid-ko-glükolid), dekstran veya diğer herhangi bir bileşene duyarlılık gösteren kişilerde kontrendikedir. UYARILAR/ ÖNLEMLER: Seks steroidlerinin serum düzeyleri belirlenerek tedavinin izlenmesi gerekmektedir. Tedaviye başlamadan önce potansiyel olarak fertli kadınların gebe olmadıkları kesin olarak saptanmalıdır. Hasta tedavi sırasında hormonal olmayan kontraseptifler kullanmalıdır. Endometriyozis veya miyom vakalarında hormonal olmayan kontraseptiflere, adet kanamaları düzene girinceye kadar devam edilmelidir. Decapeptyl® Depot tedavisi boyunca kadınlar, östrojen içeren preparatları kullanmamalıdır. Uterus miyomu tedavisi sırasında uterus ve miyom boyutları ultrasonografi yardımıyla düzenli olarak ölçülmelidir. Rahim hacminin miyom dokusuna kıyasla orantısız olarak hızla küçülmesi bazı vakalarda kanama ve sepsise neden olmuştur. Decapeptyl® Depot tedavisi sırasında adet kanamaları duracaktır. hasta rahatsız menstürasyonun sürmesi halinde doktoruna bilgi vermesi hususunda uyarılmalıdır. Yetişkinlerde ve çocuklarda alerjik ve anafilaktik reaksiyonları görüldüğü bildirilmiştir. Bu reaksiyonlara lokal yan reaksiyonları ve sistemik semptomları her ikisi de dahildir. Patogenez açıklanamamıştır. Çocuklarda görülen reaksiyonların daha sık bildirilmesi nedeniyle DECAPEPTYL® DEPO'T un çocuklarda kullanılmaması önerilir. Gebelik ve laktasyon: Gebelikte kullanım kategorisi X. İnsanlarda yetiştirilmesi amaçlanmadığından tedaviye başlamadan önce hastanın gebe olup olmadığı mutlaka tespit edilmelidir. Decapeptyl® Depot'un laktasyon sırasında kullanımına ilişkin veriler yeterli değildir. ARAÇ VE MAKİNA KULLANIMINA ETKİSİ: Decapeptyl® Depot'un araç ve makina kullanımına hiçbir etkisi yoktur veya ihmal edilebilir düzeydedir. YAN ETKİLER/ ADVERS ETKİLER: Hormon üretiminin baskılanması sonucu en çok sıcak basması olmak üzere (erkeklerde %30 ve kadınlarda %75-100) hastalarda yan etkiler görülebilir. Kanama veya deride lekelenme, terleme, vajinal kuruma ve /veya disparoni, libido azalması ve ruh hali değişiklikleri kadınların %10'unda görülür. Depresif ruh hali, bulantı, miyali, artirajli, yorgunluk; uyku bozuklukları; aşırı duyarlılık reaksiyonları (kasıntı; cilt döküntüsü; ateş), uygulama noktasında geçici ağrı ve nadir olarak serum kolesterol düzeyinde hafif artış görme bozuklukları; parestezi , sırt ağrısı, yükselmiş enzim seviyeleri (LDH ,GT, SGOT, SGPT), anafiksisi, uygulama noktasında yabancı vücut reaksiyonu gözlenmiştir. Hafif trabekül kemik kaybı görülebilir. Bu durum, tedavinin kesilmesinin takiben 6-9 ay içinde genellikle geçer. Triptorelin kullanımında iki epifizyolizis capitis femoris vakası bildirilmiştir. Nedenleşmiş bir ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. İLAÇ ETKİLEŞİMLERİ ve DİĞER ETKİLEŞİMLER: Östrojen içeren hiçbir ilaçta birlikte kullanılmamaktadır. KULLANIM ŞEKLİ ve DOZU: Decapeptyl® Depot, her 28 günde bir kez ya subkütan ya da intramüsküler olarak enjekte edilir. İnjesiyon her serisinde farklı bir yere uygulanmalıdır. Uterus miyomu ve endometriyozis: Genellikle 6 aylık bir tedavi dönemi yeterlidir. Yardımlı üreme teknikleri: Siklusun 2. ya da 3. günü (folliküler faz), veya 21. gününde (luteal faz) tek injesiyon uygulaması. DOZ AYARLAMA: Zehirlenme belirtileri: Etkin madde triptorelinin geniş tedavi alanı nedeniyle dozajı veya zehirlenme belirtileri beklenmemektedir. Böyle bir durumun olması halinde semptomatik tedavi uygulanmalıdır. SAKLAMA KOŞULLARI: Decapeptyl® Depot buzdolabında (2-8°C) saklanmalıdır. TİCARİ TAKDİM ŞEKLİ ve AMBALAJ MUHTEVASI: Bir kutuda; 3,75 mg triptorelin eşdeğeri triptorelin asetat içeren bir sıringa, süspansiyon sıvısı içeren tek kullanımlık enjektör, injesiyon izni ve sıringa adaptörü bulunur. RUHSAT SAHİBİ: FERRING İlaç San. Tic. Ltd. Şti. Büyükdere Cad. Nuru Plaza, No: 255 A Blok Kat 13, Maslak / İstanbul RUHSAT TARİHİ ve NO: 02.10.2006 ve 120/93 KDV DAHİL PERAKENDE SATIŞ FİYATI: 255,95 TL (Nisan 2009 itibarıyla). ÜRETİM YERİ: Ferring GmbH Kiel, Almanya REÇETE İLE SATILIR. Ayırtılı bilgi için lütfen firmamıza başvurunuz.

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FORMÜLÜ: Liyofilize toz içeren bir flakonda: 75 I.U. FSH (follikül stimüle eden hormon) ve 75 I.U. LH'a (Luteinizan hormon) tekabül eden yüksek derecede saflaştırılmış (HP) menotropin (insan menopozal gonadotropini, HMG) vardır. 1 ml çözücü içeren bir ampulde: 1 ml izotonik sodyum klorür solüsyonu bulunur.

ENDİKASYONLARI: Hipo veya normogonadotropik over yetersizlikleri olan kadınlarda kısırlık tedavisinde (follikül büyümesinin uyarılması), hipo veya normogonadotropik hipogonadizm olan erkeklerde kısırlık tedavisinde (HCG ile birlikte, spermatojenin uyarılması) kullanılır. **KONTRENDİKASYONLARI:** Menopur®, gonadotropinlere ve laktoza hassasiyeti olan kişilerde kullanılmamalıdır. Kadınlarda: gebelik, over büyümesi veya polikistik over sendromunun neden olmadığı kistler, nedeni bilinmeyen jinekolojik kanamalar, uterus, overde ve memede tümör. Erkeklerde: prostat kanseri, testislerde tümör.

UYARILAR/ÖNLEMLER: Menopur®, gebe hastalara verilmemelidir. Anormal genital kanaması olan hastalarda, meme, uterus, prostat, yumurtalık veya testislerin hormon duyarlı tümörler, over kistler, polikistik over sendromunun neden olmadığı over kistler veya bunların büyümesinde kullanılmamalıdır. Menopur® ile tedaviye başlamadan önce, infertilite nedenleri olarak hipofiz veya hipotalamik lezyonlar, adrenal veya tiroid bozuklukları ve hiperprolaktineminin ortadan kaldırılması için uygun şekilde tedavi edilmelidir. Over büyümesi yaşayan hastalar, ruptüre olma riski taşır. Pelvik muayeneden kaçınılmalı veya muayene dikkatle yapılmalıdır. Böyle bir risk mevcut iken cinsel ilişkiyi kaçınılmalıdır. Tedavi sırasında hastanın yakın takibi şarttır. İstmeden aşırı uyarılma olursa tedavi derhal durdurulmalıdır. Gebelik ve Laktasyonda Kullanım: Gebelik kategorisi: X. Menopur®, gebelerde kullanılmamalıdır. Anne sütüne geçip geçmediği bilinmediğinden, emziren annelerde dikkatle kullanılmalıdır. **YAN ETKİLER/ADVERS ETKİLER:** Kadınlarda: Pulmoner ve vasküler komplikasyonlar, over hiperstimülasyon sendromu, hemoperiton, adnexal torsion, hafiften ortaya değişen over büyümesi, over kistleri, abdominal ağrı, Menopur®'a duyarlılık, gastrointestinal semptomlar (bulantı, kusma, diyare, abdominal kramplar, şişkinlik), ağrı, döküntü, şişkinlik ve/veya enjeksiyon bölgesinde iritasyon, deri döküntüleri, baş dönmesi, taşikardi, dispne, takipne görülebilir (Uyarılar/Önlemler'e bakınız). Aşağıdaki olaylar, Menopur® tedavisinden sonra oluşan gebeliklerde rapor edilmiştir: Ektopik gebelik, konjenital anomali. Erkeklerde: Menopur® tedavisi sırasında bazen jinekometri, göğüs ağrı, mastit, bulantı, anormal lipoprotein fraksiyonu, anormal SGOT ve SGP7 oluşturabilir. HMG ile tedavide sık sık aşırı duyarlılık reaksiyonu oluşabilir. Bununla beraber, bu durum, daha çok HCG'nin ovülasyonu indüklemesi için uygulanmasından sonra klinik olarak ortaya çıkar. Bu durumda büyük over kistleri oluşur ve ruptüre olarak kanı içi kanamalara neden olur. Buna ek olarak, karın boşluğunda sıvı birikimi (asit), göğüs boşluğunda sıvı birikimi (hidrotoraks), idrarda azalma (oligüri), kan basıncında düşme (hipotansiyon) ve kan pıhtısıyla kan damarlarının tıkanması (tromboembolik olay) olabilir. Aşırı uyarılmanın ilk belirtileri ortaya çıktığında tedavi hemen durdurulmalıdır. Gebelikte beraber bu yan etkiler şiddetlenebilir ve uzun süre devam eder; hayati tehdit edecek nitelikte olabilir. HMG ile tedavi sırasında istenmediği halde birden çok gebelik olabilir. Çok ender olarak uzun süreli tedavi, antikör oluşumuna neden olarak tedaviyi etkisiz kılabilmektedir. **BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. İLAÇ ETKİLEŞİMLERİ:** Başka ilaçlarla etkileşimi bilinmemektedir. Kısırlık erkeklerde HMG, HCG ile bir arada enjekte edilebilir. **KULLANIM ŞEKLİ VE DOZU:** Ambalajın içindeki çözücü ile çözüldükten sonra I.M. ya da S.C. olarak uygulanır. Hekim tarafından başka türlü tavsiye edilmedikçe, aşağıdaki dozlarla uygulanır: Kadınlarda Kısırlık: Normo veya hipogonadotropik kadınlarda folliküllerin büyümesini başlatmak için verilen HMG dozu, hastaya göre değişir. HMG, intramüsküler veya subkutan olarak uygulanır ve genellikle tedaviye günlük doz, 75-150 I.U. FSH'a tekabül edecek şekilde başlanır. Eğer, overler cevap vermezse, dozaj, östradiol salgısında yükselme ve folliküllerde büyüme olana kadar yavaş yavaş yükseltilir. Aynı dozda HMG ile tedavi, ovülasyon öncesi östradiol serum düzeyleri sağlanana kadar devam ettirilir. Eğer bu düzey çok çabuk yükselirse, doz azaltılmalıdır. Not: Eğer uygulanan HMG dozu hastaya yüksek gelirse, daha sonra verilen HCG overleri aşırı uyarabilir. Erkeklerde Sterilite: Başlangıçta, haftada, 3x1000-3000 I.U. HCG/hafta uygulanır. Normal testesteron serum düzeyleri sağlandığında, birkaç ay ek olarak, haftada bir HMG intramüsküler olarak uygulanır; verilecek olan doz: 3x75-150 I.U. FSH + 75-150 I.U. LH'dır. **SAKLAMA KOŞULLARI:** Menopur®, ışıktan korunarak, 25°C'nin altında saklanmalıdır. **TİCARİ TAKDİM ŞEKLİ VE AMBALAJ MUHTEVASI:** Enjeksiyon için toz içeren, 5 adet flakon ve 5 ampul çözücü. **RUHSAT SAHİBİ:** FERRING İlaç San. ve Tic. Ltd. Şti. Ayazağa Mah. Meydan Sok. Beybi Giz Plaza, Kat 26, Daire 2626, Maslak-Şişli/İstanbul. **RUHSAT TARİHİ VE NO:** 27.07.2006 tarih ve 120/63 sayılı. **KDV DAHİL PERAKENDE SATIŞ FİYATI:** 229,12 TL (Nisan 2009 itibarıyla). Reçete ile satılır. Ayrıntılı bilgi için lütfen firmamıza başvurunuz.

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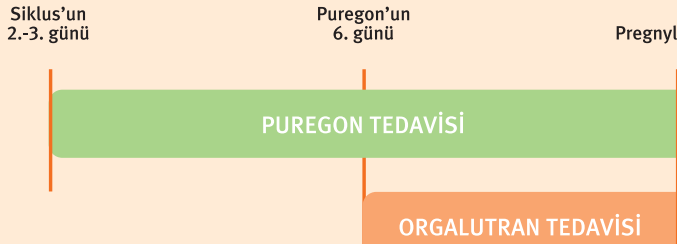
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Formülü: Önceden dolmuş bir şırınga 0,5 ml solüsyonda etkin madde olarak 0,25 mg ganirelix yardımcı maddeler olarak da 23,5 mg mannitol, 0,1 mg asetik asit, pH ayarı için sodyum hidroksit ve/veya asetik asit ve yeterli miktarda enjeksiyonluk su içerir. Orgalutran® , hipotalamik-hipofizer-gonadal eksenin hipofiz bezindeki GnRH reseptörlerine kompetitif olarak bağlanmak suretiyle etkileyen bir GnRH antagonistidir. Orgalutran®'in subkütan uygulamayı takiben biyoyararlanımı yaklaşık %91'dir.0,25 mg/gün dozunda mükerrer uygulamayı takiben 0,6 ng/ml'lik durağan durum düzeyine 2-3 gün içerisinde ulaşılmaktadır. **Endikasyonları:** Kontrollü over hiperstimülasyonu (COH) uygulanan kadınlarda prematür LH salgılanmasının önlenmesi. **Kontraindikasyonları:** Etkin maddeye veya yardımcı maddelerden herhangi birine karşı aşırı duyarlılık, GnRH veya diğer GnRH analoglarına karşı aşırı duyarlılık, Gebelik ve laktasyon. **Uyarılar ve önlemler:** Alerjisi olmakla birlikte o anda semptom sergilemeyen hastalara Orgalutran® güvenli bir şekilde uygulanabilir. Mevcut ciddi alerji semptomları olan hastalara Orgalutran® uygulanması tavsiye edilmemektedir. Alerjik reaksiyon oluşması halinde hastaların doktorla temasa geçmeleri önerilmektedir. **Gebelik ve laktasyonda kullanım:** Orgalutran® gebelik veya laktasyon sırasında kullanılmamalıdır. **Araç ve makina kullanmaya etkisi:** Araç ve makina kullanma üzerinde herhangi bir etki gözlenmemiştir. **Yan etkiler / Advers etkiler:** Orgalutran® enjeksiyon yerinde cilt reaksiyonuna yol açabilmekte fakat normal koşullarda bu reaksiyon uygulamadan 4 saat sonra kaybolmaktadır. Nadiren baş ağrısı (<%4) ve bulantı (<%2) rapor edilmiştir. Rapor edilen diğer advers olaylar, Orgalutran®'dan ziyade destekli üreme tekniklerine (ART) yönelik kontrollü over hiperstimülasyonu ile bağlantılıdır (örneğin karın ağrısı, over hiperstimülasyon sendromu (OHSS), ektopik gebelik ve düşük). **BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. Kullanım şekli ve dozu:** FSH ile kontrollü over hiperstimülasyonuna adet döneminin 2 veya 3'üncü gününde başlanılabilmektedir. Orgalutran® (0,25 mg), tercihen FSH uygulamasının 6. gününden itibaren başlanılarak günde tek sefer subkütan yoldan enjekte edilmelidir. Orgalutran® FSH ile karıştırılmamalı, fakat her iki preparat yaklaşık olarak aynı saatlerde uygulanmalıdır. Günlük Orgalutran® uygulamasına, yeterli büyüklükte ve yeterli sayıda follikül oluşana kadar devam edilmelidir. İlk Orgalutran® enjeksiyonu ile son Orgalutran® enjeksiyonu ile hCG enjeksiyonu arasındaki süre, 30 saat geçmemelidir. Orgalutran® subkütan yoldan uygulanmalıdır. Lipoatrofi oluşmaması için enjeksiyon yeri değiştirilmelidir. Hasta veya partneri, yeterli eğitim almaları ve bilgi için uzmanlara ulaşabilmeleri koşuluyla Orgalutran® enjeksiyonunu kendileri yapabilir. **Uygulama Şekli:** Orgalutran® enjektör ile yavaşça, cilt altına enjekte edilir (örneğin üst bacak). Uygulama şekli için prospektüsü inceleyiniz. **Enjeksiyonun unutulması:** Orgalutran®'i enjekte etmeyi unuttuğunuzu fark ettiğiniz anda enjeksiyonu yapınız, doktorunuza danışınız. Çift enjeksiyon yapmayınız. **Saklama koşulları:** 25°C' nin altındaki oda sıcaklığında saklayınız. Işıktan koruyunuz. Dondurmayınız. **Ticari takdim şekli:** Orgalutran® 0,25 mg/0,5ml, 5 adet önceden doldurulmuş, tek kullanımlık şırınga içinde 0,5 ml solüsyon, karton kutuda veya 1 adet önceden doldurulmuş tek kullanımlık şırınga içinde 0,5 ml solüsyon karton kutuda. **Genel uyarılar:** Çocukların ulaşamayacakları yerlerde ve ambalajında saklayınız. Hekime danışmadan kullanılmamalıdır. Başvurularda ambalaj seri numarasını belirtiniz. **Ruhsat Sahibi:** Schering-Plough Tıbbi Ürünler Ticaret A.Ş., Yıldırım Oğuz Göker Cad., Maya Plaza, 34335, Akatlar-İstanbul **Ruhsat tarihi:** 23.09.2003 **Ruhsat no:** 114/76 **Fiyat:** 5'lik Paket: PSF (KDV Dahil) 336,09 TL; 1'lik Paket: PSF (KDV Dahil) 77,27 TL (Ocak 2009)

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- Pratik tedavi



Hayalleri tamamlayan çözümler³



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Puregon[®] 300 IU/0,36 ml. kartuş, Puregon[®] 600 IU/0,72 ml. kartuş ve Puregon[®] 900 IU/1,08 ml. kartuş - Enjeksiyon için Solusyon

Formül: Puregon[®] kartuş, 0,36 ml/ik enjeksiyonluk solusyonda net toplam 300 IU, 0,72 ml/ik enjeksiyonluk solusyonda net toplam 600 IU ve 1,08 ml/ik enjeksiyonluk solusyonda net toplam 900 IU insan rekombinant folikül uyancı hormon (rec.FSH) (follitropin beta) içerir. Puregon[®] Kalem (Puregon[®] Pen) ile beraber kullanılmak üzere geliştirilmiştir. **Endikasyonlar:** Kadında: Klomifen sitrat'a cevap vermeyen anovulasyon (PCOD dahil), IVF/ET, GIFT ve ICSI gibi yardımcı üreme programlarında kontrollü over hiperstimülasyonu için. **Erkek:** Hipogonadotropik hipogonadizm nedeni spermatogenez eksikliğinde. **Kontrendikasyonlar:** Over, meme, uterus, hipofizer veya hipotalamik tümörler, gebelik veya laktasyon, tanı konmamış vaginal kanama, Puregon[®] Enjeksiyon için Solusyon daki maddelerden herhangi birine karşı aşırı duyarlılık, primer over yetmezliği, over kistleri veya büyümüş overler (Polikistik over hastalığına bağlı olmayan), genital organ malformasyonları, gebelikte bağdaşmayan fibroid tümörler, primer testiküler yetmezlik. **Uyarılar/Önlemler:** Tedavi edilmemiş gonad dışı endokrinopatiler (tiroid, adrenal, hipofizer bozukluklar) ekarte edilmelidir. Gonadotropik ilaçlarla yapılan ovulasyonu indüksiyonunu takiben oluşan gebeliklerde çoğul gebelik, ektopik gebelik, gebelik kaybı, konjenital malformasyon oranları artmaktadır. Bu ebeveyn ait karakteristiklere (anne, baba yaşı, sperm özelliği, tubalın yapısı) ve çoğul gebeliğe bağlı olabilir. Yardımla üreme tekniklerindeki hiperstimülasyon dışında oluşabilecek over hiperstimülasyon (OHS) riski ultrason ve estradiol değerleri ile takip edilmelidir. Hiperstimülasyon durumlarında Puregon[®] uygulamasına son verilmelidir. hCG uygulaması yapılmamalıdır. Hafif over hiperstimülasyonu (OHS) klinik bulgular arasında karn ağrısı, bulantı, diyare ve overlerde ve kistlerde hafif büyüme görülür. Nadir oluşan şiddetli vakalarda ise hayati tehlike söz konusu olabilir. Bu durumlarda rüptüre meyilli büyük over kistleri, hidrotoraks ve kilo artışı görülebilir. Arter veya venlerde tromboembolizm görülebilir. Tromboemboliye meyilli risk taşıyanlarda (trombofil, obezite, geçmişte kendisinde veya ailede tromboembolik şikayet olanlarda) IVF tedavisi ile riskler kıyaslanmalıdır. Erkeklerde artmış FSH düzeyleri primer testiküler yetmezliğin belirtisidir ve bu hastalar Puregon[®] tedavisine cevap vermezler. Erkeklerde tedavinin yanıtını değerlendirmek için 4-6 ay süre ile sperm analizi önerilir. Jinekometri ve akne nadiren görülebilir. **Gebelik ve Emzirme Döneminde Kullanım:** Gebelik ve emzirme sırasında kullanılmamalıdır. **Yan etkiler/Advers Etkiler:** Intramüsküler veya subkütan uygulama sonrasında çoğu kez hafif olarak ağrı, morarma, kızamık, kaşıntı görülebilir. Nadiren sistemik reaksiyon gözlenmiştir. Beklenmeyen bir etki görüldüğünde doktorunuza başvurunuz. **İlaç etkileşimleri ve diğer etkileşimler:** Klomifen sitrat ile Puregon[®] un birlikte kullanımı folikül cevabını artırabilir. GnRH agonisti kullanılan vakalarda ise Puregon[®] dozunu artırmak gerekebilir. **Kullanım şekli ve dozu:** Puregon[®] tedavisini fertilité problemlerinde tecrübeli hekim kontrolünde olmalıdır. Kullanılan doz kişinin kişiye ve kişinin kendi içinde büyük değişiklikler gösterebilir. Doz hastanın over yanıtına göre ultrason ve estradiol ölçümleri ışığında düzenlenir. Enjeksiyon kalem kullanımı ile hastaya ortalama %18 oranında daha çok FSH verilebileceği unutulmamalıdır. Puregon[®] ve üriner FSH karşılaştırılmalı çalışmalarda, Puregon[®] un üriner FSH'dan daha etkili olduğu gösterilmiştir. Üriner FSH'dan Puregon[®] a geçişlerde daha az doz tercih edilerek OHSS'dan sakınılmıştır. Uygulamaya genellikle 50 IU ile başlanıp 7 gün devam edilmeli, yanıt alınmazsa her 7 günde bir doz %40-60 oranında artırılmalıdır. Ultrasonda 18 mm folikül, 300-900 pg/ml (1000-3000 pmol/l) estradiol tesbiti preovulatuvar şartların geliştiğini gösterir. Genelikle 7-14 günlük tedavi buna yetmektedir. Günlük E2 değerinin 2 kattan fazla artması veya 14 mm'den büyük birden fazla folikül oluşumu çoğul gebelik riskini artırır. Bu durumda hCG verilmemelidir. Yardımla üreme programlarında kontrollü over hiperstimülasyonu protokolleri uygulanır. Bu tedavilerde başlangıç dozu olarak dört gün 100-225 IU, idame olarak 6-12 gün boyunca 75 - 375 IU kullanılabilir. Ultrasonda 16-20 mm foliküller (ortalama 18 mm) ve kan E2 değerlerinin 300-400 pg/mol (1000-1300 pg/mol/L) gözlenmesi ile hCG yapılab 34-35 saat sonra oositler elde edilir. **Erkek dozu:** Haftalık Puregon[®] dozu 450 IU olmalıdır. Tercihen bu doz 150 IU'lık 3 doza bölünebilir ve hCG ile birlikte kullanılabilir. Tedavi en az 3-4 ay devam etmelidir, bu süreden önce spermatogenezde gelişme beklenemez. Eğer hasta bu tedavi süresinden sonra yanıt vermezse kombinasyon tedavisi sürdürülebilir. Son klinik tecrübeler spermatogenez için tedavide 18 ay ya da daha uzun süre devam etmesinin gerekli olabileceğini göstermektedir. **Uygulama şekli:** Kartuşlardaki enjeksiyonluk Puregon[®] solusyonu, Puregon[®] Kalem ile kullanılmak üzere geliştirilmiştir ve subkütan yoldan uygulanmalıdır. Kalem kullanmak için hazırlanmış özel açıklamalar dikkatlice takip edilmelidir. Lipostatofinin önlenmesi için enjeksiyon yeri değiştirilmelidir. Doktor tarafından gerekli açıklamalar yapılmışsa, Puregon[®] un enjeksiyonu hasta tarafından yapılabilir. **Doz aşımı:** İnsanlarda Puregon[®] un akut toksisitesi ile ilgili bir veri yoktur. Çok yüksek dozda FSH overlerin hiperstimülasyonuna neden olabilir (bkz. Uyarılar/Önlemler bölümü). **Eczacı tarafından saklama koşulu:** 2 °C-8 °C'de saklayınız, dondurmayınız, ışıktan koruyunuz. **Hasta tarafından saklama koşulu:** 1) 2 °C-8 °C saklayınız, dondurmayınız, ışıktan koruyunuz. 2) 25 °C altında, oda sıcaklığında, maksimum 3 ay saklanabilir. Berrak olmayan veya partikül içerdiği görülen solusyonlar kullanılmamalıdır. Puregon[®] kalemının uygulamasında, kullanma talimatı dikkatle takip edilmelidir. Puregon[®] kartuşlar, kartuş içinde başka ilaçla karıştırılmak üzere hazırlanmamıştır. Enjeksiyonun hemen ardından kullanılan iğneler atılmalıdır. Tedavi sonunda, kullanılmamış ilaç ve artık malzeme yerel gereklilikler çerçevesinde imha edilmelidir. Çocukların ulaşamayacağı yerlerde ve ambalajında saklayınız. **Ticari takdim şekli:** Puregon[®] 300 IU/0,36 ml ve 600 IU/0,72 ml Enjeksiyon için solusyon, karton kutuda follitropin beta taşıyan bir kartuş ve Puregon[®] Kalem ile beraber kullanılmak üzere 7'günden oluşur. **KDV dahil PSF:** 300 IU kartuş 240,63 TL, 600 IU kartuş 457,64 TL ve 900 IU kartuş 671,62 TL (Ocak 2009). **Piyasada mevcut diğer farmasötik dozaj şekilleri:** Puregon[®] 50 IU/ ml ve 100 IU/ml Enjeksiyon için lyofilize toz. **Ruhsat Sahibi:** Schering-Plough Tıbbi Ürünler Ticaret A.Ş., Yıldırım Oğuz Göker Cad., Maya Plaza, 34335, Akatlar-Istanbul **Ruhsat Tarihi ve No:** 06.08.2003-114 / 40 **Üretim Yeri:** N.V. Organon, Oss, Hollanda adına Velter Pharma-Fertigung GmbH&Co.KG, Almanya. Reçete ile satılır.

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Editorial

Dear Colleagues,

We are submitting the final issue of the year 2009. With the final issue, we are introducing original research articles and case reports. As you know, all submitted manuscripts are reviewed by at least two referees, then, both the content and language of the most manuscripts are subjected to revision. If the manuscripts are considered "suitable for publication" by the referees after all these meticulous efforts, the manuscript is being sent to the publisher. Herein, manuscript is being subjected to a meticulous editing and one more revision in terms of foreign language (if necessary). The manuscript is being presented to you after these processes. This final issue is including manuscripts from educational institutions in different regions of our country and foreign manuscripts.

Our journal has begun to be indexed in two new international indexes and has been involved in Index Copernicus since November 2009. Our journal is currently indexed in SIIC, Turkish Medical Index, EBSCOhost, SCOPUS, Excerpta Medica (EMBASE), DOAJ database and Index Copernicus. As the number of international indexes including our journal increase, the number of published foreign manuscripts is also increasing. Additionally, this situation enables citation of manuscripts of Turkish scientists by more foreign authors.

Two wide congresses were conducted in autumn. The congress which was conducted by the Society of Reproductive Medicine in Antalya was beyond expectations. Furthermore, 15th Congress of MEFS (Middle East Fertility Society) took place in Cairo at the beginning of November which I attended as a guest speaker. This congress was also very successful due to the attendance of approximately 1600 participants and speakers, who are authority in their fields. The Congress of MEFS is appealed to gynecologist of all Arab countries. Although the common language spoken by these countries is Arabic, the language of the congress is English. This situation increases the international participation of MEFS and its acceptance by institutions, which are authorities in their fields, such as ESHRE (Society of Human Reproduction and Embryology) and ASRM (American Society for Reproduction Medicine). Thus, these two societies hold a Satellite Symposium in Cairo. Since English is a common language in medicine, presentations should be performed during English in international meetings arranged in our country.

I have very bad news to share with you. We lost our dear lecturers, Prof. Dr. Atilla Yıldırım and Assoc. Prof. Bülent Gökmen, who had educated many students and assistants, and had enormous contribution to medical community. Prof. Dr. Atilla Yıldırım had a great contribution to the area of reproductive medicine by innovative successful studies in Eskisehir Osmangazi University. Assoc. Prof. Bulent Gokmen was one of the leading physicians especially in hysteroscopy in Ankara Training and Research Hospital where he had been working as a clinical chief. May God rest them in peace and I share with all my colleagues condolences for our losses.

Sincerely

Prof. Dr. Cihat Ünlü
Editor in Chief of the JTGGA
President of TAJEV



The efficacy, cost and patient satisfaction of classic versus office hysteroscopy in cases with suspected intrauterine space occupying lesions with 3-dimension ultrasound and abnormal uterine bleeding

Üç boyutlu ultrasonografi ile intrauterin yer kaplayan lezyon şüphesi olan anormal uterus kanamalı olgularda ofis histeroskopi ile klasik histeroskopinin etkinlik, maliyet ve hasta memnuniyeti açısından karşılaştırılması

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Abstract

Objective: The aim of this study is to compare the diagnostic efficacy, treatment effectiveness and cost of office hysteroscopy procedure with classic hysteroscopy in women suspected of having an intrauterine space occupying lesion, after being examined for abnormal uterine bleeding.

Material and Methods: Among 544 cases admitted to our outpatient clinic due to abnormal uterine bleeding, 123 cases suspected of having an intrauterine space occupying lesion on 3D transvaginal ultrasound were included in the study. Patients were informed about classic and office hysteroscopy and asked to choose one of them. Fifty-seven cases preferred classic hysteroscopy and 66 cases preferred office hysteroscopy. The Visual analog scale was used to measure pain in office hysteroscopy cases while the Likert scale was used for patient satisfaction and cost was calculated in Turkish Lira.

Results: According to the histopathological examination, 65.9% of the cases (n=81) were diagnosed as polyp and 7.3% of the cases (n=9) were diagnosed as submucous leiomyoma. Mean operation time was 11±5.6 min. for office hysteroscopy and 42.6±18.4 min. for classic hysteroscopy (p<0.001). The level of pain before the operation was 0.3±0.1 (0-1), during the operation 2.8±2.5 (0-10) and after the operation 1.5±1.6 (0-8) in Office hysteroscopy cases. Among the Office hysteroscopy cases, 89.3% were very satisfied and 86.3% will advise other patients to have the procedure. Patients were evaluated at sixth month after the procedures and 92.4% of office hysteroscopy group and 96.4% of classic hysteroscopy group were symptom free. At sixth month of the office hysteroscopy procedure 83.3% of the cases were satisfied with the procedure and 81.8% would advice other patients to have the procedure. The mean cost of classic hysteroscopy was 3.6 times higher than the office procedure.

Conclusion: Office hysteroscopy is a safe and satisfactory procedure for the patient and provides a fast "see and treat" option at a low cost as an out patient procedure without need for general anesthesia. It should be utilized as a first line diagnosis and treatment option.

(J Turkish-German Gynecol Assoc 2009; 10: 189-93)

Key words: Intrauterine pathology, office hysteroscopy, efficacy, patient satisfaction, cost

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Özet

Amaç: Anormal uterin kanama yakınması ile başvuran, muayenesi sonrasında rutin yapılan transvajinal ultrasonografide endometriyal kavite içinde lezyon düşünülen hastaların, ofis histeroskopi ile ulaşılan tanı, tedavi sonuçlarını ve maliyeti klasik histeroskopik yaklaşımdan elde edilen sonuçlar ile karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya anormal uterin kanama ile polikliniğe başvuran 544 olgu arasından 3D transvajinal ultrasonografide uterus içinde yer kaplayıcı lezyonu olan toplam 123 olgu alındı. Hastalara klasik ve ofis histeroskopi yöntemleri anlatılarak bir işlemi tercih etmesi istendi. Bu olguların 57 tanesi klasik histeroskopi ve 66 tanesi ofis histeroskopi ile tedaviyi tercih etti. Ofis histeroskopi olgularında görsel analog skala kullanılarak, tüm olgularda Likert skalası kullanılarak memnuniyet ve Türk Lirası olarak işlemin maliyeti hesaplandı.

Bulgular: Nihai patoloji sonuçlarına göre endometrial polip görülme sıklığı %65.9 (n=81), submuköz myom görülme sıklığı %7.3 (n=9) olarak bulundu. Ortalama işlem süresi ofis histeroskopi için 11.0±5.67, klasik histeroskopi için 42.6±18.4 dakika olarak bulundu (p<0.001). Ofis histeroskopisi yapılan hastalarda işlem öncesi ağrı ortalaması 0.3±0.1 (0-1), işlem sırasındaki ağrı ortalaması 2.8±2.5 (0-10), işlem sonrası ağrı ortalaması 1.5±1.6 (0-8) olarak bulundu. Ofis histeroskopi sonrası hastaların işlemden çok memnun kalma ve tavsiye edilir bulma oranları sırasıyla %89.3 ve %86.3 olarak tespit edildi. Ofis histeroskopi grubundaki 66 hastanın tedavi sonrası 6. ayda semptomsuz fayda görme oranı %92.4 ve klasik histeroskopi grubunda ise %96.4 olarak hesaplandı (p=0.3). Ofis histeroskopi sonrası 6 ayda ise hastaların işlemden memnun kalma ve tavsiye edilir bulma oranları sırasıyla %83.3 ve %81.8 olarak tespit edildi. Maliyet analizinde ofis histeroskopinin klasik yaklaşımdan 3.6 kat ucuz olduğu tespit edildi.

Sonuç: Ofis histeroskopisi, hızlı sonuç veren, genel anestezi gerektirmeyen, doğrudan görüntülemeyi ve tedaviyi sağlayan, ayaktan hastada yapılabilen, düşük maliyetli, hasta açısından güvenilir ve tatminkar bir yöntemdir. Anormal uterin kanamalı hastalarda intrakaviter lezyondan şüpheleniliyorsa ilk basamak tanı ve tedavi aracı olarak düşünülmelidir. (J Turkish-German Gynecol Assoc 2009; 10: 189-93)

Anahtar kelimeler: İntrauterin patoloji, ofis histeroskopi, etkinlik, hasta memnuniyeti, maliyet

Geliş Tarihi: 14 Kasım 2009 Kabul Tarihi: 14 Kasım 2009

Introduction

Abnormal uterine bleeding is a common cause of admission to the gynecology outpatient clinic and constitutes 15 - 30% of admissions (1, 2). In women with normal uterine size, 20% of the hysterectomies are due to abnormal uterine bleeding (2). In order to diagnose probable pathologies causing abnormal uterine bleeding, office hysteroscopy was proposed as an alternative to ultrasonography and saline infusion sonography as it serves both as a diagnostic and treatment tool (3). Due to its smaller diameter, office hysteroscopy can be applied on an outpatient basis without the need for cervical dilatation and general anesthesia. The procedure is a "see and treat" operation which can be expected to decrease cost and labour while increasing patient satisfaction (4). Despite these expectations, only a small percentage of gynecologists apply office hysteroscopy as an office procedure (2). The main reason for this is the anxiety of the care providers that the pain experienced by the patient without general anesthesia might cause ineffective visualization and incomplete operation.

The aim of this study is to compare the diagnostic efficacy, treatment effectiveness and cost of office hysteroscopy procedure with classic hysteroscopy in women suspected to have intrauterine space occupying lesion, following examination for abnormal uterine bleeding.

Materials and Method

This prospective study was conducted between 01.01.2006 and 30.05.2008 after ethic committee approval in the Kocaeli University Obstetrics and Gynecology Clinic.

In 388 women who were admitted with abnormal uterine bleeding, 2D and real time 3D transvaginal ultrasonography scanning was performed (7.5 MHz vaginal probe, Voluson Pro 730, General Electric, USA). A total of 123 women constituted the study group providing they met all of the following inclusion criteria: 1) an intrauterine space occupying lesion was suspected on real time 3D transvaginal ultrasound scan, 2) gave written consent to be included in the study and accepted hysteroscopy. No other exclusion criteria was applied.

The women were informed about office hysteroscopy without anesthesia and classic hysteroscopy under general anesthesia. The operative technique was performed according to the patients' choice. Office hysteroscopy was preferred by 66 women. Office hysteroscopy was performed on the same day of the patients' admittance to the hospital, irrespective of the day of the menstrual cycle if there was no active bleeding. If the patient had active uterine bleeding they were asked to come back for office hysteroscopy when the bleeding ceased. A 2.7 mm in diameter telescope with a 30° angle was used within an office hysteroscopy of 5.5 mm in total diameter (RZMedizin-Technik, Germany). After speculum examination and cervico-vaginal washing a teneculum was used to grasp the cervix from 11 and 1 o'clock positions. Hysteroscopy was applied without anesthesia and cervical dilatation. However, if the patient required analgesia during the operation, 5 ml of 2% prilocain HCl (Citanest® 2%, AstraZeneca, Sweden) was used for cervical

local analgesia. If the patient still felt pain, midazolam 1 mg/20 kg intravenous (Dormicum® 1 mg/ml, Roche, Germany) was given for sedation. If the cervix was tight and operation field restricted, the next attempt was performed two hours after the patient received 200 mcg misoprostol sublingually (Cytotec® 200 mcg, Aris, Turkey) for cervical ripening. All cases of endometrial polyps, submucous leiomyomas and intrauterine adhesions were removed with scissors. Saline in 200 ml bags was used for uterine distension. If no pathology was observed during office hysteroscopy then punch biopsy forceps were used to sample the endometrium from the anterior and posterior uterine walls. If the operation was not completed due to visualization problems, the patients were asked to come back a week later.

Classic hysteroscopy was performed in 57 women. The operation was conducted, under general anesthesia. Cervical dilatation was performed via Hegar dilators. A 4 mm diameter telescope with a 12° angle was used with an operative sheath 10 mm in total diameter (Storz, Germany). All patients received 200 mcg of misoprostol sublingually for cervical ripening 2 hours prior to the operation. For uterine distension 5% mannitol (Resectisol® 3000 ml, Eczacibasi-Baxter, Turkey) was used. In the postoperative period the patients received intramuscular 75 mg diclofenac sodium (Diclomec® 75 mg, Mecom, Turkey) whenever they report pain.

The operation time, complications and need for second operation were noted for all the patients. The Visual analogue scale (VAS) over 10 was used to evaluate the pain felt by the patients before the operation, during the operation after the uterus distended for ideal visualization and 30 minutes after the operation. The Likert scale was used to evaluate patient. Satisfaction after the operation was scaled as 1- very dissatisfied, 2- dissatisfied, 3- neither satisfied nor dissatisfied, 4- satisfied, 5- very satisfied. The patients were asked if they would recommend this office procedure to other patients as 1- strongly not recommend 2- not recommend 3- neither recommend nor not recommend 4- recommend 5- strongly recommend. The satisfaction and recommendation ranking was performed when the patient was alone and pain free after operation. The patients ranked these on a sheet of paper with no name given, and this was then put into a regular envelope and placed in a locked box.

All patients were re-evaluated six months after the operation for signs and symptoms of abnormal uterine bleeding. The data of the study was analyzed using SPSS 12.0 for windows (Statistical Package for Social Sciences, IL, USA). The results are presented as number and percentages or mean±standard deviation. Independent samples t-test was used to compare categorical variables between the office and classic hysteroscopy groups. Probability (p) value <0.05 was considered to be statistically significant.

Results

The demographic variables of the patients are presented in Table 1. The mean age of the patients was 46±10.9 years in the office hysteroscopy group and 42±10.4 years in the classic hysteroscopy group (p=0.06). The percentage of menopausal, nulliparous, and primiparous women, the mean number of

previous pregnancies and the mean education in years were not statistically different in the two groups. Fourteen patients (21.2%) in the office hysteroscopy group and 12 patients (21%) in the classic hysteroscopy group had a systematic disease such as hypertension (n=10), diabetes (n=9) and chronic obstructive pulmonary disease (n=7).

The main complaints of the patients at the time of admission are presented in Table 2. Postmenopausal bleeding (n=20) was the most frequent complaint in the office hysteroscopy group, while menometrorrhagia (n=17) was the most common complaint in the classic hysteroscopy group. The distribution of the main complaints was not statistically different in the two groups. Fifty-nine (89.3%) patients in the office hysteroscopy group did not require or demand any anesthesia. Seven patients (10.6%) required paracervical infiltration with 2% prilocain and 3 (4.5%) patients required intravenous sedation with midazolam in addition to 2% prilocain infiltration due to severe pain. All 57 patients in the classic hysteroscopy group received general anesthesia.

Office hysteroscopy could not be performed in nine patients (13.6%) at the first attempt but was successful two hours after 200 mcg misoprostol sublingually. All patients in the classic hysteroscopy group received 200 mcg misoprostol sublingually 2 to 3 hours prior to the operation. In six patients, the office hysteroscopy operation was incomplete due to visualization problems in one patient, too much pain in two patients during myomectomy and the presence of more than one submucous leiomyoma. In all cases the office hysteroscopy was repeated in 2 to 4 days when the uterine bleeding stopped and the patient felt ready to undergo a second operation. The repeated office hysteroscopy was successfully accomplished in all patients. Leiomyomas were sliced and removed at the time of the operation in the classic hysteroscopy group. In the office hysteroscopy group the root of the leiomyomas were cut and they were left inside the uterus. The leiomyomas were expelled in a median of 12 days (7-22) and sent for pathological examination. All polyps were removed as a whole after their roots were cut or cauterized. No procedure related complications occurred in the two groups.

Three percent of the patients (n=2) had repeated pain before the office hysteroscopy procedure. The mean pain score evaluated via visual analogue scale (VAS) was 0.3±0.1 (0-1) prior to the operation, 2.8±2.5 (0-10) during the operation and 1.5±1.6 (0-8) after the operation. The distribution of pain scores reported by the patients is presented in Figure 1. When asked 30 minutes after the office hysteroscopy procedure, 89.3% of the patients of the patients were satisfied or very satisfied (Likert scale 4 and 5), 7.5% were neither satisfied nor dissatisfied (Likert scale 3) by the procedure. 86.3% of the patients would recommend or strongly recommend (Likert scale 4 and 5) the procedure to other patients while 6% would neither recommend nor not recommend the procedure (Likert scale 3).

There was no space occupying lesion in six patients of the office hysteroscopy group and five patients of the classic hysteroscopy group so only hysteroscopy guided endometrial sampling was performed. Surgically correctable pathologies such as polyp and leiomyoma were diagnosed in 49 (74.2%) and 41

(71.9%) of the office and classic hysteroscopy groups respectively. The pathological findings of the patients were presented in Table 3. The most common pathology in the two groups were endometrial polyps; 44 (66.7%) and 37 (64.9%) in the office and classic hysteroscopy groups respectively. The distribution of endometrial polyps, submucosal leiomyomas, secretory endometrium, proliferative endometrium, and simple and complex endometrial hyperplasia were similar among the two groups.

Table 1. Demographic variables of the patients. Data is presented as number and percentages or mean±standard deviation)

Variable	Office hysteroscopy (n=66)	Classic hysteroscopy (n=57)	P
Age (years)	46±10.9	42±10.4	0.06
Postmenopausal (%)	19 (28.8)	15 (26.3)	0.76
Education (years)	6.09±2.6	6.2±2.7	0.8
Gravida	3.1±3.3	3.2±2.3	0.9
Nulliparity	21 (31.8)	11 (19.3)	0.11
Primiparity	3 (4.5)	5 (8.8)	0.34
Multiparity	42 (63)	41 (72)	0.32
Systemic diseases*	14 (21.2)	12 (21)	0.27

*Systemic diseases include hypertension, diabetes and chronic obstructive pulmonary problems

Table 2. Main complaints of the patients. Data is presented as numbers and percentages

Variable	Office hysteroscopy (n=66) n (%)	Classic hysteroscopy (n=57) n (%)	P
Menorrhagia	12 (18.2)	10 (17.5)	0.91
Premenstrual spotting	18 (27.3)	15 (26.3)	0.90
Menometrorrhagia	16 (24.2)	17 (29.8)	0.48
Postmenopausal bleeding	19 (28.7)	15 (26.3)	0.76

Table 3. Histopathology results of the patients. Data is presented as numbers and percentages

Results	Office hysteroscopy (n=66) n (%)	Classic hysteroscopy (n=57) n (%)	P
Endometrial Polyp	44 (66.7)	37 (64.9)	0.83
Submucosal leiomyoma	5 (7.6)	4 (7)	0.89
Secretory endometrium	5 (7.6)	9 (15.7)	0.16
Proliferative endometrium	8 (12.1)	4 (7)	0.34
Simple hyperplasia without atypia	3 (4.5)	3 (3)	0.66
Complex hyperplasia without atypia	1 (1.5)	0	0.35

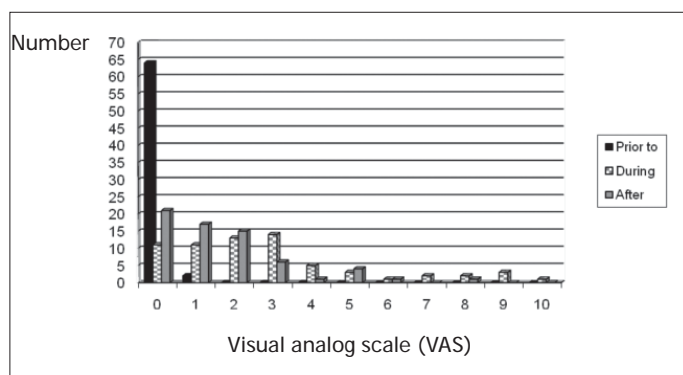


Figure 1. Pain reported by the patients prior to, during and after office hysteroscopy According to Visual analog scale

All postmenopausal women (n=34) were symptom and complaint free six months after the operation. Among the premenopausal patients, 8.5% (4/47) in the office hysteroscopy group and 7.1% (3/42) in the classic hysteroscopy group still had abnormal uterine bleeding six months after the first operation. All cases with persistent abnormal uterine bleeding were diagnosed to have endometrial hyperplasia so progesterone treatment was started in 3 patients and a Levonorgesterel containing intrauterine device was applied in one patient of the office hysteroscopy group. All three cases with persistent abnormal uterine bleeding and endometrial hyperplasia received progesterone treatment in the classic hysteroscopy group. The treatment efficacy of office hysteroscopy was 92.4% among 66 patients and 96.4% 57 patients of classic hysteroscopy. The patient satisfaction at the sixth month of treatment was 83.3% (Likert scale 4 and 5) in the office group and 81.8% of patients would recommend the procedure to other patients (Likert scale 4 and 5). The mean cost of the office hysteroscopy was 193 TL (152-203) while the mean cost of classic hysteroscopy was 696 TL (389-1277) ($p < 0.001$).

Discussion

Endometrial polyps and submucosal leiomyomas are frequent causes of abnormal uterine bleeding. These lesions constitute 40% of the causes of postmenopausal bleeding (5). The most commonly utilized diagnostic method is dilatation and curettage which can sample less than 50% of the endometrium with 65% sensitivity but can miss 30% of focal lesions (6). Dilatation and curettage might not diagnose 58% of endometrial polyps, 50% of hyperplasia and 11% cancer cases (7). Transvaginal ultrasonography has 54-85% of sensitivity and 84-90% of specificity for the diagnosis of intracavitary lesions (8, 9). The diagnostic efficacy of transvaginal ultrasound is increased by using real time 3D mode or intracavitary saline infusion during transvaginal ultrasonography with a sensitivity of 93.5-97.1% and specificity of 99.4%. Although diagnostic sensitivity of saline infusion sonohysterography is higher, up to 97.1%, it has a 6-15% false positive rate in premenopausal women with abnormal uterine bleeding (5, 10).

Apart from these factors, none of the diagnostic tools provide therapeutic opportunity at the time of diagnosis. Office hystero-

scopy is a cheap, easy to apply and safe method for the diagnosis and treatment of abnormal uterine bleeding with 98-100% sensitivity and 95% specificity (6, 11). Hysteroscopy in general is the current Gold Standard for evaluation of intrauterine pathologies and office hysteroscopy has been proposed as a first step tool for evaluating cases of abnormal uterine bleeding and rule out anatomic causes of bleeding (12).

Despite all its advantages, office hysteroscopy is still an underutilized method by the gynecologists. Pain is the main obstacle for widespread use of office hysteroscopy. The use of smaller diameter, rigid or flexible hysteroscopes and vaginoscopic entrance through the cervix did not increase acceptance of the technique (13). The cause of pain during office hysteroscopy is mainly due to cervical dilatation, distention of the uterine cavity and endometrial biopsy aggravated uterine contractions in addition to tenaculum application (14). The rates of severe pain have been reported to range from 2 to 14% in parallel with the diameter of the hysteroscope and were also reported to be 5% in another study (13, 15). Visual analogue scale (VAS) has been widely used to define the pain in a numeric system. A large series of studies reported that the mean VAS score of 4.7 in office hysteroscopy procedures was less than the endometrial biopsy mean VAS score of 5 (16, 17). Also, it was shown that the mean VAS score of thinner hysteroscopes such as 3.5 mm in diameter was 1.8 ± 0.1 , which was significantly lower than for 5 mm hysteroscopes (VAS: 3.4 ± 0.2) (18). We found that the mean VAS score of our patients was 2.8 ± 2.5 , which was similar to the literature. Whether mild or severe, pain is a frequent problem in office hysteroscopy procedure but surprisingly, patient satisfaction was high in our study. Previous studies have reported that 73-79% of the patients found office hysteroscopy comfortable (18-19). In our study patient satisfaction was 89.3%, which was higher than the previous studies. As we allow the patients to choose the procedure, this might increase the patient satisfaction. Although not evaluated, women who have higher anxiety levels for the surgical procedure and women who have lower pain threshold might have chosen classic hysteroscopy under general anesthesia.

We applied a speculum to all patients but applied a tenaculum only when the vaginoscopic approach failed. As these tools might be quite disturbing it was advised that speculum and tenaculum application should be carried out only in selected patients (14, 20, 21). In order to overcome pain, Nagele and colleagues provided local anesthesia whenever the patients requested it and found that 29.8% of the patients who requested local anesthesia were mainly nulligravid, nulliparous and postmenopausal (22). In our study 10.6% of the patients needed local anesthesia and 4.5% needed sedation. In our setting the office hysteroscopy procedure could not be completed in 9% of patients at first attempt which is higher than 0.4-4.6% reported in the literature (17, 23). This higher incidence might be due to multiple submucosal leiomyomas and higher frequency of nulliparous and postmenopausal women in our study group.

The mean operation time was reported to be 10 minutes for endometrial polyps and 22 minutes for submucosal leiomyomas (24, 25). The mean operation time was 11 ± 5.6 minutes in our study although operative procedures constitute the major-

ity. Previous reports published that it was possible to resect endometrial polyps in 81% of the cases but in our study we resected all cases of polyps (4).

The efficacy of office hysteroscopy was evaluated and it was found that 75-100% of abnormal uterine bleedings cases were cured in a follow-up of 2-25 months (26). Betocchi et al. reproduced similar rates at 6 months after the office hysteroscopy, which was 92.4% in our study group (25). When compared to classic hysteroscopy, office hysteroscopy without local anesthesia had similar rates of postoperative analgesic use and patient satisfaction rates, which was also confirmed by our study (27). In addition office hysteroscopy procedure has lower cost, shorter hospital stay and no risks due to general anesthesia (28). The mean cost of office hysteroscopy was reported to be 62 USD (40 Euro) and the cost of classic hysteroscopy was 1799 USD (1187 Euro) (29). These costs were 193 Turkish Lira (91 Euro) and 679 Turkish Lira (323 Euro) for office and classic hysteroscopy respectively in our study. These costs are especially important as they represent the total cost of diagnosis and treatment in low resource settings.

We conclude that office hysteroscopy is a cheap, outpatient one step "see and treat" procedure. It causes low pain scores, high patient satisfaction and high cure rate at six months following the procedure.

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The effect of copper intrauterine devices on the expression of mucin 1 and integrin β 1 in the luteal phase endometrium

Bakırlı rahim içi araçların luteal faz endometriyumunda musin 1 ve integrin β 1 ekspresyonu üzerine etkisi

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Abstract

Objective: To evaluate the effect of a copper intrauterine device on the expression of mucin-1 (MUC1) and Integrin β 1 in the luteal phase endometrium.

Material and Methods: 25 regularly menstruating women (25-35 years) who were willing to use copper intrauterine device contraception participated in this study. Endometrial sampling via a Pipelle canulla was performed on the 24th day of their cycle and repeated three months after insertion of TCu380A IUD. Immunohistochemical staining was performed for MUC1 and integrin β 1 in the endometrial sections. Staining intensity was graded under the conventional light microscope.

Results: The mean age of the study population was 32.8 \pm 5.3 years (25-35). MUC1 expression of the endometrial luminal epithelium cytoplasm and the luminal epithelium increased significantly after three months of IUD usage ($p=0.01$; $p<0.001$ respectively). Neither integrin β 1 expression of endometrial luminal epithelium cytoplasm nor of the endometrial stroma changed after three months of IUD usage ($p=0.16$; $p=0.22$ respectively).

Conclusion: The increase of the embryo implantation inhibitor MUC1 synthesis may be responsible for the IUD's mechanism of action for pregnancy prevention. Integrin β 1 expression of the endometrial luminal epithelium cytoplasm and stroma are not affected by the use of copper IUD. (J Turkish-German Gynecol Assoc 2009; 10: 194-8)

Key words: MUC-1, Integrin β , 1, intrauterine device, TCu380A, luteal phase endometrium

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Introduction

Mucins are a family of highly glycosylated, high-molecular-weight (>250kDa) glycoproteins present on epithelial surfaces, including human endometrial epithelial cells (1). The MUC1 is an integral membrane glycoprotein with a large ectodomain containing a variable number of 20-amino acid tandem repeats, resulting in a large and highly extended structure that is both immunogenic and extensively glycosyl-

Özet

Amaç: Bakırlı rahim içi aracın (RİA) luteal faz endometriyumunda musin-1 (MUC1) ve Integrin β 1 üzerine etkilerinin incelenmesi.

Gereç ve Yöntemler: Kontraseptif yöntem olarak bakırlı rahim içi araç kullanma konusunda gönüllü olan ve düzenli adet gören (25-35 yaş arası) toplam 25 kadın bu çalışmaya katılmıştır. Siklusun 24. gününde ve TCu380A rahim içi araç uygulanmasından 3 ay sonrasında Pipelle ile endometriyal örnekleme yapılmıştır. Endometriyum kesitlerinde MUC1 ve Integrin β 1 için immünohistokimyasal boyama işlemi uygulanmıştır. Konvansiyonel ışık mikroskobu eşliğinde boyanma yoğunluğu derecelendirilmiştir.

Bulgular: Çalışma grubunun ortalama yaşı 32.8 \pm 5.3 (25-35) olarak belirlenmiştir. Üç ay süre ile RİA kullanımının ardından endometrial luminal epitel sitoplazması ve luminal epitel MUC1 ekspresyonunda anlamlı artış belirlenmiştir (sırasıyla $p=0.01$; $p<0.001$). Ne endometrial luminal epitel sitoplazma ne de endometrial stromada üç aylık RİA kullanılması sonrasında Integrin β 1 ekspresyonunda farklılık belirlenmemiştir (sırasıyla $p=0.16$; $p=0.22$).

Sonuç: RİA'nın gebeliği önleyici etkisinden embryo implantasyon inhibitörü olarak bilinen MUC1 ekspresyonunun artışı sorumlu olabilir. Bakırlı RİA kullanılması ile, endometrial luminal epitel sitoplazmasında ve stromasında Integrin β 1 ekspresyonunda farklılık gözlenmemiştir. (J Turkish-German Gynecol Assoc 2009; 10: 194-8)

Anahtar kelimeler: MUC-1, Integrin β , 1, rahim içi araçlar, TCu380A, luteal faz endometriyum

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ated (2). A fraction of uterine epithelial cell mucins (30%-50%) appears to be released from the apical surface into the lumen; the remainder is presumably degraded intracellularly following endocytosis (3).

Expressed at high levels at the cell surface, MUC1 has the ability to inhibit cell-cell adhesion. This property depends on the presence of a long ectodomain and probably results from steric hindrance of receptor-ligand interactions mediated by families of adhesion receptors such as the cadherins (4). In a

study it was shown that progesterone combined with estradiol priming induced an up-regulation of MUC1 at the receptive endometrium and during the apposition phase, the presence of a human embryo increased endometrial epithelial MUC1 (5). These findings strongly suggest that MUC1 may act as an endometrial antiadhesive molecule that must be locally removed by the human blastocyst during the adhesion phase.

Cell adhesion molecules fall into four major groups: integrins, cadherins, selectins, and members of the Ig superfamily. Integrins are transmembrane heterodimeric glycoproteins consisting of two noncovalently associated α and β subunits. Integrins are involved in cell-to-cell binding and in cell interactions with the extracellular matrix (6). The expression of integrins on the luminal surface of the endometrial epithelium changes throughout the menstrual cycle and their expression is hormonally regulated. Several studies have provided indirect evidence that integrins are potential markers of endometrial receptivity and that they participate in embryo-endometrial interactions. Recent investigations indicate that $\alpha_v\beta_3$ binds to and activates matrix metalloproteinases and plasminogen activators in the extracellular matrix (7).

The copper intrauterine device (IUD) was shown to cause a sterile inflammation and foreign body reaction in the endometrium (8). Copper ion was shown to prevent transtubal sperm and ovum migration and prevent fertilization (9). Apart from all these facts, the exact molecular mechanism of the contraceptive effect of IUDs is still not known.

In this study, we investigated the effect of copper IUD on MUC1 and Integrin $\beta 1$ in the luteal phase endometrium.

Materials and Methods

The study population consisted of 25 women with at least two prior healthy term vaginal deliveries whose midluteal phase progesterone levels were ≥ 10 ng/mL (31.8 nmol/L) and who were willing to use copper-IUD contraception. The women were menstruating regularly (i.e. menstrual cycle varying between 28-35 days) and they were under 35 years old. The exclusion criteria were pregnancy, acute or chronic pelvic inflammatory disease, and metrorrhagia for unknown reasons, cervicitis, and dysplasia in the cervix, genital tumor, copper allergy, and usage of contraceptive pills within the previous 3 months, lactating women, hypothyroidism, hyperthyroidism, abnormalities in blood clotting and severe dysmenorrhea. Informed consent was obtained from women and the study was approved by the ethical committee of the Medical Faculty of Kocaeli University. All patients underwent a gynecological examination and had a Papanicolaou smear taken during the previous 12 months. Menstruation period and/or quantity was asked before and three months after the IUD insertion. The biopsy specimens were taken with a Pipelle canulla without dilatation of cervix and without anesthesia. Endometrial biopsies were taken from the anterior and posterior walls of the mid-uterine cavity before and 3 months after the insertion of the IUD on cycle days 20-24. All patients at the time of IUD insertion and at the third month

of IUD insertion had a progesterone level of ≥ 10 ng/mL (31.8 nmol/L) as an indicator of a luteal phase of an ovulatory cycle. The endometrial specimens were washed and soaked in a graded series of ethanol and were then embedded in paraffin wax. Sections were cut to 3-5 μ m thickness and mounted onto adhesive coated slides (Menzel-Gloser, Süperfrost® Plus). For immunohistochemical staining sections were kept at 56°C overnight and then soaked in xylene for 30 minutes. After washing with a decreasing series of ethanol, sections were washed with distilled water and phosphate-buffered saline (PBS) for 15 minutes. After the coated slides were dried in the incubator at 56°C for two hours, antigen unmasking was performed for MUC1 and Integrin $\beta 1$ antibodies in the pressure cooker.

After antigen unmasking, step slides were washed with PBS and thereafter, to block endogenous peroxidase activity, the slides were incubated in 3% hydrogen peroxide for 20 minutes. Slides were washed with PBS for five minutes. Sections were then blocked with Super Block (REF:AAA 125 LOT:12232) at room temperature for 15 minutes and afterwards washed with PBS. Slides were immunostained with commercially available epitope specific rabbit antibody MUC1 (Neo-Markers Fremant, CA Cat No:RB-9222-P, USA) at 1:100 dilution for one hour at room temperature (20-25°C) and were immunostained with commercially available mouse monoclonal antibody Integrin $\beta 1$ (CD29) Ab-3 (Clone 29C03; same as 7F10) (Neo-Markers Fremant, CA Cat No:MS-1089-S, USA) at 1:25 dilution for two hours at room temperature (20-25°C). The slides were then washed with PBS and incubated with UltraTek Anti-Polyvalent Biotinylated Antibody (REF:ABN 125, LOT:11461, Company:ScyTek Laboratories, USA) at room temperature for 25 minutes. The slides were washed with PBS again and incubated with UltraTek HRP (REF:ABL125, LOT:11460, Company:ScyTek Laboratories, USA) at room temperature for 25 minutes. The slides were washed with PBS and incubated with Ultravision Detection System Large Volume AEC Substrate System (RTU) (REF:TA-125-HA, LOT:AHA60718, Company:LabVision Fremant, CA, USA) at room temperature for 15 minutes. The sections were finally counterstained using Mayer's haematoxylin and mounted in an aqueous medium.

The slides were analyzed with a BX50 conventional light microscope (Olympus, Tokyo, Japan) by BM at 100 and 200 magnification twice. Staining intensity was graded as; "0 = no staining", "+1 or <10% staining = weak staining", "+2 or 10-49% staining = mild staining" and "+3 or 50-100% staining = strong staining". Immunohistochemical staining in luminal and glandular epithelium cytoplasm were graded in 60 sections counting 100 cells separately at 400 magnifications.

The statistical analysis of the study data was performed using SPSS 11.5 for Windows packet programme. Paired samples t-test was used for immunostaining grade and intensity before and 3 months after the IUD insertion. Analysis of classified data was performed using the Chi-square test and Fisher's exact test. Correlation of the data was determined using the Pearson correlation test. A probability (p) value smaller than 0.05 was considered statistically significant. All values given were means (\pm SD) or percentage (%).

Results

The mean age of the study population was 32.8 ± 5.3 years (25-35). The mean gravida was 2.2 ± 1.3 . Two (8%) women had one prior abortion and none had a history of infertility treatment.

Expression grade of the antibody in the luminal epithelium is presented in Table 1. MUC1 expression of endometrial luminal epithelium surface increased significantly after three months of IUD usage ($p=0.01$). The evaluation and grading of the MUC1 staining is presented in Figure 1.

Before IUD replacement, MUC1 expression of the luminal epithelium was present in 61 ± 21.5 (39-92) cells while after IUD usage, it was present in 91.4 ± 6.27 (82-98) cells. MUC1 expression of the luminal epithelium increased significantly after IUD replacement ($p < 0.001$).

Expression grade of the antibody in the luminal epithelium and endometrial stroma is presented in Table 1. Neither Integrin $\beta 1$ expression of endometrial luminal epithelium cytoplasm nor of the endometrial stroma changed after three months of IUD usage ($p=0.16$; $p=0.22$ respectively). The evaluation and grading of the integrin $\beta 1$ staining is presented in Figure 2.

Before IUD replacement, Integrin $\beta 1$ expression of the luminal epithelium was present in 17.6 ± 18.7 (0-45) cells, while after IUD usage it was present in 23.4 ± 16.2 (3-40) cells. Integrin $\beta 1$ expression of the luminal epithelium did not change after IUD replacement ($p=0.24$). Before IUD replacement, Integrin $\beta 1$ expression of the endometrial stroma was present in 2.6 ± 2.91 (0-7) cells, while after IUD usage it was present in 9 ± 16.2 (0-45) cells. Change of the Integrin $\beta 1$ expression of the endometrial stroma was found to be insignificant after three months of IUD usage ($p=0.06$).

Discussion

The IUD is reported to be used throughout the world by millions of women as an effective, safe, and convenient method of preventing pregnancy. Its mechanism of action has not been elucidated completely; however, recent research has suggested that it usually prevented fertilization rather than implantation (10). Intrauterine devices (IUDs) were known to produce a local

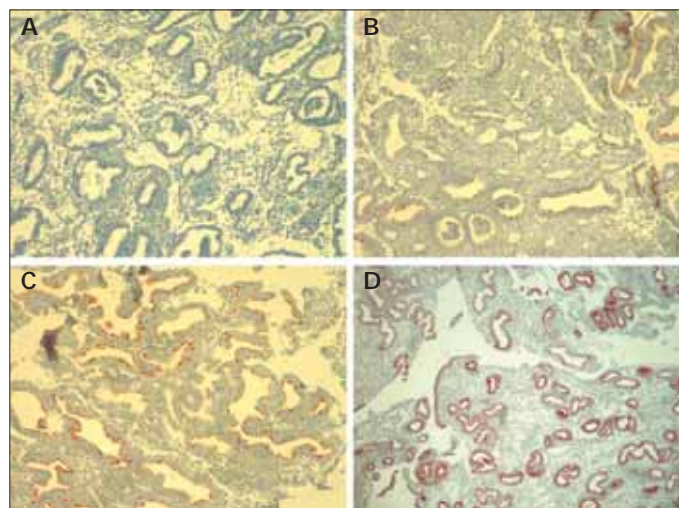


Figure 1. The evaluation and grading of MUC1 staining. Strong staining as red areas. 1a. No staining, 1b. Weak staining, 1c. Mild staining, 1d. Strong staining

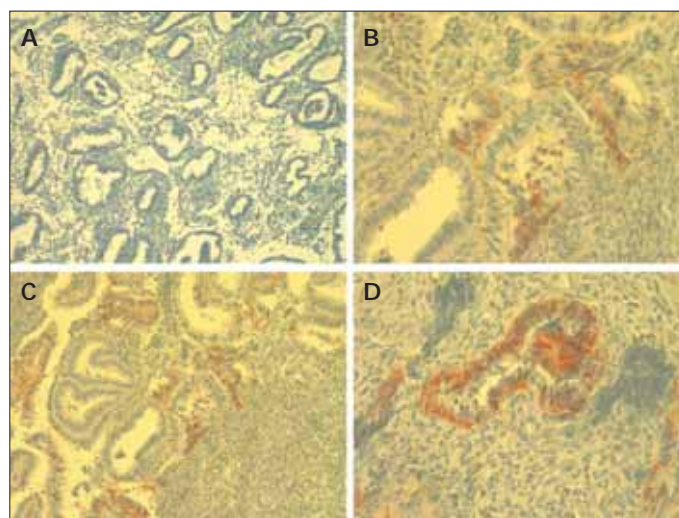


Figure 2. The evaluation and grading of integrin $\beta 1$ staining. Strong staining as orange red areas 2a. No staining, 2b. Weak staining, 2c. Mild staining, 2d.

Table 1. Expression grade of the MUC1 and Integrin $\beta 1$ antibodies in luminal epithelium and endometrial stroma

Antibody	Expression Grade	Before IUD (n=25)	After IUD (n=25)	p
MUC1 immunostaining in luminal epithelium surface	0			0.01
	+1	3 (12%)		
	+2	11 (50%)		
	+3	11 (50%)	25 (100%)	
Integrin $\beta 1$ immunostaining in luminal epithelium cytoplasm	0			0.16
	+1	5 (20%)		
	+2	11 (44%)	12 (48%)	
	+3	9 (36%)	13 (52%)	
Integrin $\beta 1$ immunostaining in endometrial stroma	0			0.22
	+1	13 (52%)	8 (32%)	
	+2	12 (48%)	14 (56%)	
	+3		3 (12%)	

foreign body inflammatory reaction within the uterus (11). In a trial, women with an IUD had shown a pattern of contractility that was uncoordinated, with decreased frequency at midcycle and they concluded that uncoordinated midcycle contractions produced by the IUD might affect sperm transport (12).

Mucins are high molecular weight glycoproteins that provide a protective layer on epithelial surfaces. They are involved in cell-cell interactions, signaling, and metastasis (13). Thus far, a total of 19 human mucins have been identified, and more are possibly awaiting discovery. The MUC1 mucin is a transmembrane glycoprotein with an extracellular domain consisting of a variable number of highly conserved tandem repeats of 20 amino acids (14). Over expression of MUC1 by cultured cells inhibits their aggregation, possibly because of its large, extended, and rigid external structure (15). This mucin is ubiquitously expressed in all reproductive tract epithelial tissues, including the fallopian tubes, uterus, endocervix, and vagina, and its immunoreactivity is observed at the apical cell surface at all levels of the fallopian tubes and throughout the secretory phase of the menstrual cycle (16, 17).

It has been widely accepted that IUDs work primarily by inhibiting fertilization due to direct toxicity (18). A systematic review on the mechanisms of action of IUDs showed that pre- and post-fertilization effects contribute to efficacy (19). An inflammatory reaction within the endometrium may have an anti-implantation effect but an IUD is not an abortifacient (20). The anti-implantation effect may be due to increased synthesis of MUC1 in the endometrium. In our study, we demonstrated that MUC1 expression increases after IUD use for a time and in our opinion, mucin is one of the major determinants responsible for the anti-implantation effect. The role of mucins have been investigated in implantation of embryos (21, 22). Large-molecular-weight mucin glycoproteins such as MUC1 are present at the apical surface of the uterine epithelium and they are antiadhesive and also appear to represent a barrier to embryo attachment. This data also suggests that increased mucin expression causes an antiadhesive barrier to embryo attachment.

In our study, we demonstrated that IUD has no effect on the endometrial expression of Integrin β_1 . Therefore, IUD may act via other integrin subunits. Subunit β_3 has been possibly implicated in early embryo-endometrial interactions during human blastocyst implantation. The immunohistochemical expression of $\alpha_v\beta_3$ in midluteal endometrial samples has been proven to be a marker of endometrial receptivity (6). In another study investigating the expression of α_4 and β_3 integrin subunit levels in the endometrium of healthy women and copper intrauterine device (IUD) T200 users, no difference was found in α_4 integrin expression between IUD users and controls in both luminal and glandular epithelium and proportionately, significantly fewer women using copper IUD had positive $\alpha_v\beta_3$ immunoreactivity in the glandular epithelium of mid-secretory endometrium (23).

The balance of evidence suggests that the use of an IUD does not affect return to fertility. The increase of the suggested embryo implantation inhibitor MUC1 synthesis may be one

of the mechanisms of action of the IUD's effect in pregnancy prevention. Integrin β_1 expression of the endometrial luminal epithelium cytoplasm and stroma are not affected with the use of the copper IUD.

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The combination of letrozole and melatonin causes regression in size not histopathological scores on endometriosis in an experimental rat model

Kombine letrozol ve melatonin tedavisinin deneysel rat endometriosis modelinde lezyon boyutları ve histopatolojik skorlar üzerine etkisi

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Abstract

Objective: To determine the effects of the combination of letrozole and melatonin on surgically induced endometriosis.

Material and Methods: This prospective, randomized, controlled, experimental study was carried out at Yeditepe University Experimental Research Center (YUDETAM). Female non-pregnant, 17 nulligravid Wistar - Hannover albino rats with surgically induced endometriosis were used in this study. Endometriosis was induced by using homologous uterine horn transplantation in the rats. Four operations were performed on each rat. The induction of endometriosis was performed in the first operation. After two weeks of estradiol treatment the second operation was performed and endometriotic lesions were evaluated. Estrogen was then discontinued and in the study groups medications were started. During two weeks the rats were given medications and the third operation was performed for the assessment of the effects of the medications on the endometriotic foci. Then all the medications were stopped and estrogen was started again. Two weeks later all the rats were euthanized and recurrence of endometriosis was evaluated.

Results: The sum of the lesion volumes in the control group was $93.6 \pm 31.7 \text{ mm}^3$ at the end of the second week. After the cessation of estradiol it decreased to $85.0 \pm 23.8 \text{ mm}^3$ ($P=0.31$) and increased to $119.7 \pm 29.4 \text{ mm}^3$ at the sixth week ($P=0.02$). A significant reduction in histopathologic scores were seen after cessation of the estradiol ($p=0.04$). At the end of the sixth week, histopathological scores reached the pretreatment values. In the letrozole and melatonin group the sum of the lesion volumes decreased significantly after the treatment ($82.8 \pm 21.0 \text{ mm}^3$ and $15.7 \pm 8.0 \text{ mm}^3$ respectively). At the end of the sixth week, the mean volume was calculated as $43.9 \pm 31.8 \text{ mm}^3$ ($p=0.002$). Histopathologic scores were 2.3 ± 0.1 , 2.0 ± 0.2 and 2.2 ± 0.3 at the end of the second, fourth and sixth weeks, respectively, in the letrozole and melatonin group.

Conclusions: Letrozole and melatonin caused a significant regression in lesion volumes; however, histopathological scores of endometriotic lesions did not change significantly.

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Key words: Endometriosis, melatonin, letrozole, rat endometriosis

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Özet

Amaç: Kombine letrozol ve melatonin tedavisinin cerrahi olarak indüklenmiş endometriosis üzerindeki etkisini belirlemek.

Gereç ve Yöntemler: Bu prospektif randomize kontrollü bir deneysel çalışma olarak dizayn edildi ve Yeditepe Üniversitesi Deneysel Hayvanlar Araştırma Merkezinde (YUDETAM) gerçekleştirildi. Cerrahi olarak endometriosis oluşturulmuş 17 tane nulligravida dişi Wistar - Hannover albino rat kullanıldı. Ratlara homolog uterus boynuz inokülasyonu yapılarak endometriosis oluşturuldu ve iki hafta aralar ile dört operasyon yapıldı. Endometriosis indüksiyonu ilk operasyonda yapıldı. İki haftalık östradiol tedavisini takiben ikinci operasyon yapıldı. Sonra östrojen kesildi ve çalışma grubuna ilaç başlandı. Takip eden iki haftanın sonunda üçüncü operasyon yapılarak endometriyal odaklar üzerinde ilaçların etkinliği araştırıldı. Üçüncü operasyondan sonra bütün ilaçlar kesildi ve östrojen tekrar başlandı. İki haftalık östrojen tedavisinin ardından tüm ratlara ötanazi yapıldı ve rekürrens oranlarına bakıldı.

Bulgular: Kontrol grubunda tedavinin başında lezyonların volüm ortalaması $93.6 \pm 31.7 \text{ mm}^3$ idi. Östradiol tedavisi kesildikten sonra $85.0 \pm 23.8 \text{ mm}^3$ ($P=0.31$) boyutlarına indi ve rekürrens zamanı $119.7 \pm 29.4 \text{ mm}^3$ e çıktı ($P=0.02$). Östradiol kesildikten sonra histopatolojik skorda anlamlı bir düşüş gözlemlendi ($p=0.04$) fakat rekürrens zamanı tedavi öncesi boyutlarına ulaştı. L+M grubunda lezyonların volümü tedavi grubunda anlamlı bir şekilde düştü ($82.8 \pm 21.0 \text{ mm}^3$ ve $15.7 \pm 8.0 \text{ mm}^3$). Rekürrens zamanı ortalama volüm $43.9 \pm 31.8 \text{ mm}^3$ olarak hesaplandı ($p=0.002$). Histopatolojik skor ise tedavi öncesi tedavi sonrası ve rekürrens zamanlarında sırası ile 2.3 ± 0.1 , 2.0 ± 0.2 ve 2.2 ± 0.3 idi.

Sonuç: Çalışmamızda Letrozol ve Melatonin endometriotik lezyonların boyutlarında gerileme orantı çıkarırken, histopatolojik skorlarda değişikliğe yol açmadı.

(J Turkish-German Gynecol Assoc 2009; 10: 199-204)

Anahtar kelimeler: Endometriosis, melatonin, letrozole, rat endometriosis

Geliş Tarihi: 12 Kasım 2009 **Kabul Tarihi:** 30 Kasım 2009

Introduction

Endometriosis is defined as the presence of a functional endometrial layer, with endometrial glands and stroma, outside the uterine cavity. Although it is common, its etiopathology is not very clearly known (1).

As early as 1940s, Sampson proposed his theory of retrograde menstruation and implantation of endometrial fragments as the origin of endometriosis, yet since that time limited progress has been made toward defining the mechanisms associated with the etiology and pathophysiology of endometriosis. There are many other theories explaining the pathophysiological mechanisms of endometriosis. Estrogen dependency, role of pro-inflammatory environment, and effects of free radicals are some of these theories. There is much speculation about these topics but the attempts for treatment has mostly been restricted since most treatment are experimental and could not easily be applied to humans. As a result, a need to develop alternate models in research animals exists. Many of these experimental animal models were previously described (2, 3). These studies proved that surgically transplanted endometrial tissue in the rat provides an animal model to study the effects of experimental drugs on ectopic endometrial tissue. Recently, we demonstrated a rat experimental model for endometriosis (4, 5). The main advantage of our model is the possibility of assessing the rate of recurrence of endometriotic lesions after cessation of medications.

Experimental and clinical observations suggest that endometriosis is estrogen dependent and that estrogens seem to be important for growth and maintenance of endometriosis (6). The attempt at reducing or antagonizing estrogen was made with GnRh analogs. However, they were not able to block estrogen synthesis appropriately. Recently, aromatase inhibitors have been used for this purpose. Aromatase (estrogen synthetase) is the key enzyme in the synthesis of estrogens and mediates the conversion of androstenedione and testosterone to estrone and estradiol. Letrozole is one of second generation aromatase inhibitors that inhibit 97-99% of estrogen production. The importance of estrogen in stimulating endometriotic tissues and the *in situ* presence of aromatase in these tissues reveal that inhibition of estrogen synthesis is a rational approach to the treatment (7). In our study, letrozol was used for the treatment of endometriotic lesions due to its availability on the market.

It is known that free radicals have a dual role in the reproductive tract and are key signaling molecules for endometriosis. Free radicals mediate their actions through a variety of pro-inflammatory cytokines, with these processes having been proposed as a common underlying factor for endometriosis. Melatonin is a documented powerful free radical scavenger and a broad-spectrum antioxidant (8). It has been shown that Melatonin causes regression and atrophy of endometriotic lesions in rats (3).

Our study evaluated the effects of the combination of letrozole and melatonin on surgically induced endometriotic lesions in a rat model.

Materials and Methods

Seventeen female non-pregnant, nulligravid Wistar-Hannover albino rats weighing 200-250 g were purchased from Yeditepe

University Experimental Research Center and used in this study. The rats were caged individually in a controlled environment (the room temperature was 21°C and humidity 60%) with 12 hours light/dark cycles and were fed *ad libitum*. This study was approved by the Experimental Animals Ethics Committee at Yeditepe University Medical Faculty. All experiments were performed in compliance with international guidelines on the ethical use of animals.

In the first operation; all rats were anesthetized with an intramuscular administration of 60 mg/kg ketamine hydrochloride (Ketalar; Eczacibasi Ilac Sanayi, Levent, Istanbul, Turkey) with 7 mg/kg xylazain hydrochloride (Rompun; Bayer Ilac Sanayi, Sisli, Istanbul, Turkey) as described by us previously (4, 5). Endometriosis was induced surgically under anesthesia as proposed by Vernon and Wilson (2) with modifications by Lebovic (9). Briefly, after adequate anesthesia a vertical incision was made to expose the uterus. Both uterine horns were removed from the cervix up to 1 cm from the ovaries. Electro-coagulation was used for haemostasis. Removed tissue was placed in phosphate-buffered saline at 37°C and split longitudinally. The parametrial tissues were removed, and then both split horns were sectioned into two 6x3 mm pieces. Two of these pieces were transplanted without removing the myometrium onto the inner surface of the right abdominal wall with the epithelial lining opposed to the peritoneal surface. Both ends of the explanted endometrial tissue were secured with non absorbable polypropylene 6-0 suture to the inner abdominal wall. The remaining two pieces were placed in the same manner on the left inner abdominal wall. All tissues were implanted just opposite to both vascular bifurcations on the inner surface of the abdominal wall. The peritoneal cavity was kept moist meticulously with controlled amounts of sterile saline solution throughout the surgery. The midline abdominal incision was closed with 3-0 silk sutures. The skin incision was closed in a continuous interlocking manner with 3-0 silk sutures. All rats were given 50 mg/kg/day cefazolin sodium (IE Ulugay Ilac Sanayi, Istanbul, Turkey) intramuscularly over a 3 day period after the operation. All rats except for Group GC (General Control) were given 50 µg/kg Estradiol -Depot (Jenapharm GmbH&Co, Germany) twice a week intramuscularly until the second operation.

The second operation was performed two weeks after the inoculation. Anesthesia and abdominal entry were carried out as mentioned above. Peritoneal washing was collected for biochemical analysis and stored at -80°C. All the implants were measured by the same author (G.Y.). One of the fourth explants was removed for histopathological analysis. After these operations estrogen was stopped. The rats were randomized to 2 groups. An excel program was used for the randomization. Group C (Control): No medication was given for a two week period after the second operation. Group L + M (Letrozole and Melatonin): These rats were given 0.04 mg/kg/day Letrozole (Femara 2.5 mg tablet, Novartis Pharma AG, Basel, Switzerland) orally with gastric lavage and injected with 10 mg/kg/day melatonin (Melatonin flacon, Acros Organics Co., Geel, Belgium) intraperitoneally and 10 mg/kg/day subcutaneously for two weeks. The melatonin was dissolved in 1:90 absolute ethanol / saline solution.

The third laparotomy was performed two weeks after the second operation. The peritoneal washout was obtained. Measurements of the lesions were taken. One of the remaining three lesions was obtained for histopathological evaluation. The active substances (Melatonin and Letrozole) were stopped. Estradiol was initiated again for the assessment of recurrence. In the fourth operation; recurrence of the endometriosis was evaluated after two weeks of estradiol treatment. All rats were euthanized under anesthesia and all measurements and tissue collections were performed as described above.

Health conditions of the rats were monitored by a veterinary doctor on a daily basis and by her assistant. Only one animal was lost in the Letrozole and Melatonin group, 2 days after the third operation due to ingesting the gastric lavage tube. The spherical volume of each ectopic uterine tissue was calculated using the prolate ellipsoid formula: $V \text{ (mm}^3\text{)} = 0.52 \times \text{length} \times \text{width} \times \text{height}$ (all in millimeters). The biopsies were fixed in 10% neutral buffered formaldehyde solution. All pieces were embedded in paraffin after routine dehydration and 5 μm -thick sections were made with a microtome. The samples were stained with hematoxylin and eosin (HE). The slides were examined under a light microscope. The pathologist (F. O.) who assessed the samples was blinded to the treatment groups. At the end of the sixth week, if there were two lesions in a rat, the mean histopathological score of these lesions was recorded. The persistence of epithelial cells in the implants was scored semi-quantitatively as follows: 3 = well preserved epithelial layers; 2 = moderately preserved epithelium with leukocyte infiltration; 1 = poorly preserved epithelium (occasional epithelial cells only); 0 = epithelial line (10).

Statistical analysis was performed using SPSS, version 11.5 (SPSS Inc, Chicago, IL, USA) for Windows. Data were expressed as mean \pm standard error of mean, unless stated otherwise. Friedman's Test was used for the evaluation of lesion volumes, histopathological scores and all the biochemical analysis before, after and recurrence time in each groups. When these parameters were evaluated between the groups, Mann-Whitney U test was applied. $P < 0.05$ was considered as statistically significant.

Results

Sixty of the 68 implants (88.2%) were formed properly. In the second operation, the pretreatment volumes were compared. The pretreatment volumes were $93.6 \pm 31.7 \text{ mm}^3$ and $82.8 \pm 21.0 \text{ mm}^3$ in the control and L+M groups, respectively ($P=0.64$). The sum of the pretreatment histopathological scores were 2.6 ± 0.5 and 2.3 ± 0.1 in the control and L+M groups, respectively ($P=0.55$). These two results defined the efficient induction and formation of endometriotic lesions (Table 1).

The effects of the medications were assessed in the third operations. The sums of the post-treatment volumes were $85.0 \pm 23.8 \text{ mm}^3$ in the control group and $15.7 \pm 8.0 \text{ mm}^3$ in the L+M group. The difference was statistically significant ($P=0.03$). The sum of the post-treatment histopathological scores in the control group was 1.6 ± 1.3 ; whereas it was 2.0 ± 0.2 in the L+M group ($P=0.07$).

Table 1. The comparison of endometriotic volumes between the groups

	Control (C) (n=7)	Melatonin + Letrozole (M+L) (n=10)	p
Pretreatment			
Volume (mm ³)	93.6 \pm 31.7	82.8 \pm 21.0	0.64
Histopathological score	2.6 \pm 0.5	2.3 \pm 0.1	0.55
Posttreatment			
Volume (mm ³)	85.0 \pm 23.8	15.7 \pm 8.0	0.03
Histopathological score	1.6 \pm 1.3	2.0 \pm 0.2	0.07
Recurrence			
Volume (mm ³)	119.7 \pm 29.4	43.9 \pm 31.8	0.02
Histopathological score	2.5 \pm 0.3	2.2 \pm 0.3	0.35

The effects of the cessation of the medications were evaluated in the final (fourth) operations. The rat lost after the third operation in the letrozole and melatonin group was removed from statistical analysis at the recurrence time. The sum of the recurrence volumes in the control group was $119.7 \pm 29.4 \text{ mm}^3$; whereas it was $43.9 \pm 31.8 \text{ mm}^3$ in the L+M group. The difference was statistically significant ($P=0.02$). The volume gained at the recurrence time were 34.7 mm^3 and 28.2 mm^3 in the control and study groups respectively ($P=0.04$). The sums of the histopathological scores at that time were 2.5 ± 0.3 and 2.2 ± 0.3 in the control and L+M groups, respectively ($P=0.55$).

The sum of the lesion volumes in the control group was $93.6 \pm 31.7 \text{ mm}^3$ at the beginning. After the cessation of estradiol it decreased to $85.0 \pm 23.8 \text{ mm}^3$ ($P=0.31$) and increased to $119.7 \pm 29.4 \text{ mm}^3$ after starting estradiol ($P=0.02$) (Table 2). A significant reduction in histopathologic score was seen after cessation of the estradiol ($p=0.04$). At the recurrence time, histopathological scores reached the pretreatment values.

In the L+M group the lesion volumes decreased significantly after the treatment ($82.8 \pm 21.0 \text{ mm}^3$ and $15.7 \pm 8.0 \text{ mm}^3$, respectively). At the time of recurrence the mean volume was 43.9 ± 31.8 ($p=0.002$). Means of the histopathologic scores were 2.3 ± 0.1 , 2.0 ± 0.2 and 2.2 ± 0.3 in the pre-treatment (at the end of the second week), post-treatment (at the end of the fourth week) and recurrence phases (at the end of the sixth week), respectively.

Discussion

The medical treatment of endometriosis has progressed significantly in the last four decades and there are more choices available for clinicians than ever before. However, the ideal medical treatment has not been developed yet. This study was conducted to investigate the effects of the combination of some new drugs such as letrozol (an aromatase inhibitor) and melatonin (an anti-oxidant) on the progression of endometriosis in the rat model. In addition to the evaluation of the efficacy of this combination, our study also focused on the recurrence rate after the cessation of the treatment.

Table 2. The mean volume of endometriotic lesions before and after treatment and at recurrence time

	Pre-treatment (Mean±SEM)	Post-treatment (Mean±SEM)	Recurrence (Mean±SEM)	p
Control with Estrogen (n=7)				
Volume (mm ³)	93.6±31.7	85.0±23.8	119.7±29.4	0.02
Histopathological score	2.6±0.5	1.6±1.3	2.5±0.3	0.04
Melatonin + Letrozole (n=10)				
Volume (mm ³)	82.8±21.0	15.7±8.0	43.9±31.8	0.002
Histopathological score	2.3±0.1	2.0±0.2	2.2±0.3	0.86

We modified and improved the rat endometriosis model developed by Vernon and Wilson (2, 4, 5). Our model is unique, since rats are in hypo-estrogenic status except for estrus state; administration of depot estrogen twice weekly induced endometriosis faster. Additionally, this methodology eliminated the need for a vaginal smear before the second surgery to detect estrus state. The design of the study provided us with the opportunity to detect the recurrence rates after cessation of the treatment. Most of the drugs used for the treatment of endometriosis have to be stopped after 6 months. One of the most important points of all treatment modalities is to prevent recurrence long after they are discontinued. With this model, we were able to detect the recurrence rate of the lesions after termination of treatment. In contrast to humans and non-human primates, estrous animals do not shed their endometrial tissue and therefore do not develop endometriosis spontaneously. However, endometriosis can be induced by transplanting endometrial tissue to ectopic sites. These models are classified into two types, homologous and heterologous models. Homologous models have been employed utilizing surgical transplantation of the endometrium of the same or syngeneic animals in immunocompetent animals, whereas in heterologous models, human endometrial fragments are transferred either intraperitoneally or subcutaneously to immunodeficient mice. In our preliminary study we preferred a homologous rodent model for induction of endometriosis; however we intend to carry out studies in endometriosis research using immunodeficient mice as heterologous models. In our study, rats were not ovariectomized and were administered exogenous estrogen. Since we wanted the uterine tissues implanted autologously to be endometriotic lesions in all rats; we carried out a pilot study controlling this hypothesis and at the end of the study we concluded that using this methodology resulted in typical endometriotic lesions in all animals.

Endometriosis is an estrogen dependent disease. Many of the medical treatment modalities for endometriosis are targeted at decreasing or antagonizing estrogenic actions. Unfortunately, the ideal medical treatment has still not been developed. Drugs such as GnRH-a (agonists) are widely used for the cure of endometriosis. A wide range of adverse effects and very high recurrence rate after cessation of the therapy limit their long term use. Aromatase inhibitors appear to be the first breakthrough in the medical treatment of endometriosis since the introduction of GnRH-a in the 1980s (7).

Yildirim et al. published the effects of letrozole on endometriosis in a rat model (4). They found that endometriotic

lesions regressed in size (p=0.02) and histopathological scores decreased as well (p=0.28) when compared to findings at the beginning of the treatment. They found a significant rise in the lesion volume (p=0.02) and histopathological score (p=0.28) after cessation of letrozole. They hypothesized this to be a rebound phenomenon. The compensatory response to estradiol depletion in the hypothalamus results in higher serum FSH secretion and ovarian stimulation (11). Simultaneously, a strong suppression of estradiol may up-regulate the estrogen receptors in the targeted tissues. The combination of these two possible mechanisms may explain the increase of the endometriotic lesion volumes and scores.

In the current literature there are prospective clinical trials that approach the effectiveness of aromatase inhibitors in the treatment of endometriosis. Aromatase inhibitors with a progestin for the treatment of 10 resistant endometriotic premenopausal women was assessed in one small phase II study and it was found that post-treatment visible endometriotic lesions were smaller when compared to the pretreatment laparoscopic findings. Ninety percent of patients responded to this regimen with decreased pelvic pain (12). It was shown that the combination of an aromatase inhibitor with combined oral contraceptive pills resulted in a effective reduction of pain in the endometriotic women (13).

The main deficiency of such hormonal treatments is the high recurrence rate of the lesions when the treatment is stopped. To solve this problem, the combination of an aromatase inhibitor and a GnRH analogue was used during 24 months for women who have endometriosis and they were followed for two years without giving any medications (14). At the end of the follow-up, the investigators concluded that a novel regimen with an aromatase inhibitor and a GnRH analogue after conservative surgery was effective in controlling recurrence and pain in patients with severe endometriosis. On the other hand, these combinations caused significantly higher bone loss in the spine of the treated patients.

The widespread side effects and high recurrence risk following cessation of the hormonal drugs limit their long term use. There has been some investigation into applying a new non-hormonal management for endometriosis, which is a multifactorial disease, and oxidative stress has been proposed as a potential factor in the pathophysiology of the disease (15). Therefore, new medical treatments are needed which are aimed at reducing the oxidative stress with improved side-effects and being at least as effective as hormonal treatment. Melatonin seems to

be promising in this sense and this is the reason why we used melatonin in our study.

Melatonin (N-acetyl-5-methoxy-triptamine) is an endogenous free radical scavenger (16). Although its mechanism is not clearly explained, some of the steps in this mechanism are known. Melatonin can enter into the cells easily because of its high diffusion ability and can show its effects by entering the cell through its receptors and also without receptors, which makes it one of the most powerful antioxidants. In addition, ME may stimulate several anti-oxidative enzymes and inhibit a prooxidative enzyme by intra-cellularly binding to calmodulin (17). The main reactive oxygen species (ROS) is considered to be superoxide anion (O_2^-). Superoxide dismutase (SOD) rapidly decomposes superoxide anion into hydrogen peroxide and oxygen. Superoxide radicals are involved in many physiological and pathophysiological processes. Activated neutrophils and macrophages can also produce a large amount during the oxidative burst. Removal of superoxide is a necessary step in cellular defense against these damages (18). Catalase is an ubiquitous antioxidant enzyme present in most aerobic cells. CAT is involved in the detoxification of hydrogen peroxide (H_2O_2), a reactive oxygen species (ROS). CAT catalyzes the conversion of two molecules of H_2O_2 to molecular oxygen (O_2) and two molecules of water (H_2O) (19). Polyunsaturated lipids are especially susceptible to this type of damage when in an oxidizing environment and they can react to form lipid peroxides. Lipid peroxides are themselves unstable, and undergo additional decomposition to form a complex series of compounds including reactive carbonyl compounds. Polyunsaturated fatty acid peroxides further react to form malonaldehyde (MDA). MDA can be found in most biological samples including foodstuffs, serum, plasma, tissues and urine, as a result of lipid peroxidation, and has become one of the most widely reported analytes for the purpose of estimating oxidative stress effects on lipids (20). The ROS have been shown to be closely related to the inflammatory process and pathophysiology of disease.

There are many suggestions that antioxidant therapy may help the patients suffering from endometriosis. It has been published that if an anti-oxidant agent joined the treatment scheme of the patients, significant clinical improvements may occur (21-23). Yildirim et al. showed that melatonin causes significant regression both in the volume and histopathological scores on endometriosis in a rat model (4). They showed that the recurrence rate in the melatonin group was significantly lower than that observed in the letrozole group. This finding shows that melatonin can prevent recurrence after cessation of the treatment.

Guney et al. published a well designed study and they concluded that melatonin caused regression and atrophy of the endometriotic lesions in rats (3). In their melatonin group, the endometrial explant levels of MDA statistically significantly decreased and activities of SOD and CAT significantly increased when compared with the control group. In our study, SOD, CAT levels were increased and MDA level was decreased in the peritoneal fluids of rats with melatonin. After cessation of melatonin, there was a decrease observed in SOD and CAT levels. No change was observed in the level of MDA after cessation of the melatonin. We combined letrozole and melatonin in this study. We observed significant volume depletion on the lesions; however, histopathological scores did not decrease. This finding can be

extrapolated to humans: the patients who have huge endometriomas can be treated with the combination of letrozole and melatonin before any surgical intervention or prior to an in vitro fertilization program.

In conclusion, the combination of letrozole and melatonin caused regression in the volume of surgically induced endometriotic lesions in a rat model. Unlike letrozol, after cessation of melatonin, the recurrence is very low. Further studies are required to evaluate the effects of this combination.

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Correlation of colposcopy using Reid colposcopic index with histopathology- a prospective study

Reid Kolposkopi endeksi kullanılarak yapılan kolposkopinin histopatoloji ile korrelasyonu- prospektif bir çalışma

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Abstract

Objective: To estimate the diagnostic efficacy of colposcopy & determine the strength of correlation between colposcopic impression using the Reid Colposcopic Index (RCI) and histopathology.

Material and Methods: This was a prospective cross sectional study carried out in the colposcopy clinic at KLES Dr. Prabhakar Kore Hospital & Medical Research Centre, Belgaum from January 2008 to June 2009. A total of 268 women who fulfilled the selection criteria were included in the study. All women underwent colposcopy and a diagnosis was made based on RCI. Colposcopy directed biopsy was obtained from the abnormal areas. In cases where colposcopy did not reveal any lesion, a four quadrant biopsy from the squamocolumnar junction was taken, which served as a gold standard.

Results: Three women who had an unsatisfactory colposcopy & eleven women with the diagnosis of cervical cancer were excluded from the analysis. The sensitivity, specificity, positive predictive value & negative predictive value of colposcopy with CIN 1 as a disease threshold was 88.5%, 86.2%, 77% & 93.5% respectively. With CIN 2 as a disease threshold the sensitivity, specificity, positive predictive value & negative predictive value of colposcopy were 85.2%, 99.6%, 95.8% & 98.3% respectively. The degree of correlation between colposcopic impression using RCI & histopathology was high ($k=0.73$).

Conclusion: Colposcopy is an indispensable tool in the diagnosis of precancerous lesions & the good correlation between colposcopic impression using RCI & histopathology makes it a reproducible technique which is easy to implement in colposcopy clinics.

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Key words: Colposcopy, Reid colposcopic index, cervical cancer, cervical intraepithelial neoplasia

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Özet

Amaç: Kolposkopinin tanısal etkinliğini değerlendirmek ve Reid Kolposkopi Endeksi (RKE) kullanılarak elde edilen kolposkopik gözlemin histopatoloji ile korrelasyon gücünü araştırmak.

Gereç ve Yöntemler: Bu çalışma prospektif kesitsel bir araştırma olarak Ocak 2008 ve Haziran 2009 tarihleri arasında Dr. Prabhakar Kore Hastanesi Kolposkopi kliniğinde yapılmıştır. Seçim kriterlerine uygun 268 kadın çalışmaya dahil edildi. Tüm kadınlara kolposkopi yapıldı ve RKE kullanılarak tanı konuldu. Anormal görünen alanlardan kolposkopi altında biyopsi yapıldı. Kolposkopik olarak patoloji izlenmeyen kişilerde skuamokolumnar bileşmeden dört kadran biyopsi yapıldı ve altın standart olarak değerlendirildi.

Bulgular: Yetersiz kolposkopik gözlemi olan üç kadın ve serviks kanseri tanısı alan 11 olgu çalışmadan dışlandı. Kolposkopinin CIN 1 tanısındaki duyarlılığı, özgüllüğü, pozitif ve negatif öngörme değeri sırasıyla %88.5, %86.2, %77 ve %93.5 idi. CIN 2 tanısındaki duyarlılığı, özgüllüğü, pozitif ve negatif öngörme değeri sırasıyla %85.2, %99.6, %95.8 ve %98.3 idi. RKE kullanılarak elde edilen gözlemin histopatoloji ile korrelasyonu yüksekti ($k=0.73$).

Sonuç: Kolposkopi prekanseröz lezyonların tanısında vazgeçilmez bir araçtır. RKE kullanılarak elde edilen görüntülemenin histopatoloji ile yüksek korrelasyonu bu aracın kolayca kolposkopi kliniklerine entegre edilebilmesini ve başka jinekologlar tarafından da kullanılabilmesini sağlamaktadır.

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Anahtar kelimeler: Kolposkopi, Reid kolposkopi endeksi, serviks kanseri, servikal intraepitelyal neoplazi

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Introduction

Cervical cancer is a global health problem and is the leading cause of death due to cancer among women in developing countries. According to the WHO projections in 2005, there were over 500,000 new cases of cervical cancer, of which over 90% were in developing countries. Almost 260,000 women died of the disease, nearly 95% of them in developing countries. Cervical cancer has a long latent phase and can be prevented

easily by early detection using various screening procedures like Pap smear, HPV DNA testing, visual inspection with acetic acid and visual inspection with lugol's iodine (1). However, colposcopy remains the reference standard for assessing the validity of all the screening procedures (2).

Colposcopy is a visual technique that requires extensive training and experience. The limiting factor in the use of this diagnostic tool is that the accuracy of the method is directly related to the expertise of its operator. Hence, to ensure that

colposcopy gives a satisfactory level of accuracy in addition to proper training and certification of colposcopists, an objective grading system needs to be incorporated (3). Reid and Scalzi proposed the Reid Colposcopic Index (RCI) to make colposcopic diagnosis less subjective (4). RCI relies on critical analysis rather than on pattern recall. This study was undertaken to evaluate the diagnostic efficacy of colposcopy using RCI and to determine the degree of correlation between colposcopic impression and histopathology.

Material and Methods

The present study is a prospective cross sectional study carried out in the colposcopy clinic at the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre from January 2008 to June 2009.

A total of 268 women referred to the colposcopy clinic with complaints of persistent vaginal discharge, suspicious looking cervix, postcoital bleeding, post menopausal bleeding, inter menstrual bleeding or with positive cervical cancer screening test results were included in the study. Exclusion criteria were frank growth on the cervix & prior total hysterectomy.

Colposcopy was performed by any one of the three gynecologists trained in colposcopy using a video colposcope. Colposcopy directed biopsy was obtained from the abnormal areas using a punch biopsy forceps and, in cases where colposcopy was interpreted as normal, a four quadrant cervical biopsy was obtained from the squamocolumnar junction (SCJ) so as to assess the efficacy of RCI. Colposcopic diagnosis was made based on RCI. The total score for detecting the lesion are as follows: 0-2, low grade lesion (likely to be CIN 1): 3-4, intermediate grade (likely to be CIN 1 or CIN 2): 5-8, high grade lesion (likely to be CIN 2 or CIN 3) (4, 5). Biopsy results were categorized as benign, CIN 1, CIN 2, CIN 3 and invasive cervical cancer.

Cases of unsatisfactory colposcopy and early invasive cervical cancer were excluded from the analysis as RCI cannot be used in their diagnosis. The sensitivity, specificity and predictive values were calculated with the disease threshold of CIN 1 as well as CIN 2. The degree of correlation between colposcopic impression using RCI and histopathology was assessed using unweighted 'k' statistics.

Results

Of the 268 women enrolled in the study, 14 were excluded from the analysis as three had unsatisfactory colposcopy and 11 had colposcopic features suggestive of invasive cervical cancer. The majority of the women who participated in the study were in the age group of 30-40 years (43.7%) with the mean age of 36 years. 46% of the women had a parity of two and 34.5% had a parity of three. The chief complaint was white discharge in 66% of the women, followed by post menopausal bleeding in 6.7%, post coital bleeding in 5.1%, inter menstrual bleeding in 0.8%, and 21.3% were referred for suspicious looking cervix. Pap smear results were known in 71.8% of the study population, of whom 29.2% had atypical squamous cells of undetermined significance (ASCUS), 23.8% had low grade squamous

intraepithelial lesions (LSIL) and 12% had high grade squamous intraepithelial lesions (HSIL).

Of the 254 biopsies taken ,101 (39.76%) were from the abnormal areas and, in 153 (60.28%) cases where colposcopy was interpreted as normal, a four quadrant biopsy was obtained from the SCJ.

The agreement between colposcopic impression using RCI & histopathology and their correlation are shown in table no.1 and 2. Of the 60 (23.62%) cases of biopsy proven CIN 1, nine were negative on colposcopy and 51 (20.07%) cases were accurately diagnosed. Of 27 (10.63%) biopsy proven cases of CIN 2 and above, one (0.4%) case was reported as benign & three (11.1%) as CIN 1. Although colposcopic diagnosis of CIN 1 was made in 76 cases, over estimation was noted in 22 cases and three cases of biopsy proven CIN 2 were underestimated. CIN 2 lesions were noted in five cases, of which one (4.1%) case was underestimated. An accurate diagnosis was made in all the 19 biopsy proven cases of CIN 3.

Out of the 167 biopsy negative cases using CIN 1 as the disease threshold, colposcopy could accurately confirm the absence of disease in 144 cases. In the remaining 23 biopsy negative cases, colposcopic diagnosis of CIN 1 was made in 22 cases and CIN 2 in one case. The association between colposcopic impression using RCI and histopathology was highly significant ($p < .001$). The 'k' value for the strength of correlation between colposcopic impression for CIN 1 using RCI and histopathology was $k=0.66$ ($p < 0.001$), for CIN 2 it was $k=0.60$ ($p < 0.001$) and for CIN 3 it was $k=1$. Overall the colpo histological correlation was $k=0.73$, $p < 0.001$.

The sensitivity & specificity of colposcopy with CIN 1 as disease threshold was 88.5% (CI 84.6-92.4) and 86.2% (CI 82-90.4)

Table 1. Agreement between colposcopic impression using RCI and histopathology

Histopathology Results	Colposcopy Results				Total
	Benign	CIN 1	CIN 2	CIN3	
Benign (%)	144 (57)	22 (8.6)	1 (0.4)	-	167
CIN 1 (%)	9 (3.5)	51 (20.1)	-	-	60
CIN 2 (%)	1 (0.4)	3 (1.1)	4 (1.5)	-	8
CIN 3	-	-	-	19 (7.4)	19
Total	154	76	5	19	254

Table 2. Correlation of colposcopy using RCI and histopathology

Colposcopy results	Over estimation (%)	Under estimation (%)	Accurate estimation (%)	Total
Benign	-	10 (6.5)	144 (93.5)	154
CIN 1	22 (29)	03 (3.9)	51 (67.1)	76
CIN 2	-	01 (20)	04 (80)	05
CIN 3	-	-	19 (100)	19
Total	22 (8.7)	14 (5.5)	218 (85.8)	254

Colpohistological correlation- 85.8 %

respectively. The sensitivity and specificity of colposcopy with CIN 2 as disease threshold were 85.2% (CI 80-89.6) and 99.6% (CI 98.9-100) respectively. The positive predictive value, negative predictive value, false positive and false negative rate with CIN 1 as the disease threshold were 77%, 93.5%, 13.8% and 11.5% respectively. With CIN 2 as the disease threshold the positive predictive value, negative predictive value, false positive and false negative rate were 95.8%, 98.3%, 0.4% and 14.8% respectively.

Discussion

The present cross sectional study aimed at evaluating the efficacy of colposcopy using RCI and determining the strength of correlation between colposcopic impression and histopathology. In our study colposcopy was performed by clinicians who were certified and experienced in this technique. Overall, there was good agreement between colposcopic impression using RCI & histopathology. However, the degree of correlation with histopathology was excellent for CIN 3 lesions as compared to CIN 1 & CIN 2 lesions. Colposcopy revealed a satisfactory sensitivity of 88.5% using CIN1 as threshold, which was slightly greater as compared to the sensitivity of colposcopy using CIN2 as threshold (85.2%). This difference was noted in the present study because three of the biopsy proven CIN2 lesions were underestimated as CIN1. Underestimation may occur when a high grade lesion may be overlooked, which may appear as an inner border of sharp acetowhite demarcation within a less opaque acetowhite area (6). When the threshold was raised to CIN 2, the specificity was more (99.6%) as compared to that of CIN1 as the disease threshold (86.2%). Confusion amongst CIN1, cervicitis and HPV infection may account for inaccuracy of diagnosis of low grade lesions by colposcopy (3). The predictive value of colposcopy was also shown to be better with increasing grades of neoplasia. This implies that colposcopy performs better in the diagnosis of high grade lesions.

The present study showed a higher sensitivity and similar specificity compared to ASCUS-LSIL triage study (7) and a study carried out by Mousavi A.S. et al. (8) where RCI was used to interpret the colposcopy findings. There was a good strength of correlation between colposcopic impression using RCI and histopathology in our study, which was comparable to a study carried out by Mousavi A.S. et al. (8). Although accuracy of colposcopy is attributed to the operator expertise, colposcopists may not be entirely responsible for the disagreement between the colposcopic impression and histologic diagnosis, as a certain degree of inter observer variability occurs among the pathologists while histologically grading CIN (9).

In the present study however, comparison was not made with colposcopic impression without the use of RCI. Another limitation of our study is that high grade lesions should have been biopsied using a loop to avoid sampling error.

Colposcopy directed biopsy provides a histopathological diagnosis and colposcopic impression provides information concerning the lesion size and location, which forms the basis for additional management (3). Women with pre invasive lesions can be effectively managed using the 'see and treat' approach to achieve maximum compliance of the screening of positive women especially in low resource countries. However the decisions are often anchored on colposcopic assessment (10, 11). The use of this scoring and grading system may guide colposcopic interpretation so that higher grade lesions are not missed and trivial findings are not over interpreted.

In conclusion colposcopy using RCI has satisfactory diagnostic efficacy and the good correlation between colposcopic impression and histopathology makes it a valid tool in the diagnosis and management of precancerous lesions.

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Hysterectomy through minilaparotomy for benign gynaecological conditions: a valid option

Benign jinekolojik hastalıklarda minilaprotomi ile yapılan histerektomi: geçerli bir seçenek

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Abstract

Objective: Efforts are continuously being made for surgery to be less invasive with a minimal access approach. This article reports our experience with minilaparotomy hysterectomy in patients with benign gynecological disease or preinvasive pathology.

Material and Methods: A prospective study to analyse the outcome and per-operative and post-operative complications was conducted in 69 patients undergoing hysterectomy by the minilaparotomy approach through 4-5cm Pfannenstiel incision.

Results: The mean operating time and postoperative hospital stay were 41.3 min and 3.1 days, respectively. Composite morbidity was encountered in 12 women (17.4%) with no major complications or mortality. None of the patients had an estimated blood loss over 500ml.

Conclusion: Minilaparotomy hysterectomy in benign gynecological disease provides an appealing, effective, expeditious, minimal access and cost-effective option/alternative to the traditional abdominal hysterectomy. It obviates the need for any additional expensive equipment and above all improves upon the per-operative and post-operative outcomes without compromising, whatsoever, the quality of surgery.

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Key words: Hysterectomy, minilaparotomy, Pfannenstiel incision

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Özet

Amaç: Cerrahinin daha az invaziv olması için çabalar devam etmektedir. Bu makalede benign jinekolojik hastalıklar ve preinvaziv patolojiler için uyguladığımız minilaparotomi ile histerektomi deneyimimizi sunuyoruz.

Gereç ve Yöntemler: Histerektomisi 4-5 cm'lik Pfannenstiel insizyondan yapılan 69 hastadaki ileriye dönük çalışmamızda operasyon sonuçlarımızı, operasyon sırasında ve postoperatif dönemdeki komplikasyonlarımızı analiz ettik.

Bulgular: Ortalama operasyon süresi 41.3 dakika ortalama hastanede kalış süresi ise 3.1 gün idi. Oniki (%17.4) kadında morbidite oluştu ancak hiçbir hastada majör komplikasyon veya mortalite gelişmedi.

Sonuç: Benign jinekolojik durumlar için minilaparotomi ile uygulanan histerektomi, geleneksel abdominal histerektominin etkili, minimal invaziv ve maliyet/etkin bir alternatifidir. Tüm bunlara ek olarak, cerrahinin kalitesinden ödün vermeden ve pahalı araçlara ihtiyaç duymadan operasyon sırasındaki ve postoperatif dönemdeki sonuçları iyileştirmektedir.

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Anahtar kelimeler: Histerektomi, minilaparotomi, Pfannenstiel insizyon

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Introduction

According to Farquhar CM and Steiner CA (1), of the 600,000 hysterectomies carried out in the United States each year (a number which has remained constant for the past 20 years), 65-75 percent are performed through large abdominal incisions. Although research indicates that vaginal hysterectomy is safer and cheaper than total abdominal hysterectomy, the latter still accounts for 60-80% of all hysterectomies in the UK and the USA (2).

LAVH and Laparoscopic hysterectomies have recently become popular due to the shorter hospital stay and minimum post-operative morbidity but have their own drawbacks such as expensive equipment, extensive training, steep learning curve and longer duration in the operation suite (3-6).

Minilaparotomy is an established technique (7) for sterilization operations for decades and is also being used for many benign

gynecological conditions, recanalisation (reversal of sterilisation) and ovarian cysts with encouraging results (8-10).

In the present study, the same concept is extended to abdominal hysterectomy for benign conditions in selected patients in an effort to establish minilaparotomy hysterectomy as a safe, minimally invasive and cost-effective technique.

Material and Methods

A prospective study was conducted in 69 patients over a period of 25 months from Feb. 2007 to Mar. 2009.

Inclusion criteria were mobile uterus with a size up to 12 weeks. Exclusion criteria adopted were patients with previous laparotomy, suspected malignancy, large adnexal masses (>5 cm) and diagnosed cases of genital tuberculosis (suspected cases were to be subjected to certain special investigations

like ELISA, Polymerase Chain Reaction, endometrial Biopsy, diagnostic laparoscopy with fluid aspiration from the pouch of Douglas, if required, as well as the routine ones).

Written informed consent was obtained from all the patients and the Departmental Ethical Committee approved the study. All the operations were performed by at least one of the consultants included as authors in this study.

Catheterisation of the bladder was done with disposable urethral catheter kept for the intra-operative duration only and thereafter removed in the operating suite itself.

Anesthesia used was either regional-spinal/epidural or general. The operation was conducted with the patient in the supine position.

The incision employed to open the abdomen in all the cases was the suprapubic Pfannenstiel, with a size of \approx <5 cm (Minilaparotomy), (Figure 1).

Subcutaneous fat was cleared to expose the Rectus fascia in the transverse axis for approximately 5 cm and then incised along the entire length corresponding to the skin incision.

Rectus muscles were retracted from the midline, exposing the underlying peritoneum, which was entered digitally above the level of the bladder dome, incising vertically until the entrance extended the full length of the fascial incision.

The uterus, adnexa and pelvis were then carefully assessed to determine the extent of any unexpected pelvic pathology or adhesions which were lysed, if necessary. Gentle packing was done to gain additional exposure.

The uterus was exteriorized by introducing the index and middle fingers and also the thumb of the left hand, followed by applying long curved Kocher's clamps lateral to the corpus on either side to achieve uterine elevation. Retraction was done with Deever's manually held abdominal retractor.

The remainder of the abdominal hysterectomy (extrafascial) proceeded in the traditional manner (11), (Figure 2).

The pelvic and parietal peritoneum were not closed but the Rectus sheath was apposed with continuous suture. Once the surgery was completed, skin incision was closed by applying sub-cuticular sutures, (Figure 3) in all the cases. The possibility of postoperative wound hematoma or seroma formation was eliminated by applying a transverse pressure dressing over the incision for 48 hours.

Intra-operative blood loss was estimated by noting the number of sponge packs soaked during surgery and by measuring the amount of blood in the suction bottles. Blood transfusion was given only if blood loss was estimated to be more than 500 ml. Patients were encouraged to become ambulatory as early as was convenient for them after the operation.

Injectable antibiotics were given for 36 hours post-operatively and then replaced by oral ones.

Injectable Diclofenac was given on demand for post-operative pain relief (3 doses in 24 hours at the most) and Injection Pentazocine was to be used as a reserve if pain relief was not adequate.

Oral fluids were started the next morning on hearing the bowel sounds, followed by semi-solids after another 12 hours.

The patients were allowed to go home when ambulatory, passing urine normally, moved their bowels and had no complications.



Figure 1. Minilaparotomy incision



Figure 2. Removed uterus through minilaparotomy incision



Figure 3. Subcuticular suturing of the minilaparotomy incision

All the observations were given consideration together with intra- and post-operative complications.

The statistical data was collected as mean (range) and as percentage.

Results

Patient profiles as regards age, parity and body weight and the indications for hysterectomy were as depicted in Table 1. Symptomatic fibroids constituted the commonest indication accounting for 52.2 percent of the hysterectomies in our cases, followed by dysfunctional uterine bleeding (26.1 percent), chronic pelvic pain (7.2 percent), adenomyosis and post-menopausal bleeding (5.8 percent each) and Cervical Intraepithelial Neoplasia (2.9 percent).

Operative details are enumerated in Table 2. Through 4-5 cm Pfannenstiel's incision, the surgery performed was total abdominal hysterectomy with unilateral or bilateral salpingo-oophrectomy (due to the indication or the presence of grossly unhealthy looking ovary/ies in our younger patients also).

No difficulty was encountered even in large uteri (up to 12 weeks size), enlarged either uniformly or irregularly by single or studied with multiple myomas. Regardless of the uterine size, the origins of the round and adnexal ligaments was always lateral to and within easy reach of a transverse minilaparotomy incision and, moreover, it was also noticed that these elongated ligaments were quite lax. In 16 cases (23 percent) adhesiolysis was required. No need was felt for vaginal packing or indwelling bladder catheterisation in any of the cases. Mean operating time was 41.3 min with a range of 30-60 minutes. Estimated blood loss was relatively low (being <500 ml) and none of the patients required blood transfusion even though venous thrombosis prophylaxis was not used in our patients. It is obvious that post-operative ambulation, and duration of hospital stay were appreciably less, with mean (ranges) of 28 (22-32) hours and 3.1 (2.5-4) days, respectively.

Moreover, the number and frequency of injectable analgesic (Diclofenac in our study) requirement were as low as 1-3 doses with a mean of 1.5 injections. Table 3 illustrates the post-operative complications. Not only were no major complications seen in any of the patients; but also, the composite morbidity was seen only in 12 women (17.4 percent).

Discussion

Hysterectomy, the commonest major gynecological operation, is the only definitive cure for many benign gynecological conditions, and rates highest in satisfaction scores compared with other treatments (2). It is a common operation which can be done via the abdominal or vaginal route. In spite of being an eminent procedure in the repertoire of gynecological practice, there is no consensus on the best way of performing hysterectomy in any particular clinical situation (12).

Conservative alternatives, including endometrial ablative techniques, the levonorgestrel-releasing intrauterine system and uterine artery embolization for fibroids, have not yet greatly reduced hysterectomy rates, which vary widely between regions and within the same geographical area (2).

Table 1. Patient Profile and Indications For Hysterectomy

AGE mean (range)	39.57 (37-66) years	
PARITY mean (range)	2.93 (0-5)	
WEIGHT mean (range)	58.41 (43-81) kg	
Indications for hysterectomy		
Symptomatic Fibroids	36	52.2 %
Intramural	27	
Submucous	3	
Subserous	2	
Cervical fibroid	2	
Myomatous polyp	2	
Dysfunctional Ut. Bleeding	18	26.1 %
Chronic Pelvic Pain	5	7.2 %
Adenomyosis	4	5.8 %
Post-menopausal Bleeding	4	5.8 %
Cervical Intraepithelial neoplasia	2	2.9 %

Table 2. Operative data

Anaesthesia-General	6	8.7%
Epidural	9	13.0%
Spinal	54	78.3%
Uterine Size- normal	17	24.6%
6-8 weeks	14	20.3%
8-10 weeks	17	24.6%
10-12 weeks	21	30.5%
Operative Procedure	Total Abd. Hysterectomy (TAH) with unilateral/bilateral salpingo-oophrectomy	
Adhesiolysis	16	23.2%
Operating Time-mean (range)	41.3 (30-60) min	
Between 20-40 min.	46	66.7%
Between 40-60 min.	23	33.3%
Estimated Blood Loss-mean	240 ml	
<300ml	62	89.8%
300-500ml	7	10.2%
Patients requiring blood transfusion	-	
Hospital stay-mean (range)	3.1 (2.5-4)days	
Post-op. ambulation-mean (range)	28 (22-32)h	
Onset of oral diet-mean (range)	22 (20.5-28)h	
Injectable Diclofenac-mean (range)	1.5 (1-3)doses	
Additional analgesic (Pentazocine)	-	

Table 3. Complications*

Blood loss >300 ml	7	10.20 %
Paralytic Ileus	1	1.45 %
Fever	2	2.85 %
Urinary tract infection	1	1.45 %
Urinary retention	-	
Wound infection	1	1.45 %
Resuturing	-	
Repeat laparotomy	-	
TOTAL	12	17.40 %
*-No Major Complications or Mortality Were Encountered		

Although laparoscopic hysterectomy offers a minimally invasive alternative to laparotomy, with a shorter hospital stay and quicker return to normal activities, it has the drawbacks not only of expensive equipment, long learning curve and prolonged operating time but also higher complication rates than abdominal hysterectomy (13).

In his comparison of hysterectomy techniques, Garry (14) found laparoscopic assisted vaginal hysterectomy to be associated with longer operating time but less post-operative pain and a shorter convalescent period. Learman LA (15), in 2004, pointed out that more major complications were experienced with laparoscopic as compared with abdominal hysterectomy (11.1% versus 6.2%) but that there was no significant difference between hysterectomies conducted by laparoscopy and through the vaginal route .

In 1995, Bronitsky C and Stuckey SJ (16) studied complication rates in 62 patients undergoing LAVH and found that a sizeable number of 6 patients (i.e. 9.7%) had had major problems requiring further surgery as is also mentioned in the later studies of 2002 and 2006 with conversion to laparotomy rates being 5 (17) and 25 percent (18), respectively. The recently concluded Cochraine study in 2009 (19), mentioned its benefits such as speedier return to normal activities, but at the cost of more urinary tract (bladder or ureter) injuries and longer operation time. Efforts have long been made for an alternative to open surgery that is minimally invasive and comparable to laparoscopic hysterectomy in post-operative pain, cosmetic results and early return to normal activities but is not as expensive and has minimal untoward effects.

Use of traditional minilaparotomy for hysterectomy has been reported only rarely. Hoffman and Lynch (20) found the procedure safe and effective in non-obese women in whom a vaginal approach was precluded. Benedetti Panicci et al. (21) also have used minilaparotomy successfully in benign gynecological diseases and hysterectomy.

As a substitute for laparoscopy and laparotomy, In 2003 Pelosi and Pelosi (22), then tried a minilaparotomy Kustner's incision (cruciate incision 3 cm-5 cm, originally reported in1896) as the sole means of surgical access, assessment and treatment for benign pelvic conditions along with certain innovative instruments. Alcalde et al. (23) conducted minilaparotomy hysterectomies in 150 patients using a self-retaining elastic abdominal retrac-

tor and regarded this approach to be a safe, minimally invasive alternative to laparoscopic hysterectomy for institutions that do not have the required expensive equipment or for gynecologists who do not have laparoscopic experience.

In 2005, Panici et al. (24) employed the minilaparotomic approach in 116 patients and inferred that it should be considered a valid alternative to the classic abdominal hysterectomy because of the excellent outcome achieved.

Our procedure-minilaparotomy through 4-5 cm Pfannenstiel incision-relies on traditional but small open technique, with only routine standard hysterectomy instrumentation, thus making it significantly faster than conventional or laparoscopic hysterectomy and easy to perform.

To summarise: conventional but significantly smaller open techniques and traditional instrumentation were employed, thus removing the need for frequent use of traumatic metal retractors, extensive bowel packing and extended incision exposure. Moreover, small incision might lead to lesser tissue trauma, nerve damage, bruising and post-operative pain.

In the present study: mean operating time, day of mobility and of starting oral diet and maximum injectable analgesic requirement were relatively low. Blood loss was less and there was no perioperative blood transfusion requirement.

No major complications were noticed in any of the patients, and the overall 17.4 percent complication rate was also appreciably low. Results of our study are comparable with those of Panici et al. (24) in whose study of 116 minilaparotomic hysterectomies, a mean operating time of 50 min (range 34-88 min), median post-operative stay of 3 days (range 2-5) and no intraoperative complications or perioperative blood transfusion were reported, while minor postoperative complications occurred in 14% of cases.

It is obvious from the present study that minilaparotomy hysterectomy is associated with minimum intra-& post-operative complications.

Hence, minilaparotomy hysterectomy procedure through a 4-5 cm Pfannenstiel incision would seem to have great potential for use in the third world countries as it can be learnt easily without the use of any extra expensive instruments.

Conclusion

This new modality-useful for normal, large and fibroid-ridden uteri-combines the technical benefits of standard laparotomy with the convalescent advantages of laparoscopic surgery. Minilaparotomy through a 4-5 cm Pfannenstiel incision is a minimally invasive procedure ideal for gynecologists who are less skilled in vaginal or laparoscopic surgery and who are more comfortable with the standard abdominal approach. The procedure is far easier to teach than laparoscopic procedures because of the high degree of technical skill required for the latter and produces excellent results.

Nevertheless, minilaparotomy has its limitations in cases where severe adhesions might exist (e.g. endometriosis, previous myomectomy, previous pelvic inflammatory disease, bowel disease or malignancy). In those cases, open laparoscopy is

strongly recommended to assess the severity of the condition and to determine whether minilaparotomy is feasible.

This approach is substantially more cost-effective than prolonged laparoscopic or laparoscopically assisted vaginal hysterectomy. Since it uses conventional open techniques and traditional instrumentation, this method can be learnt and mastered quickly.

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Assessment of ovarian reserve and Doppler characteristics in patients with multiple sclerosis using immunomodulating drugs

İmmünmodülatör ilaç kullanan multiple sklerozlu hastalarda over rezervinin ve Doppler karakteristiklerinin değerlendirilmesi

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Abstract

Objective: There is limited data about fertility in multiple sclerosis (MS) patients using immunomodulating drugs and no data exists regarding the ovarian reserve of these patients. Therefore, we aimed to evaluate the ovarian reserve and doppler characteristics of MS patients using immunomodulating drugs.

Material and Methods: MS patients using immunomodulating drugs (interferon (IFN) β and glatiramer acetate) and age-matched healthy controls were included in the study. Subjects were examined in the early follicular phase of the menstrual cycle with transvaginal ultrasound to evaluate ovarian volume, antral follicle count (AFC) and ovarian stromal artery Doppler. On the same day, blood was taken for determining serum follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) levels. A subgroup analysis was also carried out between MS patients using only IFN β and controls to compare the same parameters.

Results: Mean ovarian volume and total AFC were lower in MS patients using immunomodulating drugs than in the controls. FSH and E2 levels did not show any differences between the groups, but LH levels were significantly higher in MS patients. All the Doppler parameters of the ovarian stromal artery were higher in MS patients but not significantly. In the subgroup analysis, the same significant differences were found for ovarian volume, AFC and LH levels. In addition, MS patients showed significantly higher mean pulsatility index measurement than the controls.

Conclusion: The findings of this study demonstrated diminished ovarian volume and follicular reserve in MS patients using immunomodulating drugs compared to age matched healthy controls. However, further studies are required to elucidate whether compromised ovarian reserve in MS patients is due to drugs or the disease itself.

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Özet

Amaç: İmmünmodülatör tedavi kullanan Multipl Skleroz (MS) hastalarının fertiliteleriyle ilgili sınırlı, over rezervleriyle ilgili ise hiç data mevcut değildir. Bu çalışmadaki amacımız, immünmodülatör tedavi kullanan MS hastalarının over rezervleri ve stromal arter doppler karakteristiklerini incelemektir.

Gereç ve Yöntemler: Çalışmaya immünmodülatör tedavi (interferon-beta ve glatiramer asetat) kullanan MS hastaları ve yaş uyumlu sağlıklı kontrol grubu alındı. Hastalar erken foliküler dönemde transvajinal ultrasonografi ile incelenerek over hacmi, antral folikül sayısı (AFS) ve overyan stromal arter Doppler ölçümleri açısından değerlendirildi. Aynı gün serum folikül stimüle edici hormon (FSH), luteinize edici hormone (LH) ve estradiol (E2) ölçümleri için kan alındı. Sadece interferon tedavisi alan hastaları kontrol grubuyla karşılaştırmak için subgroup analizi de yapıldı.

Bulgular: İmmünmodülatör tedavi kullanan MS hastalarının ortalama over hacmi ve total AFS ölçümleri kontrol grubuna göre düşük bulundu. Gruplar arası FSH ve E2 seviyeleri bir fark göstermemekle birlikte LH seviyesi MS hastalarında anlamlı olarak yüksekti. Overyan stromal arter Doppler parametrelerinin tümü MS hastalarında yüksekti ancak bu yükseklik anlamlı değildi. Sırf interferon kullanan hastaların dahil edildiği subgroup analizinde, over hacmi, AFS ve LH seviyeleri arasında yine anlamlı fark bulundu. Buna ek olarak interferon kullanan MS hastalarının PI ölçümleri kontrol grubuna göre anlamlı olarak yüksekti.

Sonuç: Bu çalışmada immünmodülatör tedavi kullanan MS hastalarının over hacmi ve folikül rezervi aynı yaşta sağlıklı kontrol grubuna göre daha düşük bulundu. Ancak over rezervindeki bu düşüklüğün MS hastalığına mı, yoksa kullanılan immunomodülatuar tedaviye mi bağlı olduğunun, daha geniş hasta serileriyle araştırılması gerekmektedir.

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Anahtar kelimeler: Multipl Skleroz, immunomodülatuar tedavi, interferon-beta, over rezervi, Doppler

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Introduction

Multiple sclerosis (MS) is the most common disabling central nervous system disease of young adults, and is estimated to affect 2.5 million people worldwide, with a prevalence of ~1 in 1000. Among adults with MS, there is a clear gender bias towards females, with a female-to-male ratio of 3-2:1 with the majority (80%) being diagnosed between the ages of 20 and 45 years (1). Since women of reproductive age are commonly affected, future reproductive performance is likely to be of great importance to these women.

There are limited data available concerning fertility in MS, but spontaneous female fecundity appears to be decreased (2). A recently published review suggested reduced spontaneous fecundity due to endocrine, autoimmune and sexual dysfunction, as well as gonadotoxic therapies in MS patients (3). Alterations in tubal function due to neuronal dysfunction may also affect fertility in patients with MS. In the studies where pregnancy outcome of MS patients was evaluated, a higher frequency of low birth weight infants was observed compared to healthy women. This is suggested to result from alterations in the uterine function due to neuronal dysfunction in pelvic organs, which may produce suboptimal intrauterine conditions influencing fetal growth, or due to neuronal-mediated dysfunction of blood circulation in pelvic organs (4, 5). However, there has never been any implication that the reduced fertility in MS patients could be due to diminished ovarian reserve.

Although prospective studies evaluating fertility and ovarian follicular reserve in these patients are lacking, some of the immunosuppressive drugs such as mitoxantrone and cyclophosphamide used in MS are cited as highly gonadotoxic based on animal and human studies (6-8). However, those studies evaluated the incidence of amenorrhea, instead of evaluating ovarian reserve markers such as follicle stimulating hormone (FSH), estradiol (E2), inhibin B, anti-müllerian hormone (AMH) or antral follicle count (AFC) to determine diminished ovarian function.

On the other hand, to date, such an effect has not been attributed to the immunomodulating drugs [IFN beta (β) (IFN- β 1a (Avonex[®], Rebif[®]), IFN- β 1b (Betaseron[®] /Betaferon[®])), and glatiramer acetate (GA) (Copaxone[®])]. An International consensus statement on the use of disease-modifying agents in MS published in 2002 advised physicians that they should warn patients of the effect of disease-modifying agents on fertility, and their safety in pregnancy or breastfeeding has not yet been established (9).

There is limited data about fertility in MS patients using immunomodulating drugs and no data exists regarding ovarian reserve of these patients. Therefore, we aimed to evaluate ovarian reserve and Doppler characteristics of MS patients using immunomodulating drugs and compared antral follicle count, ovarian volume, ovarian stromal artery Doppler indices and basal hormonal levels of MS patients using immunomodulating drugs with age-matched healthy controls.

Material and Methods

Patient Recruitment and Evaluation

In this prospectively designed controlled study MS patients, who were informed of the study and wished to participate, were referred from the neurology clinics of Kirikkale and Ankara Universities and consent was obtained from each patient. The study was approved by the Ethical Committees of Kirikkale and Ankara University School of Medicine and conducted according to the guidelines for clinical studies described in the Declaration of Helsinki (as revised by the World Medical Association, <http://www.wma.net>).

The control group was recruited from healthy women who presented at the gynecology clinic of Kirikkale University School of Medicine for routine follow-up and who wished to participate in the study.

The demographic features, including age and body mass index (BMI), were recorded for all subjects. A detailed medical history was elicited from all patients, including the presence of any systemic disease including diabetes mellitus, hypercholesterolemia, atherosclerosis, hypertension, and polycythemia, history of ovarian surgery and bilateral tubal ligation, use of oral contraceptive pills or hormonal therapy in the six months prior to the study inclusion, and smoking and alcohol abuse. A detailed physical examination was performed and an initial laboratory examination, including complete blood count and lipid profiles were performed. Patients with a history or diagnosis of any of the above mentioned diseases or habits were excluded from the study for both MS and the control groups. In addition, infertility and having polycystic ovary syndrome according to Rotterdam criteria (10) were accepted as exclusion criteria for the control group.

Patients eligible for the study were examined in the early follicular phase of the menstrual cycle (day 2-3) with transvaginal ultrasound to evaluate ovarian volume, AFC, and ovarian stromal artery Doppler indices. Serum samples were obtained simultaneously to determine FSH, luteinizing hormone (LH) and E2 levels.

At this visit, the age at the first MS attack, menstrual cycle pattern, treatment for MS, treatment period, previous pregnancies and pregnancies while on therapy, and type of contraception were also recorded.

Ultrasound Evaluation

All Ultrasound examinations were performed on day 2-3 of the menstrual cycle at 9-10 am with the Siemens Acuson Antares (Mountain View, CA, USA) ultrasound machine equipped with a 4-9 MHz transvaginal probe after the bladder had been emptied. B-mode transvaginal sonography was applied first to localize the ovaries and determine any existing ovarian pathology. The length and height of the ovaries were measured in the sagittal section and width in the transverse section after 90° rotation of the transducer. Ovarian volumes were calculated as: $d1 \times d2 \times d3 \times \pi/6$, where d1, d2 and d3 are the three maximal

longitudinal, anteroposterior, and transverse diameters. The numbers of small antral follicles (2-5 mm) and of larger antral follicles (6-10 mm) were counted as the transducer was moved from the outer to the inner margin of the ovary. The follicle diameter was calculated as the mean of two perpendicular measurements.

Doppler Sonography

Both ovaries were then scanned with the power Doppler mode. Power Doppler gain settings were set to achieve maximum sensitivity to detect low velocity flow without noise. Other settings were as follows: frequency: 5 MHz and Filter: 2.

Ovarian stromal artery blood flow was then evaluated in pulsed Doppler mode to obtain flow velocity waveforms by examining vessels in the ovarian stroma (searching for any small artery in the ovarian stroma not close to the surface of the ovary or located near the wall of a follicle). For each examination, the mean value of three consecutive waveforms was obtained. Resistance index (RI), pulsatility index (PI), systolic/diastolic (S/D) ratio and peak systolic velocity (PSV) were automatically calculated from three consecutive flow velocity waveforms. Both ovaries were identified in all participants. The same investigator (A.P.C.) performed and videotaped all examinations.

Hormonal Assays

Hormone levels were measured using electro chemiluminescence immunoassay with MODULAR ANALYTICS E170 (Elecsys module) immunoassay analyzer (Roche Diagnostic, Mannheim, Germany), using the Roche kits. The intra- and interassay coefficients of variation (CV) for FSH ranged between 0.6%-2.4% and 2.5%-3.9%, respectively. The intra-assay CV range for LH and Estradiol were 0.8%-1.8%, and 2.7%-6.5%, respectively. The minimum detectable limits for FSH and LH were <0.10mIU/ml and for Estradiol this was 10 pg/ml.

Statistical Analysis

Shapiro-Wilks test was used to assess normal distribution of continuous data. Comparison of the continuous data between the MS and control groups was estimated using Student's t-test and non-parametric Mann Whitney-U test according to the distribution. Categorical data were compared using the chi-square test.

Mean ovarian volume, RI, PI, S/D, PSV and AFC measurements of right and left ovaries were compared using Paired samples t-test or Wilcoxon signed ranks test. Hence, there were no statistically significant differences between right and left ovaries, mean values of these parameters were used in comparing the MS and control groups.

A P-value ≤ 0.05 was considered as statistically significant for all tests used. Statistical analysis was performed using the SPSS 15.0 statistical package (SPSS Inc, Chicago, IL, USA).

Results

Patient Characteristics

Twenty-two patients with MS were referred to the gynecology clinic. All of the patients had a normal regular menstrual

cycle pattern. Of the 22 patients, 20 presented with relapsing-remitting, 1 with primary progressive, and 1 with secondary progressive multiple sclerosis. Of the 22 patients, 21 patients used immunomodulating drugs (17 patients IFN- β , 2 patients GA, and 2 patients IFN- β 1a and GA) and 1 patient used the immunosuppressive drug azathioprine.

Three patients were excluded from the study because one was using Azathioprine, one was 46 years old, and the other due to non-compliance. Thus, the study group for comparison purposes included 19 patients with a mean age of 33.21 ± 5.72 (range 23-41). Twenty-five healthy women with a mean (\pm SD) age of 33.04 ± 5.07 (range 21-42) were evaluated as controls.

Mean duration of disease was 88.2 ± 57.3 months (range 8-192) and mean length of drug usage was 38.7 ± 32.3 months (range 5-96) in 19 MS patients using immunomodulating drugs.

Fertility Before and After MS Diagnosis

Of the 22 patients, 4 patients had no desire to become pregnant. Apart from these 4 patients, 11 MS patients had been using an intrauterine device, condom or coitus interruptus for contraception at the time of study inclusion. None had had pelvic surgery other than cesarean section (4 patients). One patient experienced infertility prior to the diagnosis of MS and conceived after ovulation induction with clomiphene citrate. After the diagnosis of MS, the patient remained infertile and could not conceive for 5 years despite having unprotected intercourse. Eighteen patients (after excluding patients with no desire to become pregnant) had 57 pregnancies in total; 5 resulted in spontaneous abortion and 15 ended in termination of pregnancy. Eleven of these pregnancies were terminated because of a recent MS diagnosis or being on MS treatment. The total number of pregnancies after the diagnosis of MS was 17, and 7 of these pregnancies occurred while the patients were on treatment, all of which were terminated. In the control group, 5 patients had no desire to become pregnant. The total number of pregnancies was 53, eleven of which resulted in spontaneous abortion and 7 ended in termination of pregnancy. There were no statistically significant differences between miscarriages and induced abortions between the groups (Table 1).

Table 1. Fertility outcomes of MS patients and the control group

	MS patients (n=22)	Control (n=25)	P value*
Never had a desire to get pregnant	4	5	0.623
Total pregnancies	57	52	
Pregnancies before MS diagnosis	37	-	
Pregnancies after MS diagnosis	17	-	
Pregnancies while on treatment	7	-	
First trimester miscarriages	5 (8.8%)	11 (21.2%)	0.068
Induced abortions	15 (26.3%)	7 (13.2%)	0.086
*Conducted by Chi-Square test			

Ovarian Reserve Assessment

MS patients (n=19) and the controls (n=25) were comparable with regard to BMI and age at study inclusion (Table 2). Ovarian sonography revealed no pelvic pathology in any of the participants performed on cycle day 2-3. FSH and E2 levels did not show any significant differences between the groups, but mean LH level was significantly higher in MS patients than in controls. No significant differences were found in ovarian volume, AFCs and Doppler indices of the left and right ovaries between the MS and control groups (p>0.05). Therefore, mean values of right and left ovarian volume, AFCs and Doppler indices were used for comparison. Although the mean number of small antral follicles (2-5 mm) were lower in MS patients, this difference was not statistically significant. Nevertheless, mean number of larger antral follicles (6-10 mm), mean number of total antral follicles (2-10 mm) and mean ovarian volume were significantly lower in MS patients than in controls. The results of hormonal and sonographic markers of ovarian reserve are given in Table 2. The mean ovarian stromal artery RI, PI, S/D and PSV values of MS patients were higher, but this was not statistically significant (Table 3).

Analysis of patients using only IFN-β

Of the 19 MS patients, 15 used IFN-β, 2 patients GA, and 2 patients both IFN-β and GA. In order to evaluate a more homogeneous group, a subgroup analysis was conducted excluding the 4 patients who had been using GA, and comparing MS patients using only IFN-β (n=15) with controls (n=25). MS and control groups were comparable regarding age and BMI. There were no significant differences between the groups with respect to FSH and E2 levels, but mean LH levels were significantly higher in MS patients. MS patients had a significantly lower mean ovarian volume, mean number of larger antral follicles (6-10 mm) and of total antral follicles (2-10 mm). Although not statistically significant, mean number of small antral follicles (2-5 mm) was also lower in MS patients (Table 4).

The PI of MS patients were significantly higher than the controls. Other Doppler parameters were also found to be higher; however they did not reach statistical significance (Table 3).

Discussion

To our knowledge, this is the first study in which ovarian reserve and ovarian stromal artery Doppler indices are assessed

Table 3. Comparison of mean Doppler indices between MS and control patients

Patients using IFN-β ± GA	MS (n=19)	Control (n=25)	P value
RI	0.49 (0.39-0.80)	0.46 (0.34-0.60)	0.195
PI	0.79 (0.65-1.28)	0.74 (0.56-1.14)	0.098
S/D	1.94 (1.68-3.20)	1.89 (1.51-2.68)	0.222
PSV (cm/s)	10.88 (4.20-16.40)	7.78 (5.05-20.20)	0.601
Patients using only IFN-β	MS (n=15)	Control (n=25)	P value
RI	0.51 (0.41-0.80)	0.46 (0.34-0.60)	0.070
PI	0.85 (0.69-1.28)	0.74 (0.56-1.14)	0.038
S/D	1.94 (1.68-3.20)	1.89 (1.51-2.68)	0.111
PSV (cm/s)	11.23 (4.20-16.40)	7.78 (5.05-20.20)	0.515

Note: Data are median (range)
RI: Resistance index. PI: Pulsatility index. S/D: Systolic/diastolic ratio. PSV: Peak systolic velocity
Statistics were conducted by Mann Whitney-U test

Table 2. Comparison of hormonal and sonographic markers of ovarian reserve in MS patients using immunomodulating therapies (IFN-β + GA) and healthy controls

	MS patients (n=19)	Control (n=25)	P value
Age (y) *	33.21±5.72	33.04±5.07	0.917
BMI (kg/m ²)	24.38 (19.1-33.1)	23.83 (19.0-34.5)	0.318
FSH (mIU/ml)	7.16 (4.87-17.92)	6.96 (4.21-14.37)	0.935
LH (mIU/ml)	6.26 (3.49-11.9)	4.96 (3.75-8.29)	0.008
E2 (pg/ml)	47.99 (15.11-148.3)	36.54 (17.6-192.8)	0.521
AFC (2-5 mm)	5 (0-13)	6 (2-16.5)	0.144
AFC (6-10 mm)	2 (0-10)	4 (2-9.5)	0.004
Total AFC (2-10 mm)	7.5 (1.5-20)	11 (6-23)	0.012
Ovarian volume (ml)	6.13 (3.41-12.24)	7.61 (3.61-15.79)	0.040

Note: Data are mean ±SD; median (range)
BMI: Body mass index. FSH: Follicle stimulating hormone. LH: Luteinizing hormone E2: Estradiol. AFC: Antral follicle count
*Conducted by Student t-test, all other comparisons were performed by Mann Whitney-U test

Table 4. Comparison of hormonal and sonographic markers of ovarian reserve in MS patients using only IFN-β with healthy controls

	MS patients (n=15)	Control (n=25)	P value
Age (y)	36 (23-39)	32 (21-42)	0.720
BMI (kg/m ²)	24.39 (19.05-33.10)	23.83 (19.0-34.5)	0.408
FSH (mIU/ml)	6.56 (4.87-10.96)	6.96 (4.21-14.37)	0.820
LH (mIU/ml)	6.26 (3.49-11.90)	4.96 (3.75-8.29)	0.031
E2 (pg/ml)	48.04 (15.11-148.3)	36.54 (17.6-192.8)	0.604
AFC (2-5 mm)	5 (0-10)	6 (2-16.5)	0.074
AFC (6-10 mm)	2 (0-10)	4 (2-9.5)	0.001
Total AFC (2-10 mm)	7 (1.5-20)	11 (6-23)	0.002
Ovarian volume (ml)	5.34 (3.41-12.24)	7.61 (3.61-15.79)	0.009

Note: Data are median (range)
 BMI: Body mass index. FSH: Follicle stimulating hormone. LH: Luteinizing hormone E2: Estradiol. AFC: Antral follicle count
 Statistics were conducted by Mann Whitney-U test

in MS patients using immunomodulating drugs. In this study, we found that ovarian volume, larger AFC and total AFC of MS patients using immunomodulating drugs (IFN-β, GA) were significantly lower compared to age-matched healthy controls. However, no significant differences were found between the groups regarding serum FSH and E2. In order to homogenize the MS group; we excluded patients who had been using GA and compared ovarian reserve markers of MS patients using only IFN-β with controls, and found the same significant differences in the mean number of total AFC and in larger AFC (6-10 mm) between the groups. Subgroup analysis of the MS patients using GA was not possible because of the small patient number (n=4), 2 of whom had also used IFN-β. In ovarian stromal artery Doppler analysis, we found no significant differences between the groups.

In the current study we also evaluated the menstrual pattern and pregnancy outcomes of MS patients using immunomodulating drugs, and observed that none of the MS patients had menstrual irregularities or amenorrhea. There are a few studies that have evaluated the menstrual pattern and ovarian endocrine function in MS women of reproductive age (11-13). In an earlier study, 14 MS patients were compared with 14 regularly menstruating controls. Consistent with our results, all of the patients in that study had normal menstrual cycles, having no fertility problems. In contrast to that study, one of the 22 MS patients in our study had infertility and conceived after induction with clomiphene citrate. Those investigators found that basal FSH, LH and prolactin levels were significantly higher in patients with MS than in controls and suggested the possibility of lowered dopaminergic tone, since dopamine is a central inhibitor of prolactin and gonadotropin secretion. They concluded that the increase in FSH levels demonstrated reproductive aging. In this early study, which was undertaken in 1989, the authors did not emphasize the gonadotoxic effects of drugs used by MS patients (11). Furthermore, the significant increase in FSH levels could also have been due to the 3.5-year

difference in the ages of MS and control patients (36.4 vs. 32.9). In contrast to their study, there was no significant differences in FSH and E2 levels between the groups in our study.

Another study evaluating menstrual irregularities in 57 MS patients found that after IFN-β use, 23.5% of the patients had menstrual irregularities, most commonly in the form of hypermenorrhea (33.3%) and oligomenorrhea (33.3%) (12). In another study comparing menstrual pattern and hormone levels of 58 MS patients with 58 matched healthy female, they found that 55% of MS patients compared to 20% of normal women had menstrual disturbances but the type of drugs used was not defined. The LH levels in this study were significantly higher in MS patients than in controls (13).

The latter two studies were abstract presentations and thus the details of these studies were not available to make a full comparison with our results. In those studies, the authors did not mention whether the subjects were using oral contraceptives or had any gynecologic abnormalities that could have a potential effect on the menstrual pattern of these patients. However, none of the MS patients using immunomodulating drugs reported menstrual irregularities related to drug usage in our study, although one of our MS patients had an intramural myoma measuring 4 cm.

There are several studies evaluating pregnancy outcomes of MS patients using IFN-β (14-22) but it is difficult to give a pregnancy rate based on these studies because none of them evaluated the intent to conceive while on treatment or the time interval to pregnancy. We did not compare the pregnancy rates of MS patients under IFN-β treatment with controls, assuming it would be inaccurate, since most of the pregnancies in our study were not planned. In order for our comparison to reflect accurate results, both groups should have included patients who did not use any contraceptive methods and who wished to become pregnant. The number of induced abortions was higher in MS patients due to the disease and MS treatment, only four of these patients had termination of their pregnancies unrelated to MS diagnosis.

In the ovary, primordial follicles make up 95% of the ovarian reserve (23). With increasing age there is a decline in a woman's reproductive function, which is assumed to be determined by the decline of the ovarian follicle pool and the quality of the oocytes within (ovarian reserve) (24). Therefore, various endocrinological and sonographic markers have been investigated and proposed as accurate predictive markers of the primordial follicle pool. These include FSH, E2, Inhibin B, AFC and anti-Müllerian hormone (AMH) (25). A serum FSH >12IU/L, or E2 >75 pg/ml measured on the 2nd or 3rd day of the menstrual cycle reflects diminished ovarian reserve. The size of the antral follicle cohort can be directly assessed by ultrasound (26), and the observed pattern of its decline appears to correspond with that of the primordial follicle pool (27). AMH is strongly correlated to AFC, both predictors have a linear relationship with age and these markers are currently believed to be the best predictors of ovarian reserve (28-31). When assessing ovarian reserve, it should be underlined that amenorrhea is the last event of reproductive aging, and that a normal regular menstrual pattern may still persist despite extremely diminished ovarian reserve (23).

Doppler assessment of ovarian stromal blood flow in the early follicular phase of spontaneous cycles has also been studied and related to ovarian follicular response (32). Kim et al. reported a higher PI of ovarian stromal artery with a lower pregnancy rate of the corresponding IVF cycle. They related these results to the availability of good quality oocytes by better circulation when the PI of the ovarian stromal artery is lower, which results in improved supply of oxygen, nutrients, hormones and growth factors (33). Tinkanen et al. reported that infertility patients, excluding those with male factor infertility, had higher PIs in the ovarian arteries compared to the control group (34). We also found higher PIs in the ovarian stromal arteries of patients with MS in accordance with these results. The finding of significantly higher Doppler indices might have importance in MS patients apart from diminished AFC.

The presence of normal FSH and E2 levels with diminished AFC may appear to be paradoxical, but there are other studies supporting our findings (35-38). Recently, Nardo et al. (35) published their study aiming to find the best marker for ovarian response to controlled ovarian stimulation. They found that for patients with poor response, AMH was significantly a better predictor than FSH but not AFC. Studies on female cancer survivors with regular menses and normal serum FSH levels showed that they had significantly smaller ovaries along with a lower AFC as compared to age-matched controls (36, 37). A recent study on gonadal function in childhood cancer survivors showed that regular menstrual cycles and normal early follicular phase FSH did not confirm the absence of damage to the ovary (38). These observations indicate that parameters such as cycle length and FSH serum levels are not accurate markers of ovarian function. Serum AMH levels, AFC and ovarian volume appear to be more reliable predictors (31, 36, 38).

Our results show that currently the most reliable sonographic marker of ovarian reserve, AFC, is significantly decreased in

MS patients using immunomodulating drugs compared to age matched regularly menstruating controls. In addition, mean ovarian volume of MS patients is significantly lower compared to controls. Therefore, these patients are at increased risk of diminished ovarian reserve. The ovarian stromal artery Doppler findings showing high resistance also suggest decreased ovarian function in MS patients using immunomodulating drugs. We have determined that MS patients under treatment with immunomodulating drugs with normal menstrual cycles have sonographic changes suggesting impairment of ovarian potential. These results are important because most MS patients are of childbearing age and might desire to become pregnant.

Our findings are nevertheless preliminary. One of the weak points of our study is that the study population is small and the other is that we had no information regarding the ovarian and endocrine functions of MS patients who had never been treated. As a result we cannot determine whether the observed alteration in ovarian reserve and function is due to the treatment or the disease itself. We are currently conducting another prospective study on newly diagnosed MS patients, to compare baseline ovarian reserve markers including AMH and Doppler assessment of the ovaries with age-matched regularly menstruating controls and MS patients using immunomodulating drugs. This study may determine whether this difference in ovarian reserve and function is derived from the drugs or the disease itself. However, collaborating studies take a long time to complete and we wish to publish our preliminary results assuming that this study would be a guide to physicians for future studies and a beginning of investigation of the ovarian reserve in MS patients using different types of therapies.

In conclusion, AFC, the most reliable sonographic marker of ovarian reserve, is diminished in MS patients undergoing treatment with IFN- β compared to age matched regularly menstruating controls. The significant increase in resistivity marker PI supports the potential decrease in ovarian function. Future studies with larger groups of MS patients and more sensitive ovarian reserve markers are needed to enhance our understanding of the impact of immunomodulating drugs on ovarian function. Accordingly, MS patients should be counselled about their reproductive potential.

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Comparison of two dosing regimens of vaginal misoprostol for labour induction: a randomised controlled trial

Doğum indüksiyonunda iki farklı vajinal misoprostol dozunun karşılaştırılması: rastgellenmiş kontrollü bir çalışma

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Abstract

Objective: To compare the clinical efficacy of two different dosing regimens of vaginal misoprostol for labour induction.

Material and methods: This is an open label randomised controlled trial of 100 eligible women with obstetrical or medical indications for labour induction at a secondary level care hospital on the west coast of India. Women were randomised to receive either a single 50 µg dose or multiple 25 µg doses (maximum of three doses) of misoprostol in the posterior vaginal fornix. The main outcome measure was induction to vaginal delivery interval.

Results: Mean induction delivery interval was 18.58±13.73 and 14.42±13.2 hours (P=0.73) in the 50 µg and 25 µg misoprostol group respectively. Delivery rate within 24 hours were 60% (30/50), in 50 µg group and 68% (34/50) in 25 µg group (P=0.53). The rates of caesarean section and operative vaginal delivery were similar in both groups. There was no significant difference in maternal side effects and neonatal outcome among regimens.

Conclusion: There was no statistically significant difference between the two regimens in terms of clinical efficacy.

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Key words: Misoprostol, induction of labour, low dose, single dose

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Özet

Amaç: Doğum indüksiyonunda iki farklı dozda vajinal misoprostol uygulamasının klinik etkinliğinin karşılaştırılması.

Gereç ve Yöntemler: Bu açık uçlu rastgellenmiş çalışma Hindistanın batı bölgesinde ikinci basamak hizmet veren bir hastanede, doğum indüksiyonu için obstetrik veya tıbbi bir endikasyonu olan 100 gebede yapıldı. Kadınlara vajinal yoldan tek doz 50mcg veya en fazla 3 doz 25 mcg misoprostol uygulandı. Çalışmanın temel araştırma sonucu indüksiyondan doğuma kadar geçen süre idi.

Bulgular: İndüksiyondan doğuma kadar geçen süre 50 ve 25 mcg gruplarında sırasıyla 18.58±13.73 ve 14.42±13.2 saatti (p=0.73). 24 saat içinde doğum hızı 50 mcg grubunda %60 (30/50) ve 25 mcg grubunda %68 idi (p=0.53). Her iki gruptaki sezaryen ve operatif doğum oranları benzerdi. Her iki gruptaki maternal ve neonatal sonuçlar benzerdi.

Sonuç: Klinik etkinlik açısından her iki doz rejimleri arasında istatistiksel olarak anlamlı bir fark yoktu.

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Anahtar kelimeler: Misoprostol, doğum indüksiyonu, düşük doz, tek doz

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Introduction

Situations arise in obstetrics where it becomes necessary to end a pregnancy in the interest of the mother or baby or both. There is a growing interest in the use of misoprostol, a prostaglandin E1 analogue for labour induction. A large body of data exists on misoprostol use in cervical ripening and labour induction. Vaginal application of misoprostol has been reported in over 9000 women worldwide and seems to have a safety profile similar to that of dinoprostone (1, 2). Insert full stop doses as high as 200 µg of misoprostol were used for labour induction in initial trials. Due to fetomaternal complications, the dose was titrated to 50 or 25 µg every two to six hours. There is a need to examine whether the reported increase in uterine hyperstimulation leading to a higher caesarean section rate and increased

incidence of postpartum haemorrhage can be reduced with single dose or low dose regimens (3-6). The dosing interval is also a source of ongoing debate. Lower and less frequent doses cause fewer complications but result in longer insertion delivery interval (7). Although the use of lower dose (25 µg) vaginal misoprostol every 3 to 6 hours has been recommended (8, 9) the optimal dose and frequency of application is not firmly established. Hence the current trial was designed to compare the efficacy of vaginal administration of single 50 µg dose with multiple 25 µg doses of misoprostol for labour induction.

Methods

This is a randomised controlled trial conducted from October 2004 to November 2005 at the Dr TMA Pai Rotary Hospital (an

associate hospital of Manipal University), Karkala, situated in west coast of India. The study was approved by the local institutional ethical committee. All eligible women with obstetrical or medical indication for labour induction were enrolled in the trial. The inclusion criteria included singleton pregnancy >37 weeks, cephalic presentation, Bishop score ≤ 5 , amniotic fluid index ≥ 5 , reactive fetal heart rate pattern, and intact or ruptured membranes. Women with prior uterine scars (previous caesarean section and myomectomy), para ≥ 3 , multiple pregnancy, estimated fetal weight >4000 or <2000 grams, non reactive nonstress test, placenta previa, hypersensitivity to prostaglandins and severe asthma were excluded from the study. Informed written consent was obtained from all participants. One hundred women admitted for labour induction were randomly allocated to receive either 25 or 50 μg misoprostol. Allocation of treatment was done by block randomisation. Blocks of ten were prepared using a random number table at the beginning of the trial. Allocation concealment was done using sealed sequentially numbered opaque envelopes. Randomisation was done by the doctor on emergency call before induction. The trial was not masked. A preinduction Bishop score was assessed and nonstress test performed. Women received either a single dose of 50 μg misoprostol (quartering 200 μg tablets, Cytolog, Zydus Alidac, India) or 25 μg misoprostol (quartering 100 μg tablets, Cytolog, Zydus Alidac, India) in the posterior fornix of the vagina. In the 25 μg group, the dose was repeated every six hours, until adequate uterine contractions (three contractions in 10 minutes) were established or cervical ripening was achieved. The maximum number of doses was limited to three in 24 hours. Electronic fetal heart rate monitoring was performed in all patients in active labour. Oxytocin augmentation and artificial rupture of membranes were performed when clinically indicated. Augmentation was delayed for six hours after administration of misoprostol. No epidural analgesia was used in our study. A primary outcome measure was the interval from first dose of misoprostol to vaginal delivery. Secondary outcome variables included time interval from induction to onset of adequate uterine contractions, mode of delivery, indications for caesarean delivery, number of emergency caesareans performed for abnormal FHR pattern, number of doses of misoprostol used, oxytocin augmentation, incidence of adverse effects such as uterine contraction and FHR abnormalities (10). The uterine contraction abnormalities were classified as (11) a] uterine tachysystole was defined as six or more contractions in a 10-minute period for two consecutive 10-minute periods, b] uterine hypersystole / hypertonus was defined as a single contraction that lasted longer than 2 minutes, c] uterine hyperstimulation syndrome was defined as the presence of either tachysystole or hypertonus that resulted in a non reassuring FHR pattern (persistent decelerations, tachycardia or reduced short term variability). In case of uterine contraction abnormalities, the women were placed in the left lateral position, oxygen administration, subcutaneous terbutaline 0.25 mg and closely monitored until resolution of hyperstimulation. Other secondary outcome variables were incidence of postpartum haemorrhage and neonatal outcome [birth weight,

APGAR score at one and five minutes, incidence of meconium stained amniotic fluid, admission to neonatal intensive care unit (NICU)].

The women's satisfaction with induction of labour was also recorded, based on a simple scale of 0 to 100 and reported as percentage. Women were asked about overall satisfaction of intrapartum care 24 hours after delivery. The best satisfaction was scored as 100% and unsatisfied as zero. Women undelivered at 24 hours were considered as failed induction. Further action was taken based on existing departmental induction guidelines and the clinician's preferences as well as patient's wishes, i.e. repeat induction or oxytocin augmentation, non intervention for next 24 hours or delivered by caesarean after 48 hours as appropriate. Pre-trial sample size was not calculated due to feasibility of recruitment in a single centre during a limited period of course, as this trial was conducted as part of the requirement of a thesis for a two year course. Statistical analysis was performed using SPSS (version 11). Variables were analysed with chi-square test or Mann-Whitney's test and student t-test. The P value <0.05 was considered as significant. Intention to treat principle was utilised while analysing the data.

Results

One hundred and eight women were assessed for eligibility and hundred women were enrolled in the study. Two women did not meet the inclusion criteria and six women were not enrolled because they refused to participate. There was one incidence of protocol violation where one woman was inadvertently randomised to receive 50 μg misoprostol with initial Bishop score of ten which was an exclusion criteria. Data of this patient was also analysed as an intention to treat principle (Figure 1). After entering the trial no women were lost for follow up or opted out of the trial. All one hundred women enrolled were available for final analysis.

Maternal demographic characters and indications for induction were comparable in both regimens (Table 1). Mean induction delivery interval was 18.58 ± 13.73 and 14.42 ± 13.2 hours ($P=0.73$) in the 50 μg and 25 μg misoprostol groups respectively. The percentage of women delivering vaginally within 24 hours of induction were 68% (34/50), in the 25 μg group and 60% (30/50), in the 50 μg group $RR= 0.88$, 95% CI (0.66-1.19). The proportion of women delivering within twelve hours (30%, 15/50, vs. 32%, 16/50, $p=1.00$), and next 12 hours (38%, 19/50 vs. 28%, 14/50 $p=0.39$) of induction were similar among groups. A post hoc power analysis for primary outcome was 14%. There was no significant difference between groups regarding the onset of active labour (8.25 ± 6.71 vs. 11.92 ± 10.15 , $p=0.3$).

As highlighted in Table 2, there was no significant difference in the secondary outcome variables such as the use of oxytocin augmentation, uterine contraction abnormalities, abnormal cardiograph, modes of delivery and postpartum haemorrhage. The neonatal outcomes were comparable among groups. Potential adverse effects of misoprostol such as uterine rupture, nausea, vomiting, diarrhea and fever was not observed in the study population. However one primigravida in the 50 μg group died of severe atonic postpartum haemorrhage.

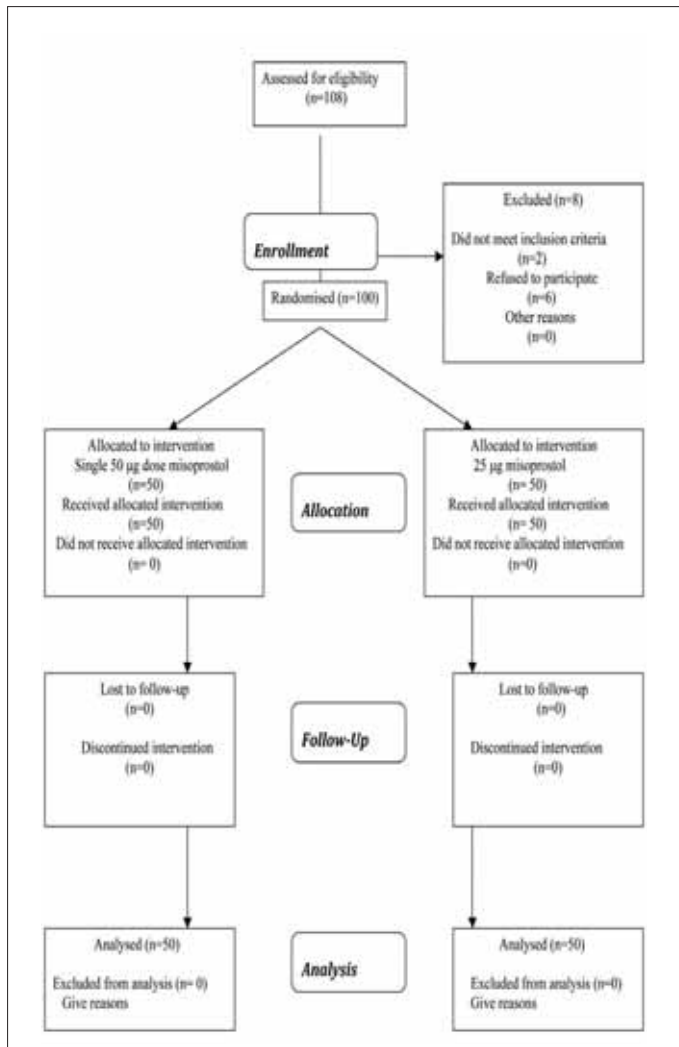


Figure 1. The consort E-flowchart for misoprostol trial

Table 1. Maternal demographic data

Variables	25 µg (N=50)	50 µg (N=50)	P value
Age (year + S.D) ^a	25.56 ± 3.32	25.32 ± 3.53	0.35
Parity ^b			
Nulliparous (n)	35 (70%)	37 (74%)	0.82
Multi (n)	15 (30%)	13 (26)	
Gestational age (weeks ± S.D) ^a	39.36 ± 1.06	39.42 ± 1.03	0.08
BMI (kg/m ² ± S.D) ^a	22.51 ± 3.45	22.51 ± 3.02	0.96
Initial Bishop score ^a	3.18 ± 1.17	3 ± 1.490.66	
Indication for labour induction ^b			
Past date	35 (70)	37 (74)	0.48
PROM	13 (26)	10 (20)	
Preeclampsia	1 (2)	3 (6)	
Patient's request	1 (2)	0 (0)	
^a Student's t-test ^b Chi square test PROM = premature rupture of membranes BMI = body mass index Data represented as mean ± SD or number and percent			

In the 25 µg group, the vaginal delivery rate with one dose was 34%, two doses 28% and three doses 6% (Table 3). Indications for caesarean section were comparable among groups (Table 4). Information on patient satisfaction was available in 48 women. Eighty eight percent, (22/25) of women in the 25 µg group and 100%, 23/23 of women in the 50 µg group had a satisfaction level of more than 50% (P=0.23).

Discussion

Although many trials used multiple doses of 50 µg misoprostol, the vast majority of women (50-87%) delivered with single dose (3, 12-16). Lokugamage et al (17) studied the efficacy of a single versus two dose regimen of 50 µg vaginal misoprostol for labour induction. Although the author concluded that the two dose regimen was more effective, the majority of patients in the two dose regimen 41/53 (77%) received only a single dose without pharmacological advantage of two doses. Hence the current trial looked at the role of single dose of 50 µg vaginal misoprostol in comparison with the currently recommended low dose regimens for labour induction.

In the current trial there was no statistically significant difference between the two misoprostol regimens in terms of clinical efficacy for labour induction. Although we found that the induction delivery interval was similar among the regimens, other investigators (3, 5, 6, 18-21) had demonstrated that it was shorter in the 50 µg group. In a meta-analysis comparing 25 and 50 µg misoprostol, the induction vaginal delivery interval was nearly five hours shorter in the 50 µg group (22). The proportion of women delivering within twelve hours and next 12 hours of induction were similar among the groups, which is consistent with other investigators (18, 20). However, more women delivered between 12-24 hours in the 25 µg group (27/49 vs 10/47, P<0.001) in one study (13) and fewer patients delivered vaginally in the 25 µg group in another study (19).

Table 2. Primary and secondary outcome variables

Outcome	25 µg (N=50) n %	50 µg (N=50) n %	P-value
Intrapartum variables			
Onset of active labour (h) ^c	8.25 + 6.71	11.92 + 10.15	0.3
Induction vaginal delivery interval ^a	14.42 + 13.2	18.58 + 13.73	0.73
< 12 h (n, %) ^b	15/50 (30)	16/50 (32)	0.19
12 - 24 h (n, %) ^b	19/50 (38)	14/50 (28)	
> 24 h (n, %) ^b	4/50 (8)	10/50 (20)	
Oxytocin augmentation ^b	11 (22)	14 (28)	0.64
Delivery method and fetal outcome			
Delivery ^b			
Spontaneous vaginal	36 (73.33)	38 (70)	0.88
Forceps	2 (6.7)	2 (3.33)	
Cesarean section	12 (20)	10 (26.7)	
APGAR score ^b			
1 minute (<7)	5 (3.3)	4 (10)	1.00
5 minute (<7)	0 (0)	0 (0)	
Meconium passage ^b	15 (30)	9 (18)	0.24
Birth weight (grams) ^a	3005 + 372	2940 + 503	0.73
NICU admissions ^b	7 (14)	8 (16)	1.00
Uterine contraction abnormalities ^b			
Uterine tachysystole	1 (2)	3 (10)	0.60
Hypertonus	0 (0)	0 (0)	
Uterine hyperstimulation syndrome	1 (2)	0 (0)	
Abnormal cardiotocograph ^b	8 (16)	4 (8)	0.35
Postpartum hemorrhage ^b			
Atonic	0 (0)	1 (2)	1.00
Traumatic	2 (4)	2 (4)	
Maternal death	1 (2)	0 (0)	
^a Student's t-test, ^b Chi-square test, ^c Mann-Whitney U test			

There was no difference in the overall caesarean delivery rates and caesarean rate for abnormal FHR pattern in the two groups. Has R et al. (18) reported an increase in caesarean section rate in the 50 µg group. However, Elhassan et al. (19) showed an increase in caesarean section rate in the 25 µg group. There was no significant difference in incidence of meconium passage among the groups with is consistent which other investigators (13, 18, 21). The reason for meconium passage is usually attributed to fetal hypoxemia as a result of excessive uterine contractions caused by a high dose of misoprostol. However, in the current series there was no significant difference in occurrence of uterine tachysystole among regimens, although some investigators have demonstrated an increased incidence of uterine contraction abnormalities in the 50 µg groups (3, 5, 18, 21). The high incidence of hyperstimulation in Dairo et al's (5) study

is possibly due to higher doses (four doses) of misoprostol received by most women.

In the current series the incidence of traumatic postpartum haemorrhage was similar among groups. However, El-Sherbiny et al. (3) reported significantly increased incidence of atonic postpartum haemorrhage in the 50 µg group (9.78 vs 2.15% $P < 0.05$). When looking at the data of traumatic postpartum haemorrhage, we cannot ignore the potential direct local effect of misoprostol on the genital tract (23). Further studies are needed to explore this concept to reduce side effects and to increase the safety profile. One maternal death in a 50 µg regimen cannot be directly attributable to misoprostol.

Body mass index (BMI) is an important maternal characteristic that can influence the dose response to vaginal misoprostol. Obese women might be expected to require higher doses or

Table 3. Induction delivery interval according to number of doses of misoprostol in 25 µg group

Induction delivery interval	Dose of misoprostol (25 µg)			P value
	Single dose	Two doses	Three doses	
≤ 24 h (n)	17	14	3	0.0022
> 24 h (n)	0	1	3	
Total	17	15	6	

Table 4. Indications for cesarean delivery

Indications ^b	25 µg (N=50)	50 µg (N=50)	P-value
Fetal distress	3	2	0.22
Non progress of labour	1	5	
Cervical dystocia	1	1	
Failed induction	1	0	
Abnormal FHR patterns	6	2	

^bChi-square test

more frequent applications, while women with a low BMI may require lower doses. Although mean BMI among groups were comparable in the current series, the overall mean BMI is much less (22 vs 32) in Indian women when compared with Western women (24).

The main strength of the study was that it was a prospective randomised controlled trial in which all the data of recruited participants could be analysed and both study groups received comparable care. However, the limitation associated with the current trial is small sample size which is prone to type II errors. Another limitation was that this trial was not masked and the outcome assessors were not blinded. Hence the possibility of inadvertent bias cannot be excluded. Although this trial is limited by the small number, it adds to the current body of literature available from different settings (rural), ethnicity and country. The safety of misoprostol cannot be established with this trial. Induction of labour is a common obstetric intervention and the use of misoprostol as an induction agent is important due to its low cost and stability at room temperature. These additional advantages make it a suitable agent, particularly in under-resourced settings and tropical countries. Due to frequent electricity failure, it is not always possible to guarantee the potency of the widely used dinoprostone gel in developing countries. Moreover, the low dose misoprostol regimens were found to have similar efficacy to dinoprostone gel for labour induction (25).

In the Cochrane systematic review (1), vaginal misoprostol (25 µg three hourly or more), was found to be more effective than conventional methods of cervical ripening and labour induction. However, uterine hyperstimulation with fetal heart rate changes were increased. Thus, although misoprostol shows promise as a highly effective, inexpensive and convenient agent

for labour induction, the lack of registration for this purpose is problematic in many countries.

Logistical problems like difficulty in cutting the tablet accurately and legal liabilities need to be addressed. In the light of available data and our findings, we suggest that clinical heterogeneity should be eliminated in future labour induction trials with vaginal misoprostol.

Conclusion

Our data indicates that there was no difference regarding the clinical efficacy between two labour induction regimens of vaginal misoprostol. However, large randomised trials on low dose and single dose regimes of misoprostol for labour induction are needed to get reliable data on the safety profile and rare events such as uterine rupture and maternal mortality.

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Antagonist use in intrauterine insemination (IUI) cycles

İntrauterin inseminasyon sikluslarında antagonist kullanımı

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Abstract

Intrauterine insemination is the first method of treatment for many causes of infertility, mainly unexplained infertility, male subfertility, and ovulatory dysfunction. Despite its popularity, the effectiveness of IUI treatment is not consistent, and the role of IUI treatment in practice protocols has not been clarified. The success of IUI depends on a number of parameters linked both to the pathology underlying the infertility and to the treatment. The midcycle LH surge in the reproductive cycle is an intriguing endocrinological phenomenon. One of the challenges to optimize the COS/IUI outcomes is to prevent the occurrence of the premature LH rise and consequent luteinization. 24% of IUI cycles suffer from premature LH surge. The potential beneficial effect of a GnRH antagonist on pregnancy rates in IUI cycles, while preventing premature LH surge, has not been adequately assessed. Administration of a GnRH antagonist almost completely abolishes premature luteinization but does not substantially improve the pregnancy rate. Co-treatment with GnRH antagonists can be restricted to the time in the cycle where there is a risk of a premature increase in LH.

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Key words: Premature LH surge, Intrauterine insemination (IUI), GnRH antagonist

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Özet

İntrauterin inseminasyon (IUI) başta açıklanamayan infertilite, erkek subfertilitesi ve ovulatuvar disfonksiyon olmak üzere birçok infertilite nedeninde ilk kullanılan tedavi seçeneğidir. Popürlüğüne rağmen intrauterin inseminasyonun etkinliği kanıtlanmamıştır ve protokollerdeki yeri netleştirilmemiştir. IUI'nun başarısı alta yatan infertilite patolojisi ve tedavi ile ilişkili bazı parametrelerle ilişkilendirilmiştir. Reprodüktif siklustaki midsiklus LH salınımı merak uyandırıcı bir endokrinolojik olaydır. KOH/IUI sikluslarının optimum olabilmesi için aşılması gereken zorluklardan biri de erken LH artışının ve takip eden lüteinizasyonun önlenmesidir. IUI sikluslarının %24'ünde erken LH artışı gözlenir. Prematür LH salınımını azaltan GnRH antagonistlerinin IUI sikluslarındaki gebelik oranları üzerine etkisi yeteri kadar araştırılmamıştır. GnRH antagonisti uygulaması erken lüteinizasyonu engellerken gebelik oranını arttırmamaktadır. GnRH uygulamaları siklus içinde erken LH artışı riskinin en fazla olduğu zaman dilimi ile kısıtlanabilir.

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Anahtar kelimeler: Erken LH artışı, intrauterin inseminasyon (IUI), GnRH antagonistleri

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Intrauterine insemination (IUI) is the first line technique for many conditions of infertility such as unexplained infertility, mild male factor infertility and minimal or mild endometriosis. It is accepted as a stop-gap treatment while waiting for, or instead of, in vitro fertilization (IVF). The first paper entitled "intrauterine insemination (IUI)" was published in 1962 (1). Since then, IUI has evolved through innovations such as sperm preparation, monitoring for pre-ovulatory timing and induction of ovulation with human chorionic gonadotrophin (hCG). Despite the fact that it has not been classified as an assisted reproductive technique (ART) (2, 3), it is widely used, often as an empirical treatment, for a broad range of pro-fertility indications. The European IVF Monitoring Programme in 2004 reported 98 388 IUI cycles from 19 countries leading to 12 081 births (12.3% per cycle), of which 87% were singleton and 13% were multiple births (4). Several studies have demonstrated that IUI with controlled ovarian stimulation (COS) is superior to IUI alone (5-14).

The success rate of IUI with ovulation induction varies widely, with pregnancy rates ranging between 8 and 18% per cycle (7, 8, 15-17). These discrepancies in pregnancy rates found

among the various published studies are due to the selection of patients, duration of infertility, aetiology of infertility, sperm preparation, total number of motile sperm inseminated, number of inseminations, monitoring of the cycle, timing of IUI and protocols of ovarian stimulation.

The midcycle LH surge in the reproductive cycle is an intriguing endocrinological phenomenon. The exact time at which ovulation occurs after LH surge begins cannot be known earlier. It varies from 24 to 56 hours. Oocyte-fertilization capacity and sperm lifetime are <1 day and 1.4 days, respectively. Insemination needs to be performed close to ovulation time, and accurate synchronization is compulsory. The LH surge can occur in various follicular sizes, and individual follicular maturation adds to the risk of trial failure. Urinary LH recording may present false-negative results when peak LH concentrations are low (<40 IU/L). One of the challenges to optimizing the COS/IUI outcomes is to prevent the occurrence of the premature LH rise and consequent luteinization which, as is well known, is a possible complication of stimulated cycles (18-21). It has been calculated that 24% of IUI cycles suffer from premature LH surge (20) and this can result in IUI

procedure cancellation. Obviously, this represents economic and psychological stress for the patients. Increasing E2 levels may induce an LH surge, with disastrous effects for follicular progress and growth. If a fertility facility and a clinician are available, IUI can be timed according to LH levels. Otherwise, LH rise leads to cycle cancellation. This is especially important if premature luteinization takes place on Friday and a weekend insemination is impossible. For that reason, some authors have administered a GnRH antagonist that rapidly inhibits LH rise. The exact details of the mechanism in many species, including humans, are still not known, while it is known that central signalling by hypothalamic GnRH is permissive (22). Complete blockade of the GnRH receptor terminates the periovulatory LH surge, although alterations in the magnitude of GnRH secretion are not crucial for timing and size of the LH surge (23). The LH surge is an absolute requirement for luteinization, final maturation of the oocyte and follicle rupture. It is obvious, too, that the organ containing the mature, ready to ovulate, follicle(s) should send out the crucial signals. Indeed, most data indicate that the timing of the occurrence of the LH surge is governed by signals from the ovaries (22). The main signal is presumably the progressive rise in estradiol secretion from the dominant follicle. The positive feedback of estradiol comes from progressive pituitary sensitization to GnRH in combination with a progressive and time dependent increase in estradiol levels. Several mechanisms underlie this phenomenon: first, estrogen enhances pituitary sensitivity to GnRH; second, non-steroidal ovarian compounds such as activin increase in concentration, whereas gonadotrophin surge inhibiting factor decreases (24); and third, subtle rises in progesterone concentration may augment LH secretory sensitivity to GnRH (25). A premature LH surge can be defined as a premature rise in LH (>10 IU/l) accompanied by a concomitant rise in progesterone ($>1\mu\text{g/l}$ - 3.2nM/l) (26). Premature LH surge in the natural cycle seems very rare (27), but may be more frequent in older women since their maximum follicle diameter at the time of ovulation is substantially smaller (27, 28). Premature LH surges also occur in 25-30% of stimulated IUI cycles (26, 29) and theoretically may interfere with timing of the IUI or result in cancellation and more treatment failures.

GnRH agonists have been the standard of care for more than a decade in reducing the incidence of premature LH surge by reversibly blocking pituitary gonadotrophin secretion in IUI stimulated cycles (15, 30-32). Nevertheless, these drugs are nowadays completely abandoned in IUI cycles because of the excessive follicular simultaneous selection they cause (with consequent higher incidence of multiple pregnancy and OHSS) and because of the long pretreatment period required. As an alternative to GnRH agonists, GnRH antagonists have been proposed to prevent the premature LH surge during IVF cycles (33, 34) and COS/IUI treatments (28, 35-38). These drugs do not produce a flare-up effect reducing synchronous follicular pool recruitment. Moreover, the potential advantage of a GnRH antagonist is that pituitary gonadotrophin secretion is suppressed immediately after the start of therapy. GnRH antago-

nists are easy to incorporate in a IUI scheme by adding it either in a fixed (day 6) protocol or in a flexible protocol. Antagonists, on either a fixed or a flexible protocol, have been proven successful in suppressing LH rise in superovulated cycles. In addition, GnRH antagonists can be safely administered in IUI cycles without compromising the luteal phase (35). In this study, lower midluteal E2 was observed in the antagonist group than in the control group, but this had no effect on progesterone concentration and pregnancy rates. Controversial evidence exists about the adverse effects of GnRH antagonists on the endometrium and oocyte quality. Some studies show that the administration of GnRH antagonist does not impose adverse effects on the endometrium (39), while others show that endometrial maturation may be accelerated by three days through genetic changes (40). In FSH-stimulated cycles, rapidly rising estradiol levels induce premature LH surge in immature follicles, but in milder stimulated cycles the process of natural LH surge allows better follicle maturation and a higher chance of pregnancy. So, the administration of GnRH antagonist could be useful in these patients. Furthermore, because LH surge could last up to two days in some women, it is better to trigger ovulation by HCG after onset of the surge, thereby increasing the chance of pregnancy (41). Therefore, co-treatment with GnRH antagonists can be restricted to the time in the cycle where there is a risk of a premature increase in LH. Probably, premature luteinization is not the cause but one of the consequences of the poor quality of growing follicle (Fig. 1) (26). In seven RCTs, the aver-

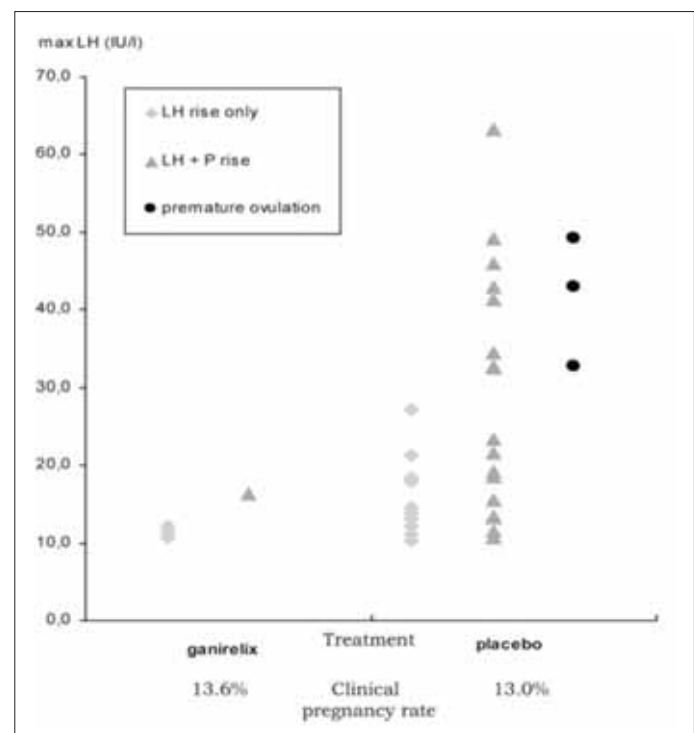


Figure 1. Premature LH surge during mild FSH stimulation with and without antagonist (203 cycles) (26). Max LH (IU/l) is shown in subjects treated with either ganirelix or placebo and having premature LH rises only, premature LH and progesterone and premature ovulation

age ongoing pregnancy rate was only 5.3% greater with GnRH antagonist treatment (95% CI: 1.5, 9.2). This means that it would take 20 cycles of GnRH antagonist administration to have one pregnancy more than without GnRH antagonist treatment (Fig. 2). From the randomized controlled trials of this meta-analysis, it is clear that allowing for follicle growth and avoiding premature LH rise, increased pregnancy rates are observed with GnRH antagonist administration. A parallel trend for multiple pregnancy rates in the GnRH antagonist group was observed, although this did not reach statistical significance. This meta-analysis of early data might enhance further research in this direction (42). There is also another study showed that OC pretreatment afforded flexibility in scheduling, while a reduced dose of ganirelix avoided excessive suppression of LH. The excellent results in this pilot study for IUI suggest this regimen could be further evaluated for scheduling IUI and IVF cycles (43).

Recent studies have already reported higher mean follicular diameter and no difference in pregnancy rates, whereas others reported a difference in pregnancy rates after GnRH antagonist administration. However, the incremental cost of antagonist administration and the possibility of not improving pregnancy outcome must be considered. This might add to the reluctance to adopt this technique as a standard method of treatment in IUI superovulated cycles. The small size of studies performed until now and the different schemes for antagonist administration might further reinforce this reluctance. The potential beneficial effect of GnRH antagonist on pregnancy rates in IUI cycles, while preventing premature LH surge, has not been adequately assessed. For the GnRH antagonist administration group, higher pregnancy rates are observed when all RCTs that reach statistical significance are synthesized (Fig. 3A). For both regimens (ganirelix and cetrorelix), a trend for higher pregnancy rates was observed. When examining for multiple pregnancy rates, a trend for difference is observed between the two groups, favoring antagonist administration (Fig. 3B, 3C). The results of the clinical pregnancy rates in this meta-analysis are consistent with the studies done by Allegra et al. and Gomez-Palomares et al. (30, 37). On the other hand, when an evaluation of the

clinical significance of antagonist coadministration was performed, 4 (95% CI 3-6) patients were needed to treat to prevent an additional LH rise and 19 (95% CI 10-81) patients to achieve an additional pregnancy. In trying to interpret these results, the use of an antagonist superovulated IUI scheme may be justified when an LH rise is expected, e.g., previous cycle LH rise, avoidance of insemination during weekend, or big follicles required. The use of such a scheme over the currently used scheme cannot be justified to increase pregnancy rates. This meta-analysis consists of six trials with 1,069 subjects. Data are pooled for all infertility groups, and no results can be drawn specifically for each group. From this meta-analysis, increased duration of therapy is observed, although this did not reach statistical difference. None of the studies included in the meta-analysis mentioned side effects from this increased duration of therapy. It is not evident whether this increased duration was responsible for the positive effect on pregnancy rates. Certain issues need to be addressed by future clinical research. Further research is needed to identify which group of patients will benefit from adding GnRH antagonist to an IUI scheme. Older patients with short follicular phase and reduced ovarian reserve might benefit. Also for women with reduced ovarian reserve, premature luteinization occurs more frequently. This is due to defective production of gonadotropin surge attenuating factor (GnSAF). On the other hand, a prolongation of follicular phase might allow for an increased number of mature follicles, which may enhance the possibility of pregnancy. In addition, patients with a previous cancelled cycle because of premature luteinization are candidates for this treatment. It is controversial whether this protocol can be used for a weekend- free IUI. During the weekend, small fertility clinics do not have a clinician available to perform the IUI. If the patient chooses such a small clinic for her treatment, she is at risk of having the added cost of antagonist. In the case that she undergoes three or more cycles, that increased cost may be significant. Cost-effectiveness analysis must be conducted in each center that uses this protocol. In most European countries, the cost of treatment cycles is covered by government funds. In addition, trained fertility nurses

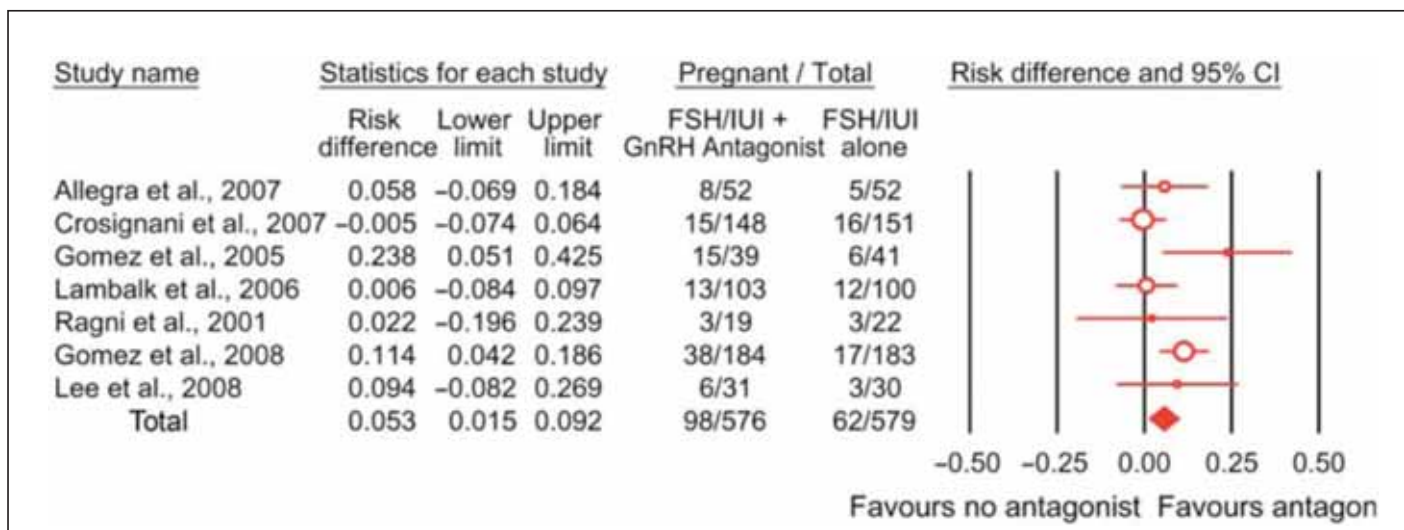


Figure 2. Ongoing pregnancy rate per couple with one cycle of FSH/IUI with and without GnRH antagonist treatment

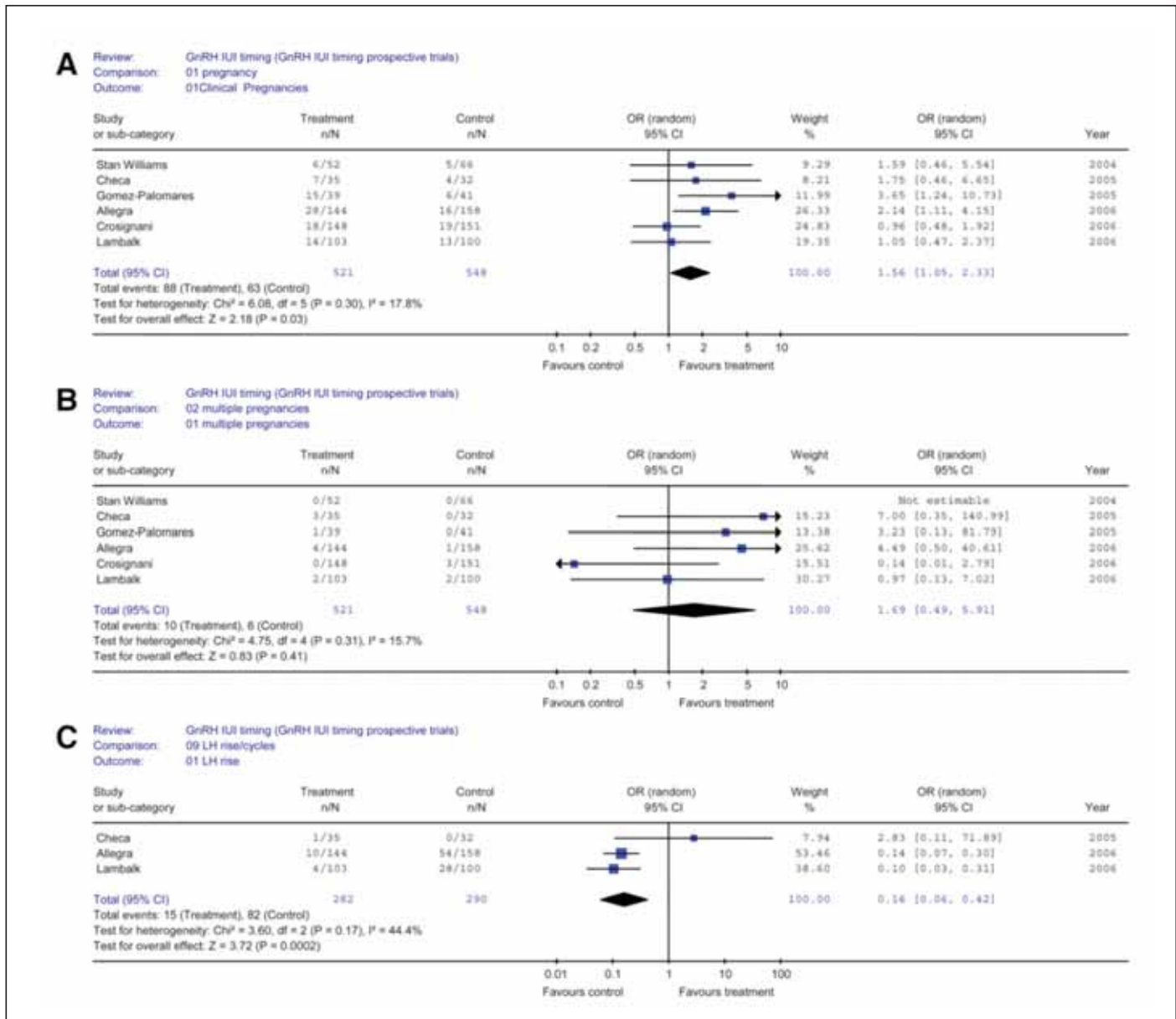


Figure 3. (A) Overall results of GnRH antagonist administration vs. control for intrauterine insemination (IUI) timing after a gonadotropin regimen and the odds for pregnancy. (B) Overall results of GnRH antagonist administration vs. control for IUI timing after a gonadotropin regimen and the odds for multiple pregnancy rates. (C) Subgroup analyses for LH rise after GnRH antagonist administration vs. control for IUI timing in a gonadotropin regimen. In all panels, each study is shown as an odds ratio estimate, with whiskers corresponding to 95% confidence intervals, and studies are ordered by year of publication. (Kosmas. GnRH antagonists for IUI timing: a meta-analysis. Fertil Steril 2008)

can perform the IUI. It is obvious that it is not an issue of an available clinician but rather of an available team and the willingness to provide extensive care. Follicle-stimulating hormone for ovulation induction in IUI has to be used as a second-line treatment (24). When this scheme is chosen, the addition at the end of GnRH antagonist and the cycle prolongation might increase pregnancy rates. Thus, prolongation of follicular phase and further follicular maturation may be important for pregnancy rates. In conclusion, more studies are needed on improving pregnancy rates in IUI superovulated cycles. It seems that antagonist schemes can help in this effort.

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Primary adnexial hydatid cyst mimicking ovarian tumor

Over tümörünü taklit eden primer adneksiyal kist hidatik

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Abstract

We report here the rare case of a 28-year-old woman with a large hydatid cyst in her left lower pelvis with an unusual sonographic presentation mimicking a multicystic ovarian tumor. Laparoscopic evaluation revealed normal uterus and ovaries with a swelling in the left retroperitoneal area. We decided to reach this tumour by the vaginal route and multiple scolex, daughter cysts were removed via a left lateral vaginal wall incision. The pericystic cavity was thoroughly washed. The patient was discharged on the first postoperative day. Mebendazole (100 mg twice daily) was administered for 4 months. This parasite should be kept in mind and considered when making the differential diagnosis of pelvic cystic masses, particularly if the patient is from an endemic area.

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Key words: Echinococcus, hydatid disease, ovarian tumour

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Özet

Bu vakada 28 yaşındaki genç bir kadında ultrasonografik görüntüsü multikistik over tümörünü taklit eden sol pelvisteki geniş bir kist hidatik vakasını sunuyoruz. Laparoskopik değerlendirilmede uterus ve overler normal iken sol retroperitoneal bölgeye şişlik izlendi. Bu tümöral oluşuma vajinal yoldan ulaşmaya karar verdik ve sol lateral vajinal duvar insizyonu ile birden çok kistik yapıdan oluşan skoleksler ve kitle eksize edildi. Kist çevresi doku tamamen yıkandı. Hasta postoperatif 1. günde taburcu edildi. Dört ay boyunca günde iki kez 100mg mebendazol uygulandı. Özellikle endemik bölgelerden gelen hastalarda kistik pelvik kitlelerin ayrıncı tanısında bu parazit akılda tutulmalıdır.

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Anahtar kelimeler: Echinococcus, kist hidatik, over tümörü

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Introduction

Hydatid disease (echinococcosis), is a parasitic infection caused by a cestode Echinococcus, mostly the form of *E. granulosus*. Echinococcosis remains a problem in endemic areas. *E. granulosus* is a 5-mm long worm, with a lifespan of 5-20 months within the jejunum of dogs. Echinococcal eggs of the adult worm are present in the small intestine of canine animals, and they are excreted with the feces. When ingested by intermediate hosts such as sheep, cattle or humans, these eggs hatch in the intestine of the intermediate hosts. Then the eggs, in the form of oncospheres, penetrate through the mucosa of the intestine and diffuse into the blood and lymphatic circulation. They are transported by the circulation to the organs, mostly to the liver and lungs, where they grow and produce cysts. Five to 20 years elapse before cysts enlarge sufficiently to cause symptoms.

Echinococcal disease, which produces cystic lesions, is an infection of humans caused by the larval stage of *Echinococcus granulosus*. It is prevalent in the Middle East, the Mediterranean region, particularly in Greece and Lebanon, Australia, Argentina and Africa. Confirmed hosts are dogs that pass eggs into their feces. Intermediate hosts, e.g. sheep, cattle, humans, goats and horses ingest the eggs and develop cysts (1). Echinococcal cysts are mostly found in the liver (60%-70% of cases), followed by the lungs (10%-

25%), spleen, ovaries, kidneys, brain, bones and heart, but rarely elsewhere in the body (1). Hydatid disease in extrahepatic locations usually remains asymptomatic unless the cyst grows and produces symptoms due to pressure, rupture to the pleural or peritoneal cavity, secondary infection, or an allergic reaction (2). We report here the rare case of a 28-year-old woman with a large hydatid cyst in her left lower pelvis with an unusual sonographic presentation mimicking a multicystic ovarian tumour.

Case

A 28-year-old gravida 2, para 2 woman presented at the Department of Obstetrics and Gynaecology with a left adnexial mass on routine examination. The patient described regular menses at 28 day intervals and her last menstrual period was 16 days prior to admission. She had had two term caesarean section deliveries. The gynecological history was otherwise unremarkable. On bimanual examination, a left adnexial cystic mass approximately 10 cm in diameter was palpated. The left-sided lesion was in close proximity to the vagina and left vaginal swelling was also noted. A year previously in a different clinic she had attended with a complaint of lower abdominal pain and was told that she had a cyst. An oral contraceptive containing 30 mg ethinyl estradiol and 3 mg drospironon was administered. She was living in

town and mostly dealing with farm animals for breeding, milking them in close contact. Transvaginal sonography with 7 MHz vaginal transducer revealed a 11x9 cm hypoechoogenic multiloculated cystic mass in the left ovarian location. The left ovary could not be visualized separately and the appearance of the cyst mimicked ovarian hyperstimulation syndrome ovaries (Fig.1). On color Doppler no vascularity was noted in the solid component of the mass. She had been asked about any medication for infertility and she used one of them. Tumour markers; CA 125, CA 19-9, CEA, AFP, B-HCG; liver enzymes, biochemical parameters and other hematologic parameters were normal. She was diagnosed as having a benign left adnexial tumour and it was decided to operate by laparoscopy. Laparoscopic evaluation revealed a normal uterus and ovaries with a swelling in the left retroperitoneal area. We decided to reach this tumour by the vaginal route and multiple scolex, daughter cysts were removed via the left lateral vaginal wall incision (Fig. 2-3-4). The pericystic cavity was thoroughly washed with hypertonic saline. The thick pericystic cavity was left open. The diagnosis of a hydatid cyst was confirmed histologically after surgical removal of the lesion. Postoperative CT scan and ultrasound of the liver, spleen and lung were normal, and no disease was

visible on chest radiograph. The patient was discharged on the first postoperative day. Mebendazole (100 mg twice daily) was administered for 4 months.

Discussion

To our knowledge, this is the first reported case of an echinococcus cyst approached by the vaginal route.

The parasite consists of the laminated membrane (ectocyst) and the germinal layer (endocyst). The ectocyst has the appearance of the white of a hard-boiled egg. It is elastic, made up of gelatinous, chitinous material and, when incised or ruptured, curls in on itself, exposing the inner layer. The innermost germinal layer is cellular and consists of a number of nuclei embedded in a protoplasmic mass. It is a very thin, vital layer of the cyst, and produces brood capsules with scolices, secretes

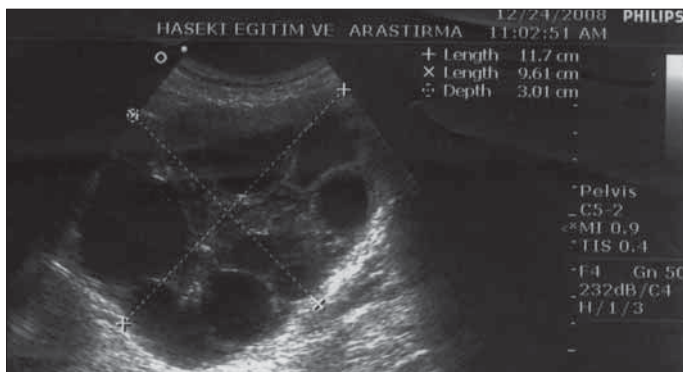


Figure 1. Transvaginal sonography 11x9 cm hypoechoogenic multiloculated cystic mass in the left ovarian location



Figure 3. The thick pericystic cavity left open



Figure 2. Tumour by vaginal route and multiple scolex, daughter cysts have been removed via left lateral vaginal wall incision



Figure 4. Multiple scolex, daughter cysts have been removed

hydatid fluid and forms the outer layer. The cyst fluid is crystal clear and colourless with a specific gravity of 1,005 to 1,010, is slightly alkaline, and is highly antigenic and toxic. Contact with the fluid can give rise to anaphylactic shock.

Hydatid cyst affects the liver and the lungs in more than 80–90% of cases. Hydatid cysts are seldom primary in other organs, and they are often part of a generalized disease. Involvement rate of the pelvis in hydatid disease is reported to be 2% (4,5). In females, genital organs are reported to be the most affected areas in the pelvis which can be attributed to their relatively rich bloodstream and true invasions from connective tissue of peritoneum of Douglas and suspensory ligaments (4, 6) Pelvic hydatid disease can present with vague abdominal pains due to irritation, swelling, menstrual irregularities, infertility and pressure symptoms involving the adjacent organs (bladder, ureters, rectum and vascular structures) (3, 4, 7, 8).

Cysts in the peritoneal cavity account for 10%-16% of cases and are mainly the result of the rupture of concomitant hepatic cysts. Extrahepatic locations of the echinococcus include the lungs (10%-15%), spleen (0.9%-8%), kidneys (1%-4%), pancreas (0.25%-0.75%), brain, heart, ovaries, bones and abdominal wall. Symptoms in such cases occur because of pressure or complications including rupture, allergic reaction and secondary infection (9).

Radiography, US and CT studies are important for diagnosis of echinococcal disease. Plain abdominal X-rays may show calcifications of the cystic wall (10). US is the method of choice for the detection of hepatic and extrahepatic echinococcal cysts.

Hydatid cysts are classified by ultrasound into six categories. Type 1 are defined as univesicular and are <50 mm in diameter. Type 2 are univesicular with a prominent laminated layer, and tend to be seropositive. Type 3 are subdivided into 3a, defined as cysts with a prominent lamination that contains daughter cysts, and 3b, characterized by lamination but a lower number of daughter cysts. Both 3a and b are highly seropositive. Type 4 appear as solid masses. Type 5 are characterized by degeneration with calcifications. Type 6 are defined as multiple cysts that may be univesicular and laminated, with daughter cysts involving one or more organs (11, 12). The sensitivity of US ranges from 93% to 98% (12).

Serological tests contribute to diagnosis. Immunoglobulin G antibody detection by ELISA has a sensitivity of 95% and a specificity of 94%. The sensitivity of indirect hemagglutination test has been found to be 87.5% (11).

Primary pelvic hydatid cyst, although rare, can be found in association with liver or lung hydatid cysts. Complications of pelvic hydatid disease may be urinary problems, rupture, or even obstructed labor (5, 7, 13-15).

The World Health Organisation has outlined the treatment guidelines for hydatid cysts. Surgery is the treatment of choice for all patients with symptomatic disease and who are fit for surgery (16). For symptomatic or large hydatid peritoneal cysts, surgery, when feasible, is the principal method of treatment. Surgical treatment can be either radical or conservative. Total cystectomy, whenever possible, is the gold standard. For peritoneal cysts firmly attached to intraperitoneal viscera, unroofing and drainage has been proven to be a safe method. It is important that the abdominal cavity is isolated with gauzes soaked in 20% hypertonic saline solution to avoid secondary hydatosis and allergic reaction (17).

Generalized toxic reaction due to hydatid cyst rupture and secondary infection are among the most common complications. The evacuation of the pelvic cyst by the vaginal route may prevent the risk of toxic reaction.

The pelvic hydatid cyst in the case of Gupta et al. (6) was located in the right pelvis, and it extended through the greater sciatic notch into the gluteal region. The recurrence incidence of hydatid disease after surgery is said to be 8-22%, with recurrences most often noted within 2 years after the operation (3). Physicians should be familiar with hydatid cyst imaging features and direct the surgeon, so that care can be taken during operation in order to prevent recurrences and choose the appropriate treatment options. This parasite should be kept in mind and considered when making the differential diagnosis of pelvic cystic masses, particularly if the patient is from an endemic area. The vaginal approach and evacuation of the cyst seems safe, effective and prevents the toxic reaction.

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Familial mediterranean fever: a diagnostic challenge in pregnancy

Ailevi akdeniz ateşi: gebelikteki tanısal güçlük”

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Abstract

Familial Mediterranean Fever (FMF) is an autosomal recessive disease which is characterized by recurrent, self-limiting, short attacks of serositis while abdominal pain is the most common symptom. The underlying clinical and pathological picture is that of acute peritonitis. These abdominal signs are often so striking that they mimic an acute abdominal calamity suggesting several possible gastrointestinal, gynecologic or urologic diagnoses. Diagnosis of acute abdomen in pregnancy also remains one of the most challenging conditions as the physiological consequence of pregnancy and nonspecific laboratory parameters. A limited number of studies addressed FMF in pregnancy and none of them mentioned the diagnostic challenging of FMF during pregnancy because the patients had al been diagnosed previously. In this paper, we discussed a 20 year old, gravida 1, parity 0 patient whose twin pregnancy wash complicated by an acute abdominal condition after amniocentesis and the difficulties of making the diagnosis of FMF with the complications during this diagnostic period in pregnancy.

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Key words: Pregnancy, diagnosis, Familial Mediterranean fever, acute abdomen

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Özet

Ailevi Akdeniz Ateşi (AAA) en yaygın belirtisi karın ağrısı olan; tekrarlayıcı, kendi kendini sınırlayan, kısa serozit ataklarıyla karakterize, otozomal resesif geçişli bir hastalıktır. Altta yatan klinik ve patolojik görünüm akut peritonitle uyumludur. Bu batın bulguları bazen o kadar dikkat çekici bir duruma gelir ki, bazı gastrointestinal, jinekolojik ve ürolojik tanıları düşündüren akut karın tablosunu taklit eder. Gebelik sırasında akut karın tanısı koymak, gebeliğin fizyolojik sonuçlarına ve spesifik olmayan laboratuvar parametrelere bağlı olarak en zor durumlardan biridir. Gebelikte AAA ile ilgili sınırlı sayıda çalışma mevcuttur ve hiçbirinde AAA' nin gebelik sürecindeki tanısal zorluğundan bahsedilmemiştir, çünkü hepsi de gebelikten önce AAA tanısı almışlardır. Bu yazıda biz, 20 yaşında, gravida 1, parite 0 bir hastada amniosentez sonrasında akut karın tablosunu taklit ederek ikiz bir gebeliği komplike eden AAA' nin gebelik sürecinde tanısının konulmasındaki zorlukları ve bu tanısal süreçte meydana gelen komplikasyonları tartıştık

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Anahtar kelimeler: Gebelik, tanı, ailevi Akdeniz ateşi, akut batın

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Introduction

Familial Mediterranean Fever (FMF) is an inherited, recessively transmitted inflammatory condition usually occurring in populations of Jewish, Armenian, Arabic, and Turkish ancestry (1). The disease is characterized by recurrent, self-limiting, short attacks of serositis (peritonitis, pleuritis or arthritis), fever and erysipelas-like skin lesions along with a marked increase in acute phase reactants. Abdominal pain is generally the main manifestation of this disease. The underlying clinical and pathological picture is that of acute peritonitis. The pain may originate from a part of the abdomen but quickly becomes generalized. These abdominal signs are often so striking that they mimic an acute abdominal calamity suggesting several possible diagnoses such as appendicitis, gallbladder disease, acute pancreatitis, porphyria, recurrent small bowel obstruction and chronic inflammatory processes of the intestine (e.g. Crohn's disease).

The incidence of acute abdomen during pregnancy is 1 in 500–635 pregnancies (2, 3). Diagnosis of acute abdomen in pregnancy remains one of the most challenging conditions

and therapeutic dilemmas today. As a physiologic consequence of pregnancy, the laboratory parameters are nonspecific and often altered. The most common cause of acute abdomen in pregnancy is acute appendicitis, but almost all causes of acute abdomen can manifest during pregnancy (4). In the literature search we did not detect FMF as a cause of acute abdomen during pregnancy. However, a limited number of studies (5-7) addressed FMF in pregnancy, but they were all previously diagnosed patients and none of them mentioned the diagnostic challenge of FMF during pregnancy. In this paper, we discussed the difficulties of making the diagnosis of FMF during pregnancy which complicated twin pregnancy by mimicking an acute abdominal condition after amniocentesis.

Case report

A 20 year old gravida 1, parity 0 patient referred to our clinic as a result of a spontaneous twin pregnancy of 6 weeks duration according to the last menstruation date. As the patient had a family history of Down's syndrome, they insisted on

an amniocentesis being performed. Amniocentesis was performed at 18 weeks 4 days of gestational age and revealed a normal karyotype. The patient presented at the hospital suffering from abdominal pain, nausea and vomiting 4 days after amniocentesis. An ultrasound examination revealed the existence of a 19-week-old twin fetus with no grossly visible anomaly. On examination, the patient demonstrated abdominal rebound tenderness on the lower quadrant, signaling peritoneal irritation. Initially the pain was localized but quickly became generalized. She had no fever and laboratory findings were normal except for a high level of C-reactive protein (CRP) of about 48.3 mg/l (0-8 mg/l), whereas white blood count was 13200/mm³ (3.6-9.6/mm³). On the second day of follow-up, the patient complained of a fever of 38.5°C and abdominal pain again. The patient was consulted in the Department of General Surgery and acute surgical pathology was eliminated. As the clinics and laboratory findings of the patient were compatible with chorioamnionitis, antibiotherapy (Ampicillin 2 g i.v. loading dose followed by 1 g i.v. every 6 hr) was initiated. A second antibiotic treatment (Clindamycin 900 mg i.v. every 8 hr) was added as a result of the continuation of fever and increasing level of CRP (120 mg/l). Uterine contractions were detected by external cardiotocography, so indomethacin (Endol 100 mg rectal loading dose followed by 25 mg oral every 6 hr during 2 days) therapy was started. The patient was clearly informed that chorioamnionitis is one of the reasons of termination in pregnancy but she refused it even she was also informed about septicemic complications and she wanted to be discharged because the symptoms were ended after antibiotherapy. So she was discharged on the fifth day with oral antibiotherapy.

On the 20 weeks and 5 days of her pregnancy, the patient presented again suffering from the same symptoms and fever (38.5°C). Vaginal examination was normal. An abdominal ultrasonographic finding of a heterogeneous, vascularized, non-mobile cystic mass lesion observed in the right lower quadrant was suggestive of an abscess or a plastron formation. After consultation with General Surgery Department, laparotomy was agreed on for appendectomy. Fibrinoid adhesions all over the abdomen and non-inflammatory appendix were noted during laparotomy. Consultation was made with the Department of Internal Medicine on the fifth postoperative day due to suspicion of FMF as one of the most probable diagnoses.

A new abdominal pain attack occurred on the 23 weeks plus 4 days of her pregnancy, colchicine therapy (1 mg/day) was initiated depending on the safety of it in pregnancy and no more attacks occurred during pregnancy. The patient was hospitalized on the 34 weeks plus 2 days of gestation with the diagnosis of preterm labor, and caesarian section delivery was performed as the first fetus was in breech presentation and the second in cephalic presentation. Genetic analysis of the patient was performed and Mediterranean Fever gene (MEFV) gene was found to be positive in the postpartum 6th week.

Discussion

This is the first report of FMF presenting as a diagnostic challenge in a mid-trimester patient with spontaneous twin pregnancy. It also emphasizes the importance of careful his-

tory taking to avoid unnecessary surgical interventions in acute abdomen during pregnancy. Despite advances in medical technology, diagnosis of acute abdomen during pregnancy is still inaccurate. Certain anatomic and physiologic changes specific to pregnancy may make the cause of the pain difficult to ascertain. Laboratory parameters also are nonspecific and often altered as a physiological consequence of pregnancy. The most common cause of the acute abdomen in pregnancy is acute appendicitis, but almost all causes of acute abdomen can manifest during pregnancy. Differential diagnosis should include FMF, which is characterized by recurrent attacks of fever and inflammation of serous membranes (8). Abdominal pain is the main manifestation of this disease. Although the majority of patients have a random pattern of attacks, without a clear precipitating factor, it has been observed that trauma, exertion, cold exposure, emotional stress and eating a fatty meal may precede attacks (9, 10). In our patient, FMF attacks occurred 4 times during pregnancy and the first attack started after amniocentesis. Therefore, the emotional and physical stress of amniocentesis may have precipitated the first attacks. There are contradictory reports relating FMF attacks during pregnancy; some patients may experience complete symptomatic remission but others may have attacks even more frequently. Acute phase reactants such as CRP, sedimentation rate and fibrinogen levels increase during an acute attack. An elevated white blood cell count with an increase in immature forms is seen. These laboratory findings are not diagnostic but when present they serve to support the diagnosis.

The reported incidence of chorioamnionitis following amniocentesis in the literature is 0.1%. Uterine tenderness, fever and high levels of infection parameters are the most important diagnostic criteria in the diagnosis of chorioamnionitis. Although we performed the procedure after an only one attempt in the midline of the abdomen 2 cm below the umbilicus under sterile conditions, laboratory findings and symptoms led us to suspect chorioamnionitis. But the continuation of fever and the changing characteristics of abdominal pain after antibiotherapy led us to a laparotomy to establish the pathology and to settle the symptoms. On laparotomy, non-inflammatory appendicitis and prevalent fibrinoid adhesions led us to suspect FMF. Then the patient mentioned abdominal pain attacks also before pregnancy when a more detailed medical history was obtained from her. Based on these findings FMF was the third probable diagnosis for our patient. Genetic analysis also confirmed our diagnosis of FMF.

In gynecological practice, FMF is usually not easily recognized. Patients often undergo exhaustive investigations and remain undiagnosed for years. Their histories often include multiple laparoscopies and laparotomies. Although genetic diagnostics are currently available (11), the diagnosis of FMF is still highly dependent on a clinical suspicion. Detailed medical history and the surgical finding during laparotomy helped us to diagnose her as FMF. To the best of our knowledge this is the first report handling the diagnostic challenge of FMF during pregnancy. This case also emphasizes the importance of careful anamnesis to avoid unnecessary surgical interventions in acute abdomen during pregnancy.

In conclusion, non-obstetric as well as obstetric reasons should be kept in mind in the differential diagnosis of acute abdomen during pregnancy. FMF should be remembered in young patients with recurrent attacks of abdominal pain and fever to avoid the hazard of misdiagnosis and to prevent unnecessary emergency operations during pregnancy.

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Prenatally diagnosed giant mesenteric cyst in the pelvis in an ICSI twin

ICSI ikizinde prenatal olarak tanısı konmuş dev mezenter kisti

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Abstract

The evidence of risk for birth defects due to artificial reproductive technology (ART) cycles is not yet clear. However, there may be a possible link between ART cycles and epigenetic abnormalities. Abdominal cysts are rarely seen pathologies after intracytoplasmic sperm injection (ICSI) cycles.

A giant mesenteric cyst was diagnosed in one of the ICSI twins by ultrasonographic examination at 14th gestational week. Infants born following ART are at increased risk of birth defects, compared to spontaneously conceived infants. When a mesenteric cyst is prenatally diagnosed, the differential diagnosis of enteric duplication cysts, ovarian cysts, urogenital tract malformations and biliary tract abnormalities should be done. Also we should keep in mind that mesenteric cysts may accommodate other pathologies. (J Turkish-German Gynecol Assoc 2009; 10: 238-40)

Key words: Giant mesenteric cyst, prenatal diagnosis, ICSI

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Özet

Yardımla üreme tekniklerine bağlı oluşan doğumsal defekt riskleri konusundaki kanıtlar açık değildir. Ancak, yardımla üreme teknikleri ve epigenetik anormallikler arasında bir ilişki olabilir.

ICSI ikizlerinin birinde 14. gebelik haftasında yapılan ultrasonografik incelemede mezenter kisti tanısı konuldu. Spontan olarak oluşan gebeliklerle karşılaştırıldığında yardımla üreme teknikleri ile oluşan gebeliklerde doğumsal defektler artmaktadır. Prenatal olarak mezenter kistinin ayrıncı tanısında enterik duplikasyon kistleri, over kistleri, ürogenital yol anormallikleri ve safra yolu anormallikleri göz önünde bulundurulmalıdır. Ayrıca mezenter kistlerinin altında yatan başka patolojilere bağlı olabileceği de unutulmamalıdır.

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Anahtar kelimeler: Dev mezenter kisti, prenatal tanı, ICSI

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Background

It is well established that pregnancies following in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have complications such as multiplicity, preterm delivery and low birth weight infants. However, the evidence related to the risk of birth defects is less clear. Despite reports of increased risk for birth defects following assisted reproductive technologies (ART), most authors have been reassuring, often dismissing increased risk estimates because they were not statistically significant (1). According to studies from different countries, the congenital malformation risk after ART is 2,2%, which is same with natural pregnancies (2-4).

However, there are also many reports about increased risk of congenital malformations in ART cycles. According to a meta-analysis of 26 studies ART have an increased risk for congenital abnormalities (5).

Here we report a case of twin pregnancy after ICSI which was prenatally diagnosed with a mesenteric cyst in one of the twins.

Case

A 26 year old G1 P0 woman referred to our clinic with the complaint of infertility for 4 years. The infertility work up yielded male

factor infertility. After the first attempt of classical long luteal protocol induction followed by ICSI, she became pregnant with twins. Leuprolide acetate was used beginning from the luteal phase of the previous cycle and ovarian hyperstimulation was supplied by follitropin alpha with a total dose of 1350 IU. The culture medium was a bicarbonate buffered medium containing hyaluronan and human serum albumin. There were no embryo manipulations. Together with these, vaginal progesterone was used during the first trimester beginning from the luteal phase.

At the 14th gestational week, an abdominal cystic lesion was detected in one of the fetuses. The lesion was anechoic, regular circumscribed and located in the pelvis. Amniotic fluid of the fetus was extremely decreased and the bladder was visualized separately. It was thought to be a benign structure, and normal antenatal care was planned for the patient. At the 18th gestational week a dichorionic twin pregnancy and a 6 cm cystic lesion filling the abdominal cavity and replacing liver and bowels were determined by magnetic resonance imaging (MRI). Initially, it was thought to be a lymphatic pathology such as a mesenteric cyst. Also, infravesical obstruction and enteric duplication cyst were considered in the differential diagnosis but at ultrasonographic examination there were no peristaltic movements. Other abdominal organs and the neural system were normal.

At the 36th gestational week the patient was referred with the complaint of vaginal bleeding. After the first examination regular uterine contractions and cervical dilatation of 2 cm were determined. Cesarean section was performed with the indication of presentation abnormality and a 2160 g female and 1630 g male live babies were born. The male fetus had lower APGAR scores at the 1st min:3rd and 5th min. He was dysmorphic and his left side was hypertrophic, and his chest was deformed. Pes equinovarus in the left foot, abdominal distention and loose abdominal skin were observed. The external auditory meatus was atresic. Intratracheal adrenaline was admitted twice and he was intubated. However, he did not respond to the resuscitation and was determined dead.

The autopsy report was compatible with the ultrasonography and MRI and revealed a giant mesenteric cyst in the pelvis.

Discussion

ART are important medical treatments for infertile people of reproductive age and account for 1-3% of the total annual births in developed countries. Recently, some human and animal studies have suggested a possible link between ART and certain birth defects related to epigenetic abnormalities, that is, genetic changes not involving DNA sequences (1).

In several studies of babies born following ART, the prevalence of major congenital malformations were comparable to those in the general population. A study from Australia showed a malformation rate of 2,2% in the first 2242 births after IVF in that country, which was no more than the corresponding figure in the general population (6).

Although the studies suggesting the safety of ART, there have also been reports of increased fetal abnormalities and other complications. A Swedish study of 5856 babies showed that 5.4% of babies born after IVF had a major malformation and that neural tube defects (anencephaly, hydrocephaly and spina bifida) and esophageal atresia were more frequent in IVF babies than in the control group (7).

A recent study of 135 ICSI pregnancies revealed that birth defects in ICSI children is significantly higher than the normal population (13,3% vs 4,6%; $p < 0,001$). However, the general health of ICSI children did not differ significantly. ICSI children required more surgery or hospitalization (8). Infants born following ART are at increased risk of birth defects, compared to spontaneously conceived infants. The main perinatal complications of ART include congenital malformations, chromosomal aberrations, multiple pregnancy, and prematurity. A large Australian study found that, by one year of age, the incidence of congenital malformations in IVF/ICSI children is increased in comparison to those naturally conceived. Multiple pregnancy is a major cause of perinatal mortality due to increase of both

prematurity and congenital malformations, as in our case. Even in singleton pregnancies conceived by ART, the risk of prematurity and newborns small for gestational age is increased. Factors that may increase the risk of birth defects include the relatively advanced age of the infertile couple, the underlying cause of infertility, and the medications used to induce ovulation (9).

Since some ART procedures have been implicated in various adverse outcomes for babies, basic research is required to elucidate the biological mechanisms underlying the genetic and epigenetic effects of ART. Large-scale prospective epidemiological studies could estimate the magnitude of the risk of ART in human pregnancy. In addition, it is important for clinicians to precisely record the ART procedures including the stimulation protocol, method of embryo culture, culture media used and timing of embryo transfer (1).

Mesenteric cysts are very rarely diagnosed defects after ICSI. They are most commonly found in the small bowel mesentery, together with omental and retroperitoneal cysts (10). Although they are normally simple cysts they may be septate and may be echogenic so that they are readily confused with ovarian and duplication cysts (11). Large cysts may cause abdominal distension and pain but otherwise they tend to be asymptomatic.

It still remains unclear whether the increased risk of adverse obstetric outcome in IVF singletons is a direct effect of the procedure involving such technology or reflects some other factors related to the underlying infertility of the couples. Recent studies have shown that infertility per se, unrelated to treatment, is associated with an increased risk of adverse obstetric outcome. Furthermore, the overall higher risk in twin pregnancies might conceal a limited risk of adverse outcome in IVF twins. The considerable higher risk of adverse obstetric outcome in IVF twins than in singletons and the 20-fold higher ART twin birth rate is still one of, if not, the most serious adverse effects of ART (12).

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Parapagus dicephalus dibrachus dipus: A case of conjoined twins

Parapagus dicephalus dibrachus dipus: Yapışık ikiz olgusu

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Abstract

In this report, we describe the case of a woman with a prenatal diagnosis of parapagus dicephalus dibrachus dipus conjoined twins at 14-15 weeks of gestation via two-dimensional ultrasonography. The parents elected to terminate the pregnancy and the patient delivered a 15-cm 130-g male fetus. There were two heads and necks which appeared grossly normal. The thoracic and abdominal cavities were shared. The fetus had four normal limbs. On internal examination, there were two separate structurally normal hearts. There were two larynges and four lungs. Two esophagi fused to enter a single stomach. The diaphragm was common and separated a single abdominal cavity. Distally, the alimentary system including the liver and gallbladder was single. (J Turkish-German Gynecol Assoc 2009; 10: 241-3)

Key words: Conjoined twins, parapagus twins, ultrasonography

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Özet

Bu vaka sunumunda 14- 15. gebelik haftasında ultrasonografi aracılığıyla tanı konulan parapagus dicephalus dibrachus dipus yapışık ikiz olgusu tanımlanmaktadır. Ebeveynler gebeliğin sonlandırılmasını tercih etmişler ve hasta 15-cm boyunda 130-g ağırlığında erkek fetus doğurmuştur. Dıştan görünümü normal, iki baş ve boyuna sahip fetüsün göğüs ve karın boşlukları ortaktır. Fetus dört adet normal ekstremiteye sahiptir. Otopsi incelemesinde fetüsün yapısal olarak normal iki ayrı kalbe, iki larenkse ve dört akciğere sahip olduğu görülmüştür. İki özofagusun distalde tek bir mideye girdiği görülmektedir. Diyafram ortak olup, tek karın boşluğunu göğüs boşluğundan ayırmaktadır. Fetüsün bir adet karaciğer ve safra kesesini de içeren tek gastrointestinal sisteme sahip olduğu görülmektedir.

(J Turkish-German Gynecol Assoc 2009; 10: 241-3)

Anahtar kelimeler: Yapışık ikiz, parapagus ikiz, ultrasonografi

Geliş Tarihi: 04 Nisan 2009 **Kabul Tarihi:** 28 Mayıs 2009

Introduction

The incidence of conjoined twins is between one in 50,000 pregnancies, and one in 650-900 twin pregnancies. The incidence of live born conjoined twins is a one set per 200,000 live births (1, 2). Conjoined twinning is a random event, unrelated to heredity, maternal age or parity (3).

Two theories have been proposed to explain conjoined twinning. Classically, the theory asserts that incomplete fission of a single embryonic disc occurs 13 to 15 days after the ovum is fertilized (fission theory). More recently, embryologic studies of conjoined twinning have indicated an alternative postulation that this developmental anomaly could originate from the secondary fusion of two separate monovular embryonic discs (fusion theory) (4).

Conjoined twins are mainly classified according to incomplete duplication (parasitic) or complete duplication. There are eight types of completely duplicated conjoined twins according to the most prominent site of union. (Table 1) (5). The most common type of union is thoraco-pagus and/ or omphalo-pagus (anterior thoracoabdominal fusion) and is found in 40-75% cases. Parapagus twins represent an extremely rare type of conjoined twins.

Here we describe the prenatal diagnosis of a case of parapagus (dicephalus, dibrachius, dipus) conjoined twins diagnosed during the first trimester with two-dimensional ultrasound at 14-15 weeks of gestation.

Case report

An 18-year old woman, gravida 2, para 1 was referred for routine scan at 14-15 weeks. Her previous pregnancy was uncomplicated and she had a 5 year old healthy child. She had no personal or family history of twins. The patient and husband were non-consanguinous. However, she is an identical twin herself.

Two-dimensional (2D) ultrasound scan demonstrated a conjoined twin pregnancy. There were two heads, two upper limbs and two lower limbs (Figure 1a). The twins were joined at the thorax and abdomen and there were two hearts. The diagnosis of dicephalus parapagus was made on the observation of two heads, one body, and one umbilical cord ultrasonographically. The couple was informed about the findings and poor outcome. They opted to have a termination of pregnancy. At autopsy, the weight of the conjoined twins was 130g, the

Table 1. Embryologic Classification of Conjoined Twins [5]

Embryonic aspect (%)	Type	Incidence (%)	Extent of union
Ventral (87)			
Rostral (48)	Cephalopagus	11	Top of head to umbilicus
	Thoracopagus	19	Thorax, upper abdomen, conjoined heart
	Omphalopagus	18	Thorax, upper abdomen, separate heart
Caudal (11)	Ischiopagus	11	Lower abdomen, genito-urinary tract
Lateral (28)	Parapagus	28	Pelvis, variable trunk; diprosopus 2 faces, dicephalus 2 heads
Dorsal (13)			
	Craniopagus	5	Cranial vault
	Pygopagus	6	Sacrum
	Rachiopagus	2	Vertebral column

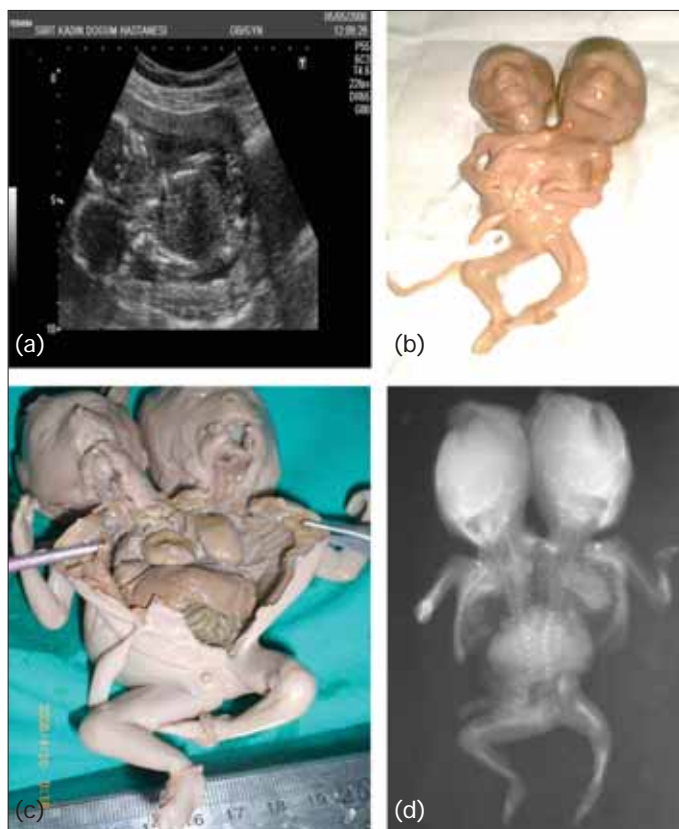


Figure 1. (a) Two-dimensional ultrasound scan of conjoined twins at 14-15 weeks of gestation. (b) Post-mortal image of the fetus anteriorly demonstrating two heads, two hands, and two lower limbs. (c) At autopsy, there were two separate structurally normal hearts. There were two larynxes and four lungs. The diaphragm is common and separated a single abdominal cavity. (d) A plain X-ray film showed two vertebral columns joining at the common pelvis and two separate chest cavities

head circumferences of the fetuses were approximately 90mm, the thorax circumference was 130 mm and the abdomen circumference was 100mm. The crown-heel length was 150 mm consistent with 14-15 weeks' gestation. There were two heads and necks which appeared grossly normal. The thoracic and

abdominal cavities were shared. The conjoined twins had two upper limbs and two lower limbs (Figure 1b). Both upper and lower limbs were normal with five digits on each hand. The anus was normal. There was male external genitalia.

On internal examination there were two separate structurally normal hearts (Figure 1c). There were two larynxes and four lungs. Two esophagi fused to enter a single stomach. The diaphragm was common and separated a single abdominal cavity. Distally, the alimentary system including the liver and gallbladder was single. There was one pair of kidneys and adrenal glands. Two ureters drained into a single bladder. There were two pairs of testes within the abdominal cavity. There was a normal placenta and a normal umbilical cord.

X-rays demonstrated that each twin had the normal complement of vertebrae and 12 pairs of ribs. A plain X-ray film showed two vertebral columns joining at the common pelvis and two separate chest cavities. Upper and lower limb bones were normal. (Figure 1d).

Discussion

Spontaneous twinning occurs in 1.6% of all human pregnancies, of which 1.2% are dizygotic and 0.4% are monozygotic. Approximately 5% of monozygotic pregnancies are monozygotic monoamniotic and 1% is conjoined.

A conjoined twin is a rare occurrence and the parapagus variety is even rarer. The developmental processes that underlie conjoined twinning are imperfectly understood, but recent research based on the analysis of large numbers of conjoined twins suggests that they form early in development due to the secondary union of two monovular embryonic discs (5). Parapagus twins lie side by side with venterolateral fusion. Most commonly; these twins are conjoined at the chest, with joined liver and diaphragm but separate respiratory and upper gastrointestinal tracts, two arms; two legs, and two complete spinal cords and vertebral columns, a single shared genitourinary system and lower gastrointestinal tract (4). All parapagus twins have one umbilicus and a conjoined diaphragm and liver. In this case, there was a single umbilical cord and a single shared pelvic region and abdomen, but two joined thoraxes having two

complete vertebral columns, two hearts and two pairs of lungs, two arms and two legs.

Although findings at autopsy were normal in this case, other dicephalus twins have had characteristic abnormal findings. Past studies described complex anomalies of the heart and abdominal laterality heart abnormality. Ventricular cardiac union is reported in parapagus twins. Many of our parapagus twins have had a common pericardium (6). Defects of lateralization including right and left atrial isomerism and mirror imagery are known to be particularly common in parapagus twins. There are generally two sets of lungs, which may be underdeveloped or anomalous. Neural tube defects, cystic hygroma, clubfoot, and imperforate anus have occurred in parapagus twins (7).

Before the recent improvement of quality of ultrasound depiction, the diagnosis of conjoined twins was not always easy and therefore often missed. Sonography is now used widely in obstetrics, and it can detect conjoined twins as early as 12 weeks of gestation. Whenever monozygotic twinning is observed, conjoining should be suspected. The presence of polyhydramnios and both twins in breech or in face-to face position alert the sonographer to the possibility of conjoined twins (8).

In conclusion, conjoined twins have intrigued physicians for centuries. Their management is often extremely complex and experience with large numbers restricted to a few centers worldwide. Most of the conjoined twins are born prematurely, around 40% are stillborn, and 35% die in the first 24 hours of life (9). Postnatal separation can be achieved in rare cases. Overall, the prognosis depends on the type of fusion and presence of

associated structural defects. Accurate antenatal assessment allows the parents to be counseled as to the probable outcome of the pregnancy and the likelihood of successful postnatal separation. First or second trimester detection of conjoined twins enables obstetricians to counsel parents about potential termination, or about delivery and treatment options if pregnancy is continued.

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Rescue cerclage in IVF pregnancies with second trimester cervical dilatation: Case report and literature review

IVF gebeliklerinde ikinci trimester servikal dilatasyonda acil serklaj: Vaka sunumu ve literatürün gözden geçirilmesi

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Abstract

Despite being available for over 50 years, cervical cerclage remains one of the controversial interventions in obstetrics. Rescue cerclage is the operative cervical closure of a widely dilated cervix with or without unruptured membrane prolapsus. In the literature, the effectiveness of rescue cerclage in the prolongation of pregnancy is debatable. Prolongation of pregnancy and improvement of neonatal survival is of utmost importance in pregnancies achieved by in vitro fertilization (IVF). We report here two IVF pregnancies with second trimester cervical dilatation treated with rescue cerclage and who delivered healthy babies near term without maternal and neonatal morbidities. (J Turkish-German Gynecol Assoc 2009; 10: 244-7)

Key words: Rescue cerclage, IVF, pregnancy, cervical dilatation

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Özet

50 yıl önce tanımlanmış olmasına rağmen servikal serklaj halen obstetrideki tartışmalı girişimlerden biridir. Acil serklaj ise dilate olmuş bir servikste membranlar prolabe olmuş iken veya prolabe olmamış iken serviksin cerrahi olarak kapatılmasıdır. Literatürde acil serklajın gebeliği uzatmadaki rolü tartışmalıdır. Özellikle IVF sonrası elde edilmiş gebeliklerde, gebelik süresinin uzatılması ve yenidoğanın yaşama şansının artırılması çok önemlidir. Bu çalışmada ikinci trimester servikal dilatasyonu nedeniyle acil serklaj uygulanan iki IVF gebeliğinin önemli bir maternal ve neonatal morbidite olmadan terme yakın doğum ile sonuçlanmasını sunuyoruz.

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Anahtar kelimeler: Acil serklaj, IVF, gebelik, servikal dilatasyon

Geliş Tarihi: 26 Şubat 2009 **Kabul Tarihi:** 06 Haziran 2009

Introduction

Cervical cerclage is a prophylactic operative intervention that has been used in the management of second trimester loss since it was first described by Shirodkar and then McDonald in the 1950s. However, it remains one of the controversial interventions in obstetrics. Despite being available for over 50 years, very few randomized controlled trials have been conducted comparing cerclage with expectant management (1-3). Despite the confusion regarding the terminology of the cerclage procedure, three groups of indications were identified: elective or prophylactic cerclage based on obstetrical history alone, emergency cerclage performed upon the objective manifestation of cervical insufficiency, that is, cervical shortening (which might be named also as ultrasound-indicated cerclage) and rescue cerclage performed upon a dilated cervix with or without prolapsed unruptured membranes. However, the distinction between emergency and rescue cerclage is not clear in the literature and cervical suturing in the case of dilated cervix is named either as emergent, urgent or rescue cerclage.

Rescue cerclage is the operative cervical closure of a widely dilated cervix with or without unruptured membrane prolap-

pus. Prolongation of pregnancy and improvement of neonatal survival (birthweight greater than 1500 gr and preterm birth not before 28 weeks) is of utmost importance in pregnancies achieved by in vitro fertilization (IVF). Therefore IVF pregnancies with second trimester cervical dilatation constitute a challenge for the treating physician. In the literature, the effectiveness of rescue cerclage in prolongation of pregnancy is debatable.

With this report we present two pregnancies achieved in infertile couples who had undergone IVF treatment and were complicated by second trimester cervical dilatation and managed with so-called rescue cerclage. We wished to suggest that the rescue cerclage should be 'must' when the cervix was dilated and even membranes prolapsed in pregnancies achieved after IVF treatment.

Case 1

Mrs D.E., 22 years-old, had been married for three years and achieved a twin pregnancy following an IVF treatment for tubal factor infertility. At 16 weeks gestation, she presented with spotting and abdominal pain for the previous four hours.

On transabdominal ultrasound examination, both fetuses were alive and appropriately developed for the gestational age, however the cervix was observed to be dilated and effaced. On vaginal examination with a speculum, the membranes were bulging through the external cervical os and the legs of the underlying fetus were seen within it. Emergency cervical cerclage was performed promptly. The patient was placed in the Trendelenburg position and the herniating membrane was gently reduced with the aid of an inflated Foley catheter. Cervical cerclage was carried out by the McDonald technique with single stitch Mersilene tape under general anesthesia. She was hospitalized for the following four days with antibiotics and tocolysis. No complication occurred afterwards and she was discharged. The follow-up of the pregnancy was uneventful. No further hospitalization was required. At 35 weeks gestation, cesarean section was planned and two healthy babies, a boy of 1910 gr and a girl of 1950 gr, were delivered. Cerclage suture was removed during the operation. The infants did not need the intensive care unit and the patient was discharged with her babies on the second postoperative day.

Case 2

Mrs Y.İ., 34 years-old, had been married for 13 years and achieved a singleton pregnancy following an IVF treatment for unexplained infertility. At 20 weeks gestation, she presented with vague abdominal pain and spotting for the previous two hours. On ultrasound examination, the fetus was alive and appropriate for 20 weeks gestation. With transvaginal ultrasound, the cervix was observed to be 14 mm in length and funnelling was noted (Figure 1, 2). She was hospitalized and emergency cerclage was inserted immediately. The McDonald technique was applied (Figure 3). She was administered antibiotics and tocolysis during the postoperative period for one week and discharged at 21 weeks gestation. However, she noted abdominal and pelvic pain at home and although no cervical dilatation was observed on ultrasound, she was

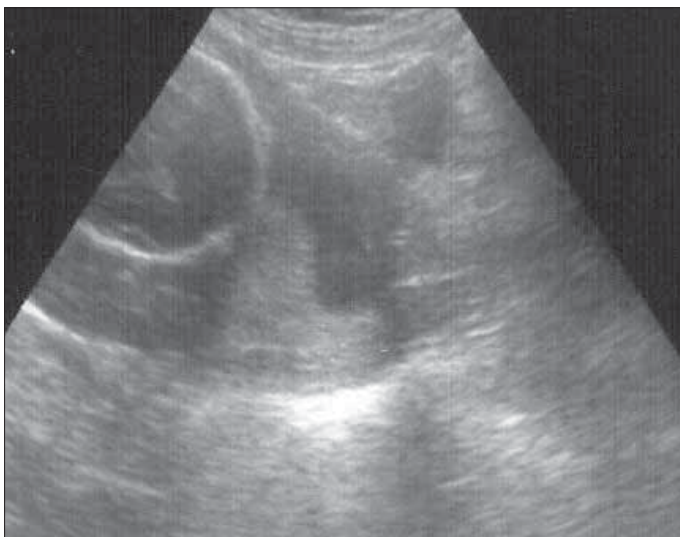


Figure 1. Ultrasound appearance of cervical dilatation and funnelling in case 2

hospitalized again. Because of her anxiety and recurrent pain complaints she was hospitalized intermittently until 34 weeks. Her pregnancy continued without any problem except her severe anxiety. At 34 weeks gestation the cerclage suture was removed and at 36 weeks of gestation she delivered a healthy 2600 gr girl with a normal vaginal delivery. Her baby did not need the intensive care unit and she was discharged with her baby on the postpartum day one.

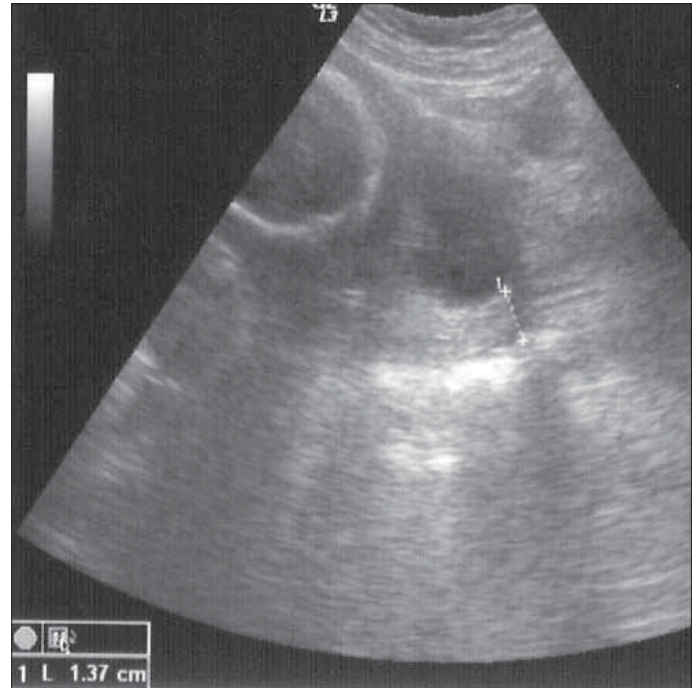


Figure 2. Precerclage ultrasound measurement of cervical length in case 2 (1.37 cm)

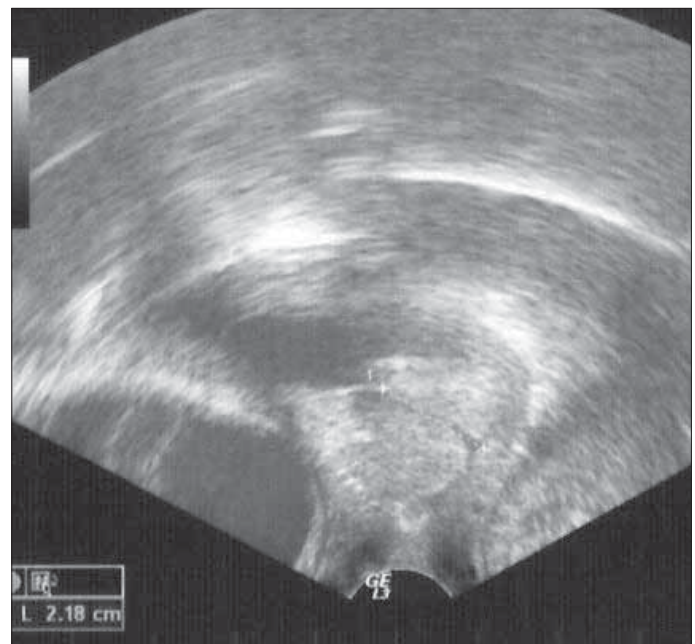


Figure 3. Postcerclage ultrasound measurement of cervical length in case 2 (2.18 cm)

Discussion

Cervical cerclage was first proposed by Shirodkar in 1955 (4) and then his technique was simplified by McDonald in 1957 (5). Despite being used in the management of suspected cervical insufficiency for nearly 50 years, there is still a wide variation in the use of cervical cerclage, which reflects the lack of evidence on the efficacy of the procedure. Traditionally, the decision to perform cervical cerclage has been based on a past obstetric history of a previous three or more preterm deliveries/second trimester losses. Cervical transvaginal ultrasound is being used by some as a screening test to identify those women who are at risk of preterm delivery, with an ultrasound-indicated cerclage inserted, based on the findings of a short cervix. For early preterm delivery a cervical length of less than or equal to 15 mm has a positive predictive value of approximately 50% and a negative predictive value of over 95% (6). The presence of cervical funnelling, an ultrasonographical finding whereby there is dilatation of the internal os with prolapse of the fetal membranes into the endocervical canal, was also noted to be associated with an increased risk of preterm delivery (7), although this may only be true for those with a short cervix (8). The evidence regarding whether ultrasound-indicated cervical cerclage reduces the risk of preterm delivery is conflicting. Study designs of the randomized controlled trials comparing ultrasound-indicated cerclage with conservative management make interpretation of their results difficult. Inclusion of high or low risk women makes a great difference. Furthermore, the appropriate threshold for ultrasound-indicated cerclage is unknown. Some investigators accepted the threshold as 15 mm, at which length intervention might be too late as a preoperative length of less than 15 mm is associated with visible fetal membranes at the time of suture placement, and a poor outcome (9). It was noted that the gestational age at delivery was higher if the cerclage was placed before 18 weeks of gestation and if cervical length was ≥ 25 mm (10).

In our report, case 1 presented with cervical dilatation and visible fetal membranes protruding into the vagina at 16 weeks. Case 2 presented with cervical funnelling and cervical length of 14 mm on transvaginal ultrasound at 20 weeks. Both were treated with emergency cervical cerclage.

Pregnancy outcome in women with a dilated cervix is usually grim. Management of advanced cervical dilatation can be rest in bed or cerclage. There has been no randomized study evaluating the effectiveness of rescue cerclage. In a study including 225 women, cervical cerclage was found to prolong gestation and improve neonatal survival compared with expectant management in women with cervical dilatation between 14 and 26 weeks (11). Another non-randomized prospective study comparing emergency cerclage with bed rest found that those treated with cerclage had a significantly higher mean birth weight, however no difference was observed in perinatal mortality (12). Factors associated with delivery prior to 28 weeks in those women treated with emergency cerclage were reported to be membranes bulging into the vagina through the cervical os, need of cerclage prior to 22 weeks gestation and nulliparity (13).

Despite being known for more than 50 years, there is still little evidence as to the efficacy of cervical cerclage. Furthermore, it

is unlikely that future trials comparing cerclage with no cerclage in women at high risk of preterm delivery will be performed. However, IVF pregnancies are a special group as intensive treatments probably have been performed to achieve a pregnancy and the loss of a pregnancy certainly would be more tragic both for the couple and the physician. Therefore, it would be prudent to offer cervical cerclage to women having IVF pregnancies even at an advanced cervical dilatation with bulging membranes. Those women with the highest risk of preterm delivery are the most likely to have the highest probability of deriving benefit from cervical cerclage. Therefore, even if miscarriage is inevitable, rescue cerclage might be considered in IVF pregnancies. The placement of rescue cerclage should be considered as a therapeutic procedure to prolong pregnancy and improve neonatal survival even in cases with membrane protrusion. In a meta-analysis, it was noted that cerclage should be avoided in multiple pregnancies (14). However, our first case was a successful rescue cerclage case with twin IVF pregnancy.

Cervical cerclage definitely carries risks. Reported adverse events are vaginal bleeding, premature preterm rupture of membranes (PPROM), and chorioamnionitis (15). In our cases no complication occurred either during or following the cerclage procedure. In both cases patients were managed in the postcerclage period with hospitalization, bed rest, antibiotics and tocolysis.

In conclusion, favorable pregnancy outcome might be accomplished in patients with advanced cervical dilatation in the second trimester of pregnancy following emergency cervical suturing even if performed when the membranes are bulging through the cervix into the vagina. Rescue cerclage in combination with antibiotics and tocolysis should be strongly advised in pregnancy prolongation in IVF pregnancies.

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Erratum

J Turkish-German Gynecol Assoc 2009; 10: 3/132-6'da yayınlanan makalede eksik basılan Tablo 1 aşağıda yayınlanmıştır. Below is the missing Table 1 in the manuscript printed in J Turkish German Gynecol Assoc 2009; 10(3): 132-6.

Table 1. Demographic features and cycle characteristics of women who became pregnant and those who did not following ART

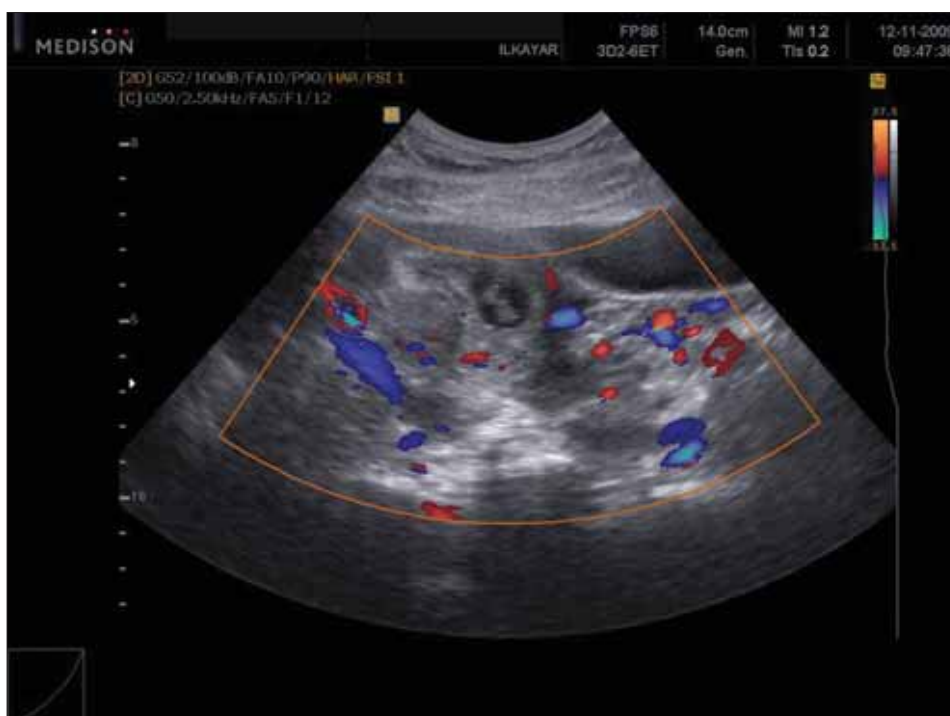
Variable	Pregnant (n=51)	Non-pregnant (n=34)	P
Age (years)	29.7±4.7	32.2±4.8	0.02
Infertility duration (years)	6.8±4.1	8.0±5.2	NS
Cause of infertility %, (n)			
Tubal	6 (3)	12 (4)	NS
Male	69 (35)	62 (21)	NS
Unexplained	25 (13)	26 (9)	NS
Gonadotropins used (IU)	2500±967	3278±1265	0.002
Stimulation duration (days)	9.9±0.9	10.1±1.2	NS
E2 on the day of HCG administration (pg/ml)	2637±971	2644±1154	NS
Total oocytes retrieved (n)	13.0±6.2	10.0±6.2	0.03
MII oocyte (%)	86±11	87±15	NS
Fertilization (%)	84±13	85±15	NS
ET day	2.9±0.9	2.7±0.9	NS
Grade I embryos transferred (n)	2.1±1.1	1.7±1.1	NS

The values are given as mean±SD or percent (numbers).

(HCG, human chorionic gonadotropin; E2, estradiole; MII, metaphase II; ET, embryo transfer; NS, not significant, p>0.05).

Student's t-test, Chi-squared test and Fisher's exact test

What is your diagnosis ?



Answer

Heterotopic pregnancy is defined as the co-existence of an intrauterine and extrauterine pregnancy. Current studies demonstrated that its incidence has increased from 1 in 30000 pregnancies to 1 in 7000 pregnancies, which may be even more frequent after assisted conceptions (1). This potentially fatal condition for both the pregnant women and intrauterine gestation is difficult to diagnose and needs a high level of suspicion and scanning of the adnexa in every pregnant women. But still more than half of the women are diagnosed after emergent operation for acute abdomen during pregnancy (2).

Heterotopic pregnancies implant most commonly in the fallopian tubes (77.6%) and less frequently in the cornual region, uterine cervix, ovary and the abdomen. The risk factors causing ectopic pregnancy, such as a history of pelvic inflammatory disease, endometriosis, tubal damage, previous ectopic pregnancy and tubal surgery are also risk factors for heterotopic pregnancy. Ovulation induction increases heterotopic pregnancy by causing multiple follicular ovulation and by decreasing tubal motility due a high estrogen milieu (3). In in vitro fertilization cycles heterotopic implantation is increased if i) the patient has tubal factor infertility, ii) if the tip of the transfer catheter is placed near the fundus, iii) if five or more embryos are transferred with more than 20 μ l of transfer medium, which increases the tubal flushing of the medium with the embryos. Unlike ectopic pregnancies, there is no diagnostic value of progesterone and β -hCG serum levels in heterotopic pregnancies. Vaginal bleeding is rare due to the presence of intrauterine pregnancies in heterotopic gestations. Heterotopic gestation should be suspected in the presence of adnexal mass, abdominal pain, peritoneal irritation and abnormally increased uterine size (4) Besides all these complaints it should be kept in mind that 45% of the heterotopic gestations remain asymptomatic until rupture.

Transvaginal ultrasound scanning is much more sensitive than transabdominal ultrasound scanning (sensitivity 93% vs 50% respectively). The transvaginal ultrasound pictures presented here are of a heterotopic pregnancy with fetal heart beat in both of the fetuses (Figure 1). The presence of a 2-6mm thick ring around the gestational sac which is more hyperechogenic than the ovarian tissue surrounding the corpus luteum help in the diagnosis. The embryonic heart beat is usually rare at

the time of the diagnosis and usually appears a week after salpingectomy for the ectopic gestation. A low resistance high velocity flow pattern around the suspected sac and the presence of fluid in the pouch of Douglas aid in the diagnosis (Figure 2). In the differential diagnosis, multiple follicular cysts in the ovary after superovulation and gestational sac in both of the cavities of a didelphic or bicornuate uterus should be kept in mind. In difficult cases, magnetic resonance imaging can be performed. The diagnosis of heterotopic pregnancies are made between 5 to 8 gestational weeks in 70% of the cases and later than 11 weeks of gestation in 10%.

Laparotomy and laparoscopy can be performed after the diagnosis. Ultrasound guided aspiration of the sac and KCL instillation has been successful in selected cases. On the other hand, methotrexate, misoprostol, mifepristone and prostaglandins are not used due to their possible adverse effect on the intrauterine pregnancy. These options can be used if the patient is hemodynamically stable and the intrauterine embryo is dead at the time of diagnosis.

During operation care should be taken to avoid damaging the corpus luteum and using low pressure (12-15 mmHg) pneumoperitoneum during laparoscopy. With these precautions the intrauterine pregnancy can continue in 66 to 75% of the cases.

Eray Çalışkan, Emek Doğer

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We continue to see an increase in the number of submissions to JTGGA as well as the quality. JTGGA is clearly becoming the journal of choice for obstetrics and gynecology healthcare issues in our region. We can afford to be somewhat more selective, and our rejection rate of 43.3% approaches that of other major medical journals. The reviews submitted by you are among the best that we have seen among a number of major medical journals. The office regularly receives letters from authors thanking JTGGA for such thorough and helpful reviews, which enables them to produce much better manuscripts.

That fulfills one of our primary missions of teaching authors, especially young authors, how to write better manuscripts. We have several new and exciting programs under review for implementation during the coming year, and we certainly look forward to your ongoing support, suggestions and recommendations as to how to continue to improve the overall quality of JTGGA.

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<http://www.isfp-fertility.org/pdf/FSA-Brussels>
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www.tsrn.org.tr
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0.5 ml IM Enjeksiyon İçin Süspansiyon İçeren Kullanıma Hazır Enjektör [Human Papillomavirüs Tip 16 ve 18 Rekombinant AS04 adjuvanlı aşı] Kas içine uygulanır.

Formülü: Human Papillomavirüs Tip 16 ve 18 Rekombinant AS04 adjuvanlı aşı, rekombinant DNA teknolojisi ile üretilen ve alüminyum hidroksit ile absorbe edilmiş infeksiyöz olmayan virüs benzeri partikül (VLP'ler) formunda L1 proteinini içerir, 0.5 ml dozu, 20 mikrogram İnsan Papillomavirüs Tip 16 L1 proteinini ve 20 mikrogram İnsan Papillomavirüs Tip 18 L1 proteinini içerir. **Endikasyonları:** Cervarix® aşı, 10 yaş ile 25 yaş arası kız çocukları ve kadınlarda Human Papilloma Virüs (HPV) Tip 16 ve 18 ile nedensel ilişkisi olan yüksek gradeli servikal intraepitelyal neoplazilerin (CIN grade 2 ve 3) ve servikal kanserin önlenmesi için endikedir. **Kontrendikasyonları:** Cervarix®'in içeriğinde bulunan maddelere ve aşının kendisine duyarlı olan kişilerde yan etkilere neden olabilir. **Uyarılar/Önemler:** Eğer sizde veya çocuğunuzda aşağıdaki durumlardan herhangi biri varsa; Aşının içerdiği maddelerden herhangi birine karşı gelişen aşırı duyarlılık (yardımcı madde listesine bakınız). Aşının bir dozunu aldıktan sonra gelişen aşırı duyarlılık, Aşırı duyarlılık belirtileri: Kaşıntılı deri döküntüsü, nefes darlığı ve yüz veya dilde şişme olarak sıralanabilir. Kanama bozukluğu olanlarda dikkatle yapılmalıdır. Bu uyarılar geçmişteki herhangi bir dönemde dahi olsa, sizin veya çocuğunuz için geçerliyse lütfen doktorunuza danışın. Bütün diğer enjektabl aşılarla olduğu gibi, aşının uygulanmasının ardından seyrek olarak anafilaktik reaksiyon görüldüğü takdirde gerekli olabilecek tıbbi tedavi olanakları hazır bulundurulmalıdır. Cervarix® 10 yaş altı çocuklarda kullanılmaz. **Gebelik ve Emzirme Döneminde Kullanımı:** Gebelik Kategorisi: C. Bu aşının hamilelik dönemindeki güvenliliği henüz tam olarak belirlenmiş değildir. Hamilelik sırasında ya da Cervarix® kullanıp kullanmamanıza doktorunuz karar verecektir. Cervarix®'in anne sütüne geçip geçmediği bilinmemektedir. Bu nedenle, emziriyorsanız doktorunuza bilgilendiriniz. Emzirmenin durdurulup durdurulmayacağına ya da Cervarix® kullanımının durdurulup durdurulmayacağına ilişkin karar verilirken, emzirmenin çocuk açısından faydası ve Cervarix® kullanımının emziren anne açısından faydası dikkate alınmalıdır. Cervarix® gerekli olmadıkça gebelik döneminde kullanılmamalıdır. Aşı kesinlikle damar içine uygulanmamalıdır. **Yan Etkiler/Advers Etkiler:** Tüm ilaçlar gibi, Cervarix®'in içeriğinde bulunan maddelere ve aşının kendisine duyarlı olan kişilerde yan etkilere neden olabilir. Aşı uygulama yerinde bölgesel olarak ağrı, kızamık, şişlik hissedebilirsiniz. Bu belirtiler genel olarak tüm aşılarla aşılamaya bağlı olarak görülen hafif yan etkilere ve uzun süreli değildir. Baş ağrısı, egzersiz ile ilişkili olmayan kas ağrısı, yorgunluk, 38°C ve daha yüksek ateş, bulantı, kusma, işhal ve karında ağrı, baş dönmesi, eklem ağrısı, deride döküntü, kaşıntı diğer bildirilen yan etkilere dir. **İlaç Etkileşimleri:** Cervarix® bağışıklık sistemini baskılayan diğer ilaçlarla birlikte kullanıldığında beklenen etkisini en iyi şekilde gösteremeyebilir. Klinik çalışmalar, Cervarix® ile elde edilen korunmanın ağızdan alınan doğum kontrol ilaçlarıyla azalmadığını göstermiştir. **Kullanım Şekli ve Dozu:** Optimal koruma sağlamak amacıyla üç intramüsküler enjeksiyon olacak şekilde 0, 1 ve 6 aylık uygulama şeması kullanılmalıdır. Cervarix® intramüsküler olarak uygulanmalıdır. Cervarix® intravenöz yoldan kesinlikle uygulanmamalıdır. **Aşırı Dozaj:** Uygulanamaz. **Saklama Koşulları:** Aşı +2°C ile +8°C arasında saklanmalıdır. Aşırı kesinlikle dondurulmamalıdır. Eğer aşı donmuşsa kullanılmadan atınız. **Ruhsat Sahibinin Adı ve Adresi:** GlaxoSmithKline İlaçları Sanayi ve Ticaret A.Ş., 1. Levent/İstanbul. **Ruhsat Tarihi ve Numarası:** 28.12.2007 - 4 Reçete ile satılır. 10.11.2008 tarihi itibarıyla perakende satış fiyatı KDV dahil (%8) 226.09 TL'dir. **Kullanma Talimatı Onay Tarihi:** 28.12.2007 **Kullanma talimatı Kodu:** Cervarix_KT_PFS,10/19,12.07/v.2/C Cervarix® GlaxoSmithKline şirketler grubunun tescilli markasıdır. **Daha geniş bilgi için firmamıza başvurunuz.**

Hiç olmadığı kadar özgür



YAZZ 24 +4 KISA PROSPEKTÜS

YAZZ® 24+4 film kaplı tablet: Herbiri 3 mg drospirenon ve 0,02 mg etinilestradiol içeren 24 film kaplı tablet ve bunları takip eden 4 placebo tablet. **Terapötik endikasyonlar:** •Gebelliği önleyici etkisinin yanı sıra antimineralokortikoid ve antiandrogenik etkileri sayesinde, hormona bağlı su tutulması ve buna bağlı belirtiler gösteren kadınlarda, •Oral kontrasepsiyon isteyen hastalarda akne vulgaris tedavisi, •Premenstruel disforik bozukluk (PMDD); Premenstrual Dysphoric Disorder) semptomlarının tedavisinde endikedir. **Pozoloji/uygulama sıklığı, süresi ve şekli:** Tabletler paketin üstünde gösterildiği yönde, hergün yaklaşık aynı zamanda bir miktar su ile alınmalıdır. Tablet alımı süreklidir. Birbirini izleyen 28 gün boyunca hergün bir tablet alınır. Her bir sonraki pakete önceki kutudaki son tablet alınımın ertesi günü başlanır. Tabletler normal siklusun ilk günü (kanamanın ilk günü) alınmaya başlanmalıdır. **Kontrendikasyonlar:** Kombine oral kontraseptifler aşağıdaki koşulların varlığında kullanılmamalıdır ve ilk kez kombine oral kontraseptif kullanımı sırasında bunlardan herhangi biri ortaya çıkacak olursa, tedavi hemen kesilmelidir. •Venöz veya arteriyel trombotik/tromboembolik olayların (örn. derin ven trombozu, pulmoner emboli, miyokard enfarktüsü) veya serebrovasküler bir olayın varlığı ya da öyküsü, •Tromboz prodromu varlığı veya öyküsü (örn. geçici iskemik atak, anejma pectoris), •Fokal nörolojik belirtili migren öyküsü, •Vasküler tutulumlu diabetes mellitus, •Venöz veya arteriyel tromboz için ciddi olan tek, ya da birden fazla risk faktörünün varlığı da bir kontrendikasyon oluşturabilir (bkz. Uyarılar/Önlemler), •Ağır hipertansiyon, •Ağır hipertrigliseridemi ile bağlantılı pankreatit veya pankreatite benzer öykü, •Karaciğer fonksiyon değerleri normale dönmedikçe, ciddi karaciğer hastalığı öyküsü veya varlığı, •Ağır veya akut böbrek yetmezliği, •Karaciğer tümörü varlığı veya öyküsü (iyi veya kötü huylu), •Eğer seks steroidlerinden etkileniyorsa genital organların veya memenin bilinen ya da şüpheli malign hastalıkları, •Tanı konulmamış vajinal kanama, •Bilinen gebelik veya şüphesi •Etkin ya da yardımcı maddelerin herhangi birine aşırı duyarlılık hali. **Özel kullanım uyarıları ve önlemleri:** Özel kullanım uyarıları: Aşağıda belirtilen durumlardan herhangi birinin ortaya çıkması durumunda kombine oral kontraseptiflerin kullanımına ait yararlar olası risklere karşı tartılmalı ve tedavie başlamadan önce kullanacak olan kadınla birlikte tartışılmalıdır. Dolajsım bozuklukları: Epidemiyolojik çalışmalar, kombine oral kontraseptif kullanımıyla miyokard enfarktüsü, inme, derin ven trombozu ve akciğer embolisi gibi arteriyel ve venöz trombotik/tromboembolik hastalıkların risk artışı arasında bir ilişki bulunduğunu belirtmektedirler. Bu olaylar ender olarak ortaya çıkmaktadır. Derin ven trombozu ve/veya pulmoner emboli şeklinde ortaya çıkan venöz tromboemboli (VTE) tüm kombine oral kontraseptiflerin kullanımını sırasında ortaya çıkabilir. Tümörler: Servikal kanser için en önemli risk faktörü süregelen human papilloma virus (HPV) enfeksiyonudur. Bazı epidemiyolojik çalışmalarda uzun süre kombine oral kontraseptif kullanımının servikal kanser riskinde artışa neden olabileceği bildirilmiştir ancak bu bulguların kombine oral kontraseptif kullanımıyla ilişkisine bağlı olarak değerlendirilmelidir. 54 epidemiyolojik çalışmayı kapsayan bir meta-analiz sonuçlarına göre halen kombine oral kontraseptif kullanan kadınlarda meme kanseri teşhis edilmesinde (bağlı risk = 1,24) hafif bir artış olduğu rapor edilmiştir. Bu risk artışı kombine oral kontraseptif kullanımının kesilmesiyle birlikte 10 yıl içinde göreceği olarak ortadan kalkar. Diğer uyarılar: Böbrek yetmezliği olan hastalarda potasyum atılım kapasitesi sınırlı olabilir. Hipertansiyonlu hastalarda, kombine oral kontraseptif kullanımıyla pankreatit gelişimi riskinde artış ortaya çıkabilir. Kombine oral kontraseptif alan kadınların çoğunda kan basıncında hafif artış görüldüğü bildirilmesine rağmen, klinik olarak anlamlı artış enderdir. Drospirenon, antimineralokortikoid etkisinden dolayı diğer kombine oral kontraseptifler kullanan normal tansiyonlu kadınlarda etinilestradiol'e bağlı gelişen tansiyon yükselmesini olumlu yönde etkileyebilir. Bununla beraber, kombine oral kontraseptif kullanımı sırasında ortaya çıkan klinik olarak belirgin bir hipertansiyon gelişiminde, hekimin kombine oral kontraseptif kullanımını kesmesi ve hipertansiyon tedavisine başlaması gerekir. Kolestaza bağlı sarılık ve/veya kasıntı, safra taşı oluşumu, porfiri, sistemik lupus eritematozus, hemolitik üremik sendrom, Sydenham koreisi, herpes gestationis, otosklerozaya bağlı işitme kaybı gibi durumların gebelik ve kombine oral kontraseptif kullanımı sırasında ortaya çıkması ya da kötüleştiği bildirilmiştir de, bunların kombine oral kontraseptiflerle olan ilişkisi kesinlik kazanmamıştır. Ailesel anjiyodemi olan kadınlarda egzojen estrojenler anjiyodemi belirtilerinin ortaya çıkmasına veya alevlenmesine yol açabilirler. Karaciğer fonksiyonlarında görülen akut ve kronik değişiklikler, kombine oral kontraseptif kullanımının fonksiyon testi değerleri normale dönene dek kesilmesini gerektirebilir. Gebelik sırasında ilk kez ortaya çıkan ya da daha önce seks steroidlerinin kullanıldığı sırada görülmüş olan kolestatik sarılığın nüks etmesi kombine oral kontraseptif kullanımının kesilmesini gerektirir. Crohn hastalığı ve ülseratif kolit kombine oral kontraseptif kullanımı ile ilişkilendirilmiştir. Özellikle kloazma gravidamum öyküsü olan kadınlarda daha belirgin olmak üzere kloazma ortaya çıkabilir. Azalmış etkinlik: Kombine oral kontraseptiflerin etkinliği tablet alımı unutulduğunda (bkz. Tablet alımı unutulduğunda), mide-bağırsak bozuklukları olması halinde (bkz. Mide-bağırsak bozuklukları durumunda), ya da eş zamanlı ilaç tedavilerinde (bkz. İlaç etkileşimleri) azalabilir. Azalmış siklus kontrolü: Tüm kombine oral kontraseptiflerde, özellikle kullanım ilk aylarında düzensiz kanamalar (kekelenme veya kırılma kanamaları) gelişebilir. Bu nedenle herhangi bir düzensiz kanamanın araştırılması yaklaşık 3 siklusluk bir adaptasyon süresinden sonra anlamlıdır. Etkileşimler: Oral kontraseptifler ve diğer ilaçlar arasındaki etkileşimler kırılma kanamalarına ve/veya kontraseptif başarısızlığa yol açabilirler. Aşağıdaki etkileşimler literatürde bildirilmiştir. Hepatik metabolizma: Mikroozmal enzimleri etkileyen ilaçlarla (örn. fenitoin, barbitüratlar, primidon, karbamazepin, rifampisin ve multimedlen okskarbazepin, topiramet, felbamet, griseofulvin ve St. John's wort (Sarı kantaron)) içeren ürünler) olan etkileşimler, seks hormonlarının konsantrasyonlarının artması ile sonuçlanabilir. Gebelik kategorisi: X'dir. YAZZ® 24+4 gebelik döneminde uygulandığı takdirde ciddi doğum kusurlarına yol açmaktadır. YAZZ® 24+4 gebelik döneminde kontrendikedir. YAZZ® 24+4 film kaplı tabletlerin kullanımı sırasında gebelik meydana gelmesi durumunda kullanımı durdurulmalıdır. Laktasyon: Anne sütünün miktarında azalmaya ve bileşiminde değişikliğe yol açabileceğinden, kombine oral kontraseptifler tarafından etkilenebilir. **İstenmeyen etkiler:** Kombine oral kontraseptiflerin kullanımıyla ilişkilendirilen en ciddi yan etkiler "Uyarılar/önlemler" bölümünde ele alınmıştır. Aşağıdaki diğer yan etkiler kombine oral kontraseptif kullanıcılarında bildirilmiş ve ilişkileri ne doğrulanmış ne de yanlışlığı kanıtlanmıştır. **Göz:** Seyrek: Kontak lensle toleranssızlık **Gastrointestinal sistem:** Yagın: Bulantı, batında ağrı, Yagın olmayan: Kusma, diyare **İmmün sistem bozuklukları:** Seyrek: Hipersensitivite **İncelemeler:** Yagın: Kiloda artış, Seyrek: Kiloda azalma **Metabolizma ve beslenme:** Yagın olmayan: sıvı tutulumu **Sinir sistemi:** Yagın: Baş ağrısı, Yagın olmayan: Migren **Psikiyatrik düzensizlikler:** Yagın: Depresif duygu durumu, duygu durum değişiklikleri, Yagın olmayan: Libido azalması, Seyrek: Libido artışı **Üreme sistemi ve memeler:** Yagın: Memede ağrı, meme hassasiyeti, Yagın olmayan: Memede hipertrofi, Seyrek: Vajinal akıntı, memede akıntı **Cilt ve cilt altı:** Yagın olmayan: Dokümant, ürtiker, Seyrek: Eritema nodosum, eritema multiforme. Ailesel anjiyodemi olan kadınlarda egzojen estrojenler anjiyodemi belirtilerinin ortaya çıkmasına veya alevlenmesine yol açabilirler. **Raf ömrü:** 48 ay. **Saklamaya yönelik özel tedbirler:** 25 C'nin altında oda sıcaklığında saklayınız. **Ambalajın niteliği ve içeriği:** PVC/Aluminyum blister'de etkin madde içeren 24 adet ve etkin madde içermeyen 4 adet film kaplı tablet. **Ruhsat Sahibi:** Bayer Türk Kimya San. Ltd. Sti., Cakmak Mah. Balkan Cad. No:53 34770 Ümraniye – İstanbul Tel: (0216) 528 36 00 Faks:(0216) 538 37 40 **Ruhsat Numarası:** 126/93 **Ruhsat Tarihi:** 02.03.2009 Fiyat: KDV dahil perakende satış fiyatı: 21,53 TL Ayrıntılı bilgi için Firmamıza başvurunuz.



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