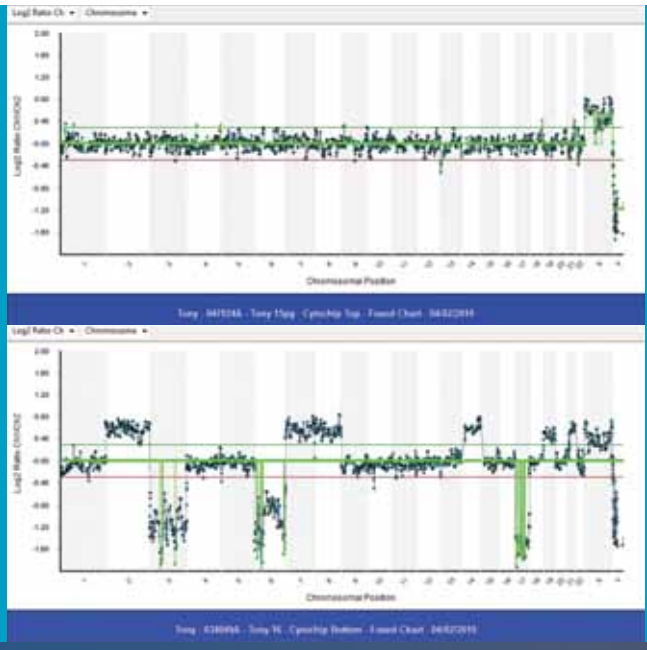
ISSN 1309-0399

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association



Volume 11
Issue 4
December
2010

Original Investigations

AVES

Official Journal of the
Turkish-German Gynecological Education and Research Foundation
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Turkish-German Gynecological Association
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O'nu bir kez denedikten sonra gözü başkasını görmeyecek[1,2]

YENİ

aylık doğum kontrol halkası

- 3 hafta boyunca sürekli olarak progestin ve östrojen salan, benzersiz bir uygulama sistemidir[1]
- Ovülasyonu inhibe eder[1]
- >%99 oranında etkilidir[3,5]

- En düşük etinil östradiol düzeyi[3,4]
- Kullanım kolaylığı[1]

NUVARING®

(Günde 120 µg etonogestrel/15 µg etinil östradiol)
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Etkin madde: NUVARING 11.7 mg etonogestrel ve 2.7 mg etinilöstradiol içerir. Günde 0.120 mg etonogestrel ve 0.015 mg etinilöstradiol salgılayan vajinal yolla uygulanan doğum kontrol halkasıdır. **Terapötik endikasyonu:** Kontrasepsiyon. **Uygulama şekli ve dozajı:** NUVARING menstrüasyonun ilk gününde yerleştirilmelidir Başlangıç 2.-5. günlerde olabilir, fakat NUVARING kullanımının ilk 7 günü sırasında ek olarak prezervatif gibi bir bariyer yöntemi kullanımı önerilmektedir. **Uygulama şekli:** NUVARING vajinaya kadının kendisi tarafından yerleştirilebilir. Yerleştirme sırasında kadın, örn. bir bacağını kaldırma, çömelme ya da uzanma gibi kendisi için en uygun pozisyonu seçecektir. NUVARING iki yandan sıkıştırılmalı ve rahat hissedilene kadar vajina içine sokulmalıdır. NUVARING, yerleştirme sonrasında 3 hafta kullanıldıktan sonra yine haftanın aynı günü çıkartılmalıdır. Yeni halka, bir haftalık halkasız dönem sonrası yerleştirilir NUVARING işaret parmağının kanca şeklinde kıvrılması ve halkanın işaret parmağı ve orta parmak arasında kavranması ve dışarı doğru çekilmesi yoluyla çıkartılabilir. **Kontrendikasyonlar:** NUVARING aşağıda belirtilen koşulların herhangi birinin varlığında kullanılmamalıdır. Pulmoner emboli ile ilişkili ya da ilişkisiz venöz trombozun varlığı ya da öyküsü, tromboz öncüsü olaylar veya arteryel trombozun varlığı ya da öyküsü veya risk faktörlerinin varlığı, fokal nörolojik semptomların eşlik ettiği migren öyküsü, vasküler tutulumun eşlik ettiği diabetes mellitus,pankreatit veya ciddi hipertrigliseridemi ile birlikte pankreatit öyküsü, karaciğer fonksiyonu ile ilgili değerlerin normale dönmediği ciddi karaciğer hastalığı varlığı veya öyküsü, karaciğer tümörlerinin (selim ya da habis) varlığı ya da öyküsü, bilinen veya kuşkulanılan, seks-steroid etkili genital organların veya memelerin habis durumlar,tanısı konmamış vajinal kanama,bilinen veya kuşkulanılan hamilelik, NUVARING aktif bileşenlerine ya da herhangi bir yardımcı maddeye aşırı duyarlılık. **Özel kullanım uyarıları ve önlemleri:** Aşağıda belirtilen durumlar ya da risk faktörlerinden herhangi birinin varlığında, NUVARING kullanımının yararları her bir kadındaki olası risklere karşı değerlendirilmelidir. Dolaşım bozuklukları Epidemiyolojik çalışmalar kombine oral kontraseptif (KOK) kullanımı ile miyokard infarktüsü, inme, derin venöz trombozu ve akciğer emboli gibi artan arteriyal ve venöz trombotik ve tromboembolik rahatsızlıklar riski arasında bir bağlantı kurmuştur, Bunlar nadiren gerçekleşir, Diğer kombine hormonal kontraseptifler ile risk kıyaslandığında NUVARING'in nasıl bir etkisi olduğu bilinmemektedir. Hormonal kontraseptif kullanımı sırasında migrenin sıklığı veya şiddetinde bir artış (bir serebrovasküler olayın habercisi olabilir) hormonal oral kontraseptif kullanımının aniden kesilmesini gerektirebilir. Tümörler Servikal kanserin en önemli risk faktörü persistan human papilloma virus (HPV) enfeksiyonudur, Epidemiyoljik çalışmalar, uzun süre KOK kullanılmasının bu risk artışına katkıda bulunduğunu göstermiştir ama; söz konusu bulgunun; servikal taramaların daha sık yapılması ve bariyer kontraseptif kullanımı dahil cinsel davranış farklılıkları gibi, sonuç üzerinde etkili olabilecek diğer faktörlere ne derece bağlı olduğu veya arada bir nedensellik ilişkisi olup olmadığı konusundaki belirsizlik, devam etmektedir. Bu etkinin Nuvaring ile nasıl ilişkili olduğu bilinmemektedir. Seyrek olgularda, KOK kullanıcılarında, selim karaciğer tümörleri ve daha seyrek olarak habis karaciğer tümörleri bildirilmiştir. İzole olgularda bu tümörler yaşamı tehdit eden intra-abdominal hemorajilere yol açmıştır. Bu nedenle, NUVARING kullanan kadınlarda ciddi üst abdomen ağrısı, karaciğer büyümesi ya da intra-abdominal hemoraj oluşması durumunda, ayrıcı tanıda karaciğer tümörü düşünülmelidir.Gerek hamilelik gerekse hormonal kontraseptif kullanımı sırasında aşağıdaki durumlara ilişkin belirti ya da kötüleşme bildirilmiş olmakla birlikte kullanımı ile ilişkinin kanıtı kesin değildir: sarılık ve/veya kolestaza bağlı sarılık, safra taşı oluşumu, porfiri, sistemik lupus eritematoz, hemolitik üremik sendromu, Sydenham koresi, herpes gestationis, otosklerozla ilişkili işitme kaybı, anjiyoödem (kalıtımsal),Akut ya da kronik karaciğer bozukluklarında karaciğer fonksiyonları belirteçleri normale dönene kadar NUVARING kullanımına ara verilmesi gerekebilir. İlk olarak hamilelik ya da daha önceki seks steroidi kullanımları sırasında ortaya çıkmış olan kolestatik sarılık ve/veya kolestaz ile ilişkili pruritin tekrarlaması halka kullanımının bırakılmasını gerektirebilir,NUVARING kullanan diabetik kadınlar özellikle ilk kullanım aylarında dikkatle izlenmelidir, Crohn hastalığında ve ülseratif kolitte, hormonal kontraseptif kullanımı ile ilişkin bir kötüleşme bildirilmiştir,Özellikle chloasma gravidarum öyküsü bulunan kadınlarda nadir olarak chloasma oluşabilir, Chlosma'ya eğilimli kadınlarda NUVARING kullanımı sırasında güneş ya da ultraviyole ışınlarına maruz kalmaktan kaçınmalıdır.Uterus boynu prolapsusu, sistosel ve/veya rektosel, ciddi ya da kronik konstipasyon bulunan kadınlar NUVARING'i doğru olarak yerleştirmede başarılı olmayabilir ya da halkayı kaybedebilirler,Çok nadir olarak, NUVARING'in üretraya ve mesane çıkışına yanlışlıkla yerleştirildiği bildirilmiştir, Sistit semptomları karşısında ayrıcı tanıya gidilirken, bu nedenle halkanın yanlış yere yerleştirilmiş olma olasılığı üzerinde durulmalıdır.NUVARING kullanımı sırasında kadınlar, çok seyrek olarak vajinit yaşayabilirler, Ne NUVARING etkinliğinin vajinit tedavisinden etkilendiği ve ne de NUVARING kullanımının vajinit tedavisini etkilediğine ilişkin bir kanıt bulunmamaktadır, Halkanın vaginal dokuya, bir doktor ya da hemşire tarafından çıkarılmasını zorunlu kılacak derecede yapıştığı, çok seyrek bildirilmiştir, Kadınlara NUVARING'in HIV enfeksiyonlarına (AIDS) ve cinsel yoldan geçen diğer hastalıklara karşı koruma sağlamadığı belirtilmelidir. **Diğer tıbbi ürünler ile etkileşimler ve diğer etkileşim şekilleri:** Seks hormonlarının klirensinde artışa sebep olan mikrozomal enzimleri indükleyen ilaçlarla (örn. fenitoin, fenobarbital, pirimidon, karbamazepin, rifampisin ve muhtemelen de okskarbazepin, topiramat, felbamat, ritonavir, griseofulvin ve St. John's wort içeren ürünler) etkileşimler ortaya çıkabilir, Bu ilaçları kullanan kadınların NUVARING'e ilaveten geçici olarak ek bir bariyer metodunu kullanmaları veya başka bir kontrasepsiyon metodunu seçmeleri önerilir, Mikrozomal enzim indükleyici ilaçlarla bariyer metodu eş zamanlı ilaç uygulamaları sırasında ve ilacın kesilmesini izleyen 28 gün boyunca kullanılmalıdır. Kontraseptif yetersizlikler ayrıca penisilinler ve tetrasiklinler gibi antibiyotikler ile birlikte bildirilmiştir, Antibiyotiklerle (amoksisilin ve doksisiklin haricinde) tedavi olan kadınlar, verilen ara sonrası 7 güne kadar bariyer yöntemi kullanmalıdırlar. Eş zamanlı ilaç uygulamasının 3 haftalık bir halka sıklusunu aşması durumunda, olağan halkasız dönem atlanarak derhal bir sonraki halka yerleştirilmelidir. Farmakokinetik verileri esas aldığımızda, vajinal yoldan uygulanan antimikotikler ve spermisidlerin NUVARING'in kontraseptif etkinliği ve güvenirliği etkileme olasılığı bulunmamaktadır, Halkanın düşme olasılığı, eş zamanlı antimikotik ovüller kullanılırken kısmen artabilir, Hormonal kontraseptifler diğer ilaçların metabolizması ile etkileşebilir, Buna göre, plazma ve doku konsantrasyonları hem artabilir (örn, siklosporin) hem de azalabilir (örn. lamotrigin). **Gebelik ve laktasyonda kullanım:** Gebelik kategorisi X'dir. **Çocuk doğurma potansiyeli bulunan kadınlar/Doğum kontrolü (Kontrasepsiyon).** NUVARING gebelik döneminde uygulandığı taktirde ciddi doğum kusurlarına yol açmaktadır/yol açtığından şüphelenilmektedir. **Laktasyon dönemi:** Emzirme, meme sütünün miktarını azaltabilen ve bileşimini değiştirebilen östrojenlerden etkilenebilmektedir, Bu nedenle, çocuk sütten tamamen kesilene kadar geçen sürede NUVARING kullanımı genellikle önerilmemelidir, Küçük miktarlarda kontraseptif steroidler ve/veya metabolitleri süt ile atılabilmektedir ancak bunun bebeğin sağlığını olumsuz etkilediğine ilişkin bir kanıt bulunmamaktadır. **Araç ve makine kullanımı üzerindeki etkiler:** Farmakodinamik profilin temelinde, NUVARING'in araç ve makine kullanımı üzerinde herhangi beklenen bir etkisi yoktur. **1.** Advers olayların listelenmesi spontan raporlamaya dayanır, Tam sıklığı tanımlamak mümkün değildir. **2.** 'Penis rahatsızlıkları' penis üzerindeki lokal reaksiyonları kapsar. **Doz aşımı ve tedavisi:** Hormonal kontraseptiflerin bir doz aşımının herhangi bilinen bir ciddi olumsuz etkisi yoktur. Bu olguda oluşabilecek semptomlar şunlardır: mide bulantısı, kusma ve genç kadınlarda hafif vajinal kanama, Antidotu yoktur ve sonraki tedavi semptomatik olmak durumundadır, **Yardımcı maddelerin listesi:** Etilen vinilasetat kopolimer, % 28 vinilasetat; Etilen vinilasetat kopolimer, % 9 vinilasetat; Magnezyum stearat, **Raf ömrü:** 40 ay **Saklamaya yönelik özel tedbirler:** Hastaya satış öncesi:36 ay, buzdolabında saklanmalıdır (2°C - 8°C). Satış sırasında:Eczacı kutu üzerine bir satış tarihi koyar. Ürün, önce geliş sırası esas alınarak, satış tarihinden 4 ay sonra ya da son kullanım tarihinden sonra takılmamalıdır. Satış sonrası: 4 ay, 30°C'nin üstünde saklamayınız. **Ambalajın niteliği ve içeriği:** Bir adet NUVARING içeren saşe, Saşe, iç kısmı düşük yoğunlukta polietilen ve dış kısmı polyester kaplı aluminyumdan yapılmıştır, Açılıp kapanabilir ve su geçirmezdir. Saşe, baskılı karton kutuya kullanma talimatı ile birlikte konmuştur, Her kutu 1 veya 3 halka içerir, **RUHSAT SAHİBİ:** Schering-Plough Tıbbi Ürünler Tic. A.Ş. Büyükdere Cad. No:127, Astoria Kuleleri, B Blok, Kat:8 34394, Esentepe-İstanbul **RUHSAT NUMARASI:** 117/33 İLK **RUHSAT TARİHİ:** 02.03.2005/**RUHSAT YENİLEME TARİHİ KÜB'ÜN YENİLENME TARİHİ:** 12 Ocak 2010 **"Daha geniş bilgi için firmamıza başvurunuz."**
Nuvaring reçete ile satılır. KDV dahil parekende satış fiyatı 22,41 TL(Aralık 2009)

WHCNUV1002-05

Kaynaklar: 1. Ahrendt H-J, Nisand I, Bastianelli C, et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 µg of ethinyl estradiol and 3 mg of drospirenone, Contraception, 2006;74:451–457. **2.** Novák A, de la Loge C, Abetz L, van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing®: an international study of user acceptability. Contraception. 2003;67(3):187–194. **3.** NuvaRing prospektüs bilgisi. **4.** Yasmin, Yazz, Desolett, Myralon prospektüs bilgileri, **5.** Roumen FJME, Etonogestrel-ethinylestradiol vaginal ring for hormonal contraception. Expert Rev Obstet Gynecol. 2008;3(6):705–714.

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IX. TURKISH - GERMAN GYNECOLOGY CONGRESS

May 4 - 8 2011

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CONTACT INFORMATION
Scientific Secretariat - Turkey

TAJEV
L. Cem Demirel
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IX. TURKISH - GERMAN GYNECOLOGY CONGRESS

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Registration Type	Before March 11th, 2011	After March 11th, 2011
Specialist	200 Euro	250 Euro
Assistant - Student	150 Euro	175 Euro
Accompanying Person - Company Rep	100 Euro	125 Euro

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ISUOG	International Society of Ultrasound in Obstetrics and Gynecology	120 Euro
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SuSesi Resort Hotel	595 Euro	440 Euro	635 Euro	480 Euro
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Daily Participation Fee without Accommodation				
60 Euro				

* VAT 8% should be added on the accommodation fees.
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Journal of the
Turkish-German Gynecological Association

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Editorial Office | Address: Abdi İpekçi cad. 2/7 34367 Nişantaşı, İstanbul-Turkey
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Cover Picture: CGH array technology for preimplantation genetic screening of polar body and embriyo, Eray Calışkan, Kocaeli University, IVF Center

ISSN 1309-0399

Publisher | AVES
Address: Kızılelma cad. 5/3 34096 Fındıkzade-İstanbul
Phone: +90 212 589 00 53 Fax: +90 212 589 00 94
E-mail: info@avesyayincilik.com
İmtiyaz Sahibi ve Sorumlu Yazı İşleri Müdürü: Cihat Ünlü
Basım Yeri: Görsel Dizayn Ofset Matbaacılık Tic. Ltd. Şti. - +90 212 671 91 00
Basım Tarihi: Aralık 2010
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O'nu koruyun![1]

1) Pitkin R.M. Folate and neural tube defects. Am. J. Clin. Nutr. 2007;85 (suppl):285S - 8S

FORMULU: Her bir 15 ml'lik flakon etken madde olarak 40 mg. Fe3+ (üç değerlikli demir)'e eşdeğer demir proteinsüksinilat ve rezervuarlı kapak içerisinde, bastırmakla çözelti içerisine giren (0.185 mg. folinik asit'e eşdeğer) 0.235 mg. kalsiyum folinat pentahidrat içerir. **ENDİKASYONLARI:** Demir ve folik asit eksikliğinin tedavisi veya önlenmesi. **KONTRENDİKASYONLARI:** İçerdiği maddelerden herhangi birine karşı aşırı duyarlılıkta, hemokromatozis, hemosiderozisde, aplastik, hemolitik, sideroakrestik anemilerde, kronik pankreatit ve karaciğer sirozunda, kalıtımsal fruktoz intoleransı olanlarda kullanılmamalıdır. Pernisiyöz anemide eğer B12 vitamini ile beraber uygulanmıyorsa, kullanılmamalıdır. **UYARILAR/ÖNLEMLER:** Sürekli kanama, menoraji veya hamilelik durumları haricinde tedavi süresi 6 aydan uzun olmamalıdır. Süt proteinlerine duyarlılığı olanlarda, alkolizm, hepatit, aktif infeksiyoz durumlar, enterit, kolit, divertikülit ve ülseratif kolit, gibi intestinal sistemin enflamatuvar durumları, pankreatit ve peptik ülser durumlarında kullanımı dikkatle değerlendirilmelidir. **GEBELİK DÖNEMİNDE KULLANIMI:** Gebelik kategorisi A' dır. YAN **ETKİLER /ADVERS ETKİLER:** Alerjik belirtiler, diyare, bulantı, epigastrik ağrıya neden olabilir. Demir preparatlarının oral kullanımı ile birlikte feçes genellikle siyah bir renk alır. **İLAÇ ETKİLEŞİMLERİ:** Demir türevleri tetrasiklinler, bisfosfonatlar, kinolon grubu antiinfektif ilaçlar, penisilamin, tiroksin, levadopa, karbodopa, alfa-metildopa gibi ajanların emilimini ve biyoyararlanımını azaltabilir. Demir emilimi, 200 mg'ın üzerinde askorbik asitin eş zamanlı uygulaması ile artabilmekte veya antiasid kullanımı ile azalabilmektedir. Kloramfenikol demir tedavisine terapötik yanıtı geciktirebilir. Bitkiler, süt, kahve ve çay içerisinde yer alan ve demir ile kompleks yapan ajanlar (fosfat, fitat, oksalat gibi) demir emilimini baskılar. Bazı antineoplastik ve antilösemik ilaçlar, sülfamid ve trimetoprim gibi antibakteriyel ajanlarla ile birlikte kullanılmamalıdır. Süt ve yumurta ile birlikte kullanılması durumunda demirin emilimi engellenir. **KULLANIM ŞEKLİ VE DOZU:** FERPLEX FOL. **YETİŞKİNLERDE:** Günde 1-2 flakon iki eşit doza bölünmüş olarak ve tercihen yemeklerden önce alınır. **ÇOCUKLARDA:** Hekimin önerisine göre tercihen yemeklerden önce günde 1.5 ml./kg. şeklindeki dozaj 2 veya 3'e bölünerek uygulanır. **DOZ AŞIMI:** Demirin yüksek dozda alınımını izleyen 6 – 8 saat süresinde hastada abdominal ağrı, bulantı, kusma, diyare ve hematemez görülebilir. Beraberinde uyku hali, sararma siyanoz, şok ve koma hali de eşlik edebilir. Ipeka şurubu ile emesis oluşturulup; hasta komatoz ise sodyum bikarbonatla lavaj yapılır. Sıvı ve elektrolit dengesi sağlanır, ve asidoz için i.v. sodyum bikarbonat uygulanır. Antidotu deferoksamindir. **TİCARİ TAKDİM ŞEKLİ VE AMBALAJ MUHTEVASI:** Kutuda 15 mL'lik renkli cam flakon + rezervuarlı kapaklı ambalajlarda 10 adet **RUHSAT TARİHİ VE NUMARASI:** 12.11.2003 – 203/ 40 **RUHSAT SAHİBİ:** Italfarmaco S.p.A./İtalya lisansı ile Abdi İbrahim İlaç San. ve Tic. A.Ş. **İMAL YERİ:** Abdi İbrahim İlaç San. Ve Tic.A.Ş. Hadımköy-İstanbul **PERAKENDE SATIŞ FİYATI (KDV dahil):** 17.12 TL (Ocak 2010). Reçete ile satılır. Ayrıntılı bilgi için firmamıza başvurunuz. Abdica İlaç San. ve Tic. A.Ş. Kore Şehitleri Caddesi No:19 Zincirlikuyu-İstanbul T. +90 212 365 49 00 F. + 90 212 72 90 46

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FRXFOL/2010/04/05

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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Subscription Information
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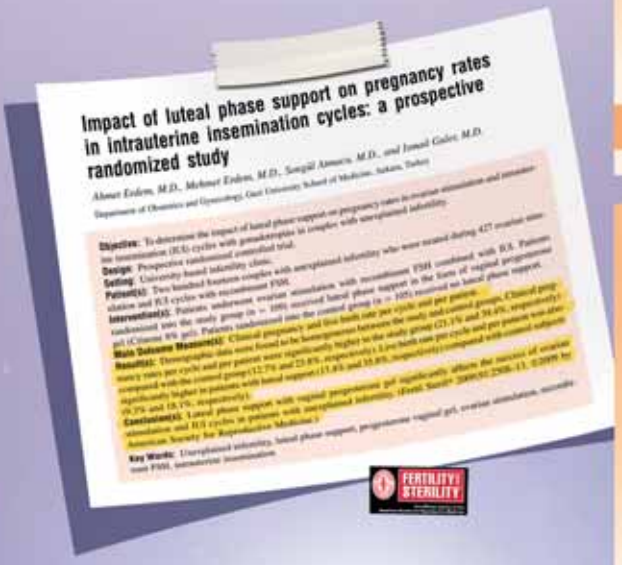
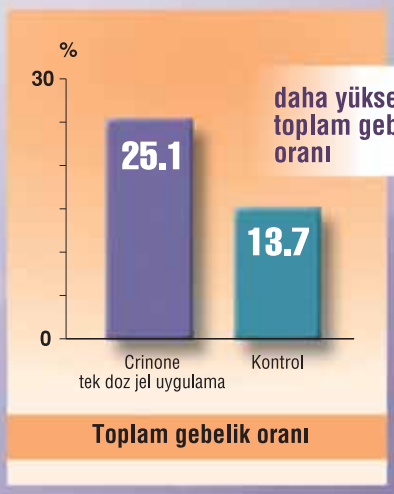
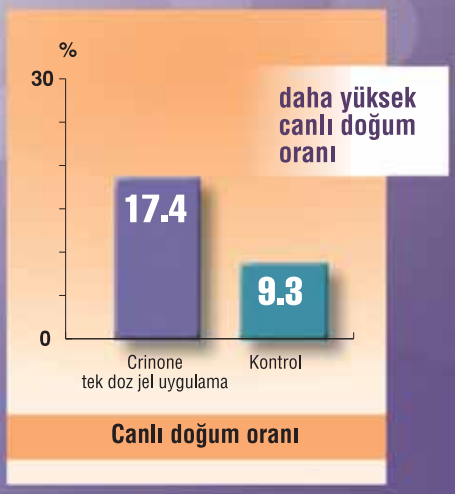
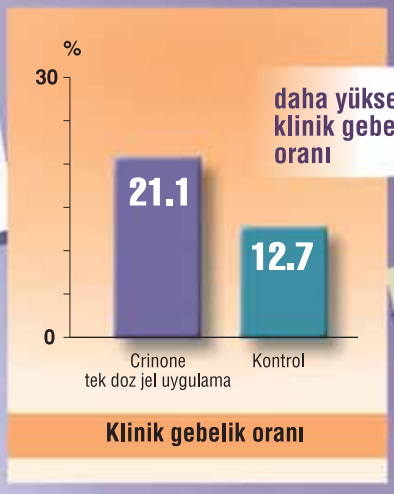
"Crinone Jel ile luteal faz desteği IUI 'da gebelik şansını yaklaşık **2 kat** artırır"[1]

Crinone® progesterone jel 8%









427 IUI siklusun değerlendirildiği çalışma sonucuna göre IUI sonrası uygulanan Crinone %8 jel tedavisi gebelik oranını yaklaşık 2 kat artırmıştır.[1]

referans:
1. 1. Erdem et al. Impact of luteal phase support on pregnancy trates in intrauterine insemination cycles: a prospective randomized study. Fertility and Sterility Vol.91,No.6,June 2009:2506-2513
2. Ürün monografı

CRİNONE® %8 (vajinal jel) Formülü: Her vajinal aplikatör aktif madde olarak 90 mg progesteron ve koruyucu madde olarak sorbik asit içerir. **Endikasyonlar:** 1. Estrojen replasman uygulamalarında ek tedavi, 2. Olası hormonal dengesizliğe bağlı bozukluklar - Premenstrual sendroma bağlı rahim kramplan ve anormal / ağrılı kasılmalar, - Organik patoloji yokluğunda disfonksiyonel rahim kanaması - Estrojen tedavisi görenlerde sekonder amenore 3. İnfertilite tedavisi Progesteron eksikliği dokümante edilmiş veya progesteron eksikliğinden şüphelenilen kadınlarda, Yardımcı Üreme Teknikleri (ART) uygulamalarının bir bölümü olarak progesteron takviyesi veya progesteron replasmanı. **Kontrendikasyonlar:** 1. Göğüste veya genital organlarda bilinen veya şüphelenilen malignansi, 2. Missed abortion (atlanmış düşük), 3. Teşhis edilmemiş rahim kanaması, 4. Aktif tromboflebit veya tromboembolik bozukluklar veya hormona bağlı bir tromboflebit veya tromboembolik bozuklıklar geçmişi, 5. Karaciğer fonksiyon bozukluğu veya karaciğer hastalığı, 6. Crinone® formülasyonunun bileşenlerinden herhangi birine karşı bilinen hipersensitivite. **Uyarılar/önlemler:** Crinone® ile trombotik bozukluklar bildirilmemiştir, Bununla birlikte, bazı araştırmalarda, hormon replasman tedavisine bağlı olarak tromboflebit ve/veya tromboembolik bozukluklarda bir artış riski bildirilmiştir, Hormon replasman tedavisi sırasında hekim, trombotik bozukluklar (tromboflebit, retinal tromboz, serebral embolizm ve pulmoner embolizm dahil) olasılığına karşı dikkatli olmalı ve bunların erken belirtilerine karşı hazır bulunmalıdır. Bunlardan herhangi birinin meydana gelmesi veya şüphelenilmesi halinde hormon replasman tedavisi hemen kesilmelidir. Trombotik bozukluklara ilişkin risk faktörü taşıyan hastalar dikkatle gözlenmelidir. Tedavi öncesi ve sırasında periyodik muayenelerde tıbbi anamnez ve fiziki muayenede özellikle göğüsler ve pelvik organlar üzerinde durulmalı ve bir Papanicolaou smear alınmalıdır. Progestojenler bir ölçüde sıvı tutulmasına neden olabilecekleri için bu faktörden etkilenebilecek epilepsi, astım, migren ve kalp veya böbrek fonksiyon bozukluğu gibi hastalıkları olan kadınların dikkatle gözlem altında tutulması gerekir, Bütün düzensiz vajinal kanama vakalarında olduğu gibi ara kanama vakalarında, organik hastalığın bulunup bulunmadığını değerlendirmek üzere diyagnostik uygulamalar gerekli olabilir, Depresyon geçmişi olan hastalar dikkatle gözlenmeli ve depresyon ciddi bir ölçüde tekrar ortaya çıkarsa Crinone® kesilmelidir. Progestojenlerle tedavi, postmenopozal semptomların ortaya çıkışını maskeleyebilir, Progestojenlerin endometriyum gibi organların yapısında ve patolojisindeki etkisi nedeniyle ilgili numuneler verilen patologlara, progestojen tedavisi uygulandığı söylenmelidir. Progestojenler önceden mevcut porfirya belirtilerini kötüleştirebilir. Bu nedenle, bu gibi hastalarda Crinone® kullanılması önerilmez. **Yan etkiler/advers etkiler:** Crinone® genellikle iyi tolere edilmektedir. Klinik araştırmalarda, Crinone® tedavisi sırasında aşağıdaki advers etkiler bildirilmiştir: Bütün vücutta - kanın, sırt, eklem, bacak ağrısı veya perineal ağrı; şişkinlik, göğüslerde şişkinlik/hassasiyet, yorgunluk, sıcak basması, laktasyon, su tutulması. Gastrointestinal sistem - konstipasyon, diyare, dispepsi, geğirti, flatülans, mide ağrısı, mide bulantısı, kusma. Genitoüriner sistem - cinsel arzunun azalması, dismenore, disparoni, sık idrara çıkma, lökore, noktüri, vajinal kaşıntı/ irritasyon, vajinal kanama ve lekelenme, vajinal sekresyonda artma. Sinir sistemi - baş dönmesi, depresyon, ruhsal durumda değişkenlik, başağrısı, uykusuzluk, irritabilite, sinirlilik, somnolans. Cilt - akne, genital prürit. Yukarıdaki bütün olaylarla Crinone® tedavisinin ilişkisi bilinmemektedir. Çoğu yan etki hafif ve geçicidir ve Crinone® tedavisinin sürdürülmesi ile ortadan kalkmaktadır. **İlaç etkileşmeleri ve diğer etkileşmeler:** Diğer ilaçlarla hiç bir etkileşim bildirilmemiş olmakla birlikte Crinone®'un diğer intravajinal preparatlarla birlikte kullanılması önerilmemektedir, Hastaya intravajinal antifungal bir tedavi uygulanıyorsa oral tedaviye geçilmesi önerilir, Laboratuvar testleri etkileşimleri: Crinone®'un laboratuvar testleri üzerinde herhangi bir etkisinin olup olmadığı bilinmemektedir. **Kullanım şekli ve dozu:** Crinone® ile intravajinal tedavi, spesifik endikasyona ve her hastanın terapötik cevabına göre ayarlanmalıdır, En düşük etkin doz uygulanmalıdır, Crinone®'un, endometriyumda sekretuar bir transformasyonu endüklemek üzere vajinal yoldan uygulanması ancak endometriyum endojen veya eksojen estrojen ile yeterli ölçüde hazırlanmışsa endikedir, Bu gibi vakalarda, gebelik meydana gelmemişse Crinone® tedavisinin kesilmesinden sonraki 3-7 gün içinde kesilme kanaması meydana gelir, Crinone®, temin edilen aplikatörle intravajinal olarak uygulanır, Crinone® her gün aynı zamanda uygulanmalıdır, Bir Crinone® dozunu unuttuğunuzu hatırlar hatırlamaz, o dozu hemen uygulayın ve önceki programa göre uygulamaya devam edin, Önerilen günlük dozdan fazlasını uygulamayın, Olağan Doz Aralığı: Crinone® %4 (45 mg) veya Crinone® %8 (90 mg), Dozaj programında, bir menstruel siklusun veya estrojen siklusların 28 gün olduğu ve 1. günün, kanamanın veya siklik estrojen tedavisinin ilk günü olduğu kabul edilmektedir. ESTROJEN REPLASMAN UYGULAMALARINDA EK TEDAVİ: 28 günlük her bir estrojen tedavisinin son 12 gününde, gün aşırı (6 uygulama) bir vajinal Crinone® uygulaması. OLASI HORMONAL DENGESİZLİKLERLE İLGİLİ BOZUKLUKLAR: Estrojen verilerek hazırlanmış kadında, tercihen sabahları olmak üzere toplam 6 doza kadar gün aşırı bir vajinal Crinone® uygulaması. İNFERTİLİTE TEDAVİSİ – ART UYGULAMASINDA PROGESTERON TAKVİYESİ VEYA REPLASMANI: Progesteron eksikliğinden şüphelenilen, normal olarak ovülasyon görülen kadınlarda progesteron takviyesi olarak, dokümante edilen ovülasyondan sonra başlamak üzere günde bir veya iki kez Crinone® %8 (90 mg) uygulaması, Çoğu kadında günde 90 mg ile cevap alınır, Gebelik meydana gelirse tedavi 12 haftaya kadar devam edebilir, Luteal faz eksikliği gibi bir progesteron eksikliğinden şüphelenilen, normal olarak ovülasyon görülen kadınlarda daha düşük dozlar kullanılabilir, Bir ART rejiminin bir bölümü olarak endometrial takviye için günde bir veya iki kez Crinone® %8 (90 mg) ile uygulamaya başlanır, Çoğu kadında günde 90 mg ile cevap alınır, Bununla birlikte bazı kadınlarda günde iki kez 90 mg gerekli olabilir, Gebelik kesinleşirse, 12 haftaya kadar Crinone® %8 (90 mg)'a devam edilir, Crinone® %8 (90 mg) her gün aynı zamanda uygulanmalıdır, %4'lük jelden doz artışının, ancak %8'lik jel kullanılarak gerçekleştirilebileceği unutulmamalıdır, Uygulanan %4'lük jelin hacminin artırılması, absorbe olan progesteron miktarını artırmamaktadır. **Saklama koşulları :** 25°C'nin altındaki oda sıcaklığında saklayınız. **Ticari takdim şekli :** Crinone® v %8, 15 aplikatör içeren ambalajlarda sunulmaktadır. **Ruhsat sahibi:** Merck İlaç Ecza ve Kimya Tic. 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22 Ocak 2011, Cumartesi

Kocaeli Üniversitesi Araştırma ve Uygulama Hastanesi Konferans Salonu

TOPLANTI BAŞKANI: DOÇ. DR. ERAY ÇALIŞKAN

13:00 - 13:20 Açılış ve ESIDOG Türkiye sunumu - *Prof. Dr. Cihat Ünlü (ESIDOG Türkiye Başkanı)*

13:20 - 15:00 1. OTURUM - JİNEKOLOJİK ENFEKSİYONLAR

Oturum başkanları: Prof. Dr. İzzet Yücesoy, Prof. Dr. Aydın Çorakçı

13:20 - 13:40 Akut ve kronik kandidiazis tedavisi
Doç. Dr. Eray Çalışkan

13:40 - 14:00 Akut vajinal enfeksiyonlarda tanı ve tedavi
Uzm. Dr. Esra Esim Büyükbayrak

14:00 - 14:20 Kronik vajinal enfeksiyonlarda tanı ve tedavi
Doç. Dr. Oluş Api

14:20 - 14:40 HPV enfeksiyonlarında tedavi ve prognoz
Yrd. Doç. Dr. Gazi Yıldırım

14:40 - 15:00 Vulva ülserlerinde ayırıcı tanı ve tedavi
Doç. Dr. Serhan Cevrioğlu

15:00 - 15.20 Kahve arası

15:20 - 17:20 2. OTURUM - OBSTETRİK ENFEKSİYONLAR

Oturum başkanları: Prof. Dr. Füsun Varol, Doç. Dr. Gülseren Yücesoy

15:20 - 15:40 Gebelikte aşılama
Doç. Dr. Cenk Sayın

15:40 - 16:00 Gebelikte genitoüriner sistem enfeksiyonlarının tarama ve tedavisi
Doç. Dr. Ömer Kandemir

16:20 - 16:40 Konjenital viral enfeksiyonlarda tarama, tanı ve tedavi
Doç. Dr. İsmail Özdemir

16:40 - 17:00 Gebelikte enfeksiyon ve preterm doğum ilişkisi
Doç. Dr. Ahmet Gül

17:00 - 17:20 Kontrasepsiyon ve pelvik enflamatuvar hastalık
Doç. Dr. Özlem Pata

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Preparation of Manuscripts
The "Journal of the Turkish German Gynecological Association" follows the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (International Commitee of Medical Journal Editors: Br Med J 1988; 296: 401-5). Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate: Consort statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91), the QUOROM statement for meta-analysis and systemic reviews of randomized controlled trials (Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. Quality of Reporting of Meta-Analyses. Lancet 1999: 354: 1896-900) and the MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analyis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Human and Animal Studies
Manuscripts submitted for publication must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1975 Declaration of Helsinki. It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted.
Reports of animal experiments must state that the "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985) were followed, as well as specific national laws where applicable.
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In a cover letter the authors should state if any of the material in the manuscript is submitted or planned for publication elsewhere in any form including electronic media. The cover letter must contain address, telephone, fax and the e-mail address of the corresponding author.

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Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research. They should also state that they have had full control of all

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Title Page
The first page should include the title of the article, name(s), affiliations and major degree(s) of the author(s) and source(s) of the work or study. The name, address, telephone and fax numbers and e-mail address of the corresponding author should be listed on the title page.

Abstract
All manuscripts in Turkish and German should be accompanied by a structured abstract in English and in the language of the manuscript. Only English abstract suffice for manuscripts written in English. The structured abstract(s) should present the study objective, material and method, results and conclusions. Word limitation is 250 words for original articles and 150 words for brief reports and case reports.

Key Words
Below the abstract provide up to 5 key words or short phrases. Do not use abbreviations as key words.

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

Material and Methods
Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures.

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

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

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

Examples:
Journals;
Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol 1996; 7: 182-8.
Book chapter;
Ertan AK, Tanriverdi HA, Schmidt W. Doppler Sonography in Obstetrics. In: Kurjak A, Chervenak FA, editors. Ian Donald School Textbook of Ultrasound in Obstetrics and Gynecology. New Delhi, India: Jaypee Brothers; 2003. p. 395-421.
Book;
Kohler G; Egelkraut H. In Kohler G and Egelkraut H (edts).Munchener Funktionelle Entwicklungsdiagnostik im zweitem und drittem Lebensjahr. Handanweisung. Munchen: Uni Munchen, Institut fur Soziale Paediatrie und Jugendmedizin; 1984.
Tables and Figures
Tables and figures should work under "Windows". Color figures or gray-scale images must be at least 300 dpi. Figures using "*.tiff", "*.jpg" or "*.pdf" should be saved separate from the text. All tables and figures should be prepared on separate pages. They should be numbered in Arabic numerals. Each table must have a title indicating the purpose or content of each table. Each figure must have an accompanying legend defining abbreviations or symbols found in the figure.

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Revisions will be sent to the corresponding author. Revisions must be returned as quick as possible in order not to delay publication. Deadline for the return of revisions is 30 days. The editoral board retains the right to decline manuscripts from review if authors' response delay beyond 30 days. All reviewers' comments should be addressed and revisions made should be started with page and line of the text. Send a highlighted copy indicating the revisions made and a clear copy of the revised manuscript. Authors are responsible for the truth of presented data and references. The Editors have the right to withdraw or retract the paper from the scientific literature in case of proven allegations of misconduct.

Journal and Society Web sites:
www.dtgg.de (Deutsch-Türkische Gynäkologengeselleschaft)
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www.jtgga.org (Journal of the Turkish German Gynecological Association)

- Citation of published manuscripts in J Turkish German Gynecol Assoc should be as follows:
Tews G, Ebner T, Sommergruber M, Marianne M, Omar S. Ectopic Pregnancy in the Assisted Reproduction, J Turkish German Gynecol Assoc. 2004;5(1):59-62.
- The Journal name should be abbreviated as "J Turkish German Gynecol Assoc"

DECAPEPTYL® 0.1 mg Ürün Kısa Prospektüs Bilgisi

FORMÜLÜ: Triptorelin asetat **ENDİKASYONLARI:** IVF, Endometriozis, uterus miyomu **KONTRENDİKASYONLARI:** Klinik olarak belirgin osteoproz ya da osteoproz riski (örn. Azalmış kemik yoğunluğu), Hamilelik , Laktasyon Yardımlı üreme tekniklerinde kullanımında; özellikle polikistik overli hastalarda, ultrasonografi ile tespit edilen foliküller 10'dan fazla olduğunda Decapeptyl kullanımında önlemlerin sayısı artırılmalıdır.Triptorelin, poli (DL-laktid-ko-glikolid), dekstran veya diğer herhangi bir bileşene duyarlılık gösteren kişilerde kontrendikedir. **UYARİLAR/ ÖNLEMLER:** Tedavi seks steroidlerinin serum düzeylerine göre ayarlanmalıdır. Özellikle polikistik overleri olanlarda aşırı uyarılmayı önlemek için foliküler büyüme ve luteal faz dikkatle izlenmelidir. Tedaviden önce gebelik durumu kontrol edilmelidir. Tedavinin ilk ayında kadınlar hormonal olmayan kontraseptifler kullanmamalıdırlar. Decapeptyl® tedavisi sırasında kadınlar östrojen pereparatı kullanmamalıdırlar. 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 kullanma 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, miyalji, artralji, yorgunluk; uyku bozuklukları; aşırı duyarlık reaksiyonları (kaşıntı; 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), anafilaksi, uygulama noktasında yabancı vücut reaksiyonu gözlenmitir. Hafif trabekül kemik kaybı görülebilir. Bu durum, tedavinin kesilmesini takiben 6-9 ay içinde genellikle geçer. Triptorelin kullanımında iki epifizyoliziz capitis femoris vakası bildirilmiştir. Nedensel ilişki saptanamamıştır. BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. **İLAÇ ETKİLEŞİMLERİ ve DİĞER ETKİLEŞMELER:** Östrojen içeren hiçbir ilaçla birlikte kullanılmamalıdır. **KULLANIM ŞEKLİ ve DOZU:** Mutad doz, 7 gün süreyle 0.5 mg'dır ve deri altına zerkedilir. Daha sonra idame dozu, 0.l mg uygulanır. IVF'te dozaj uygulanan protokole göre değişir. Genellikle, siklus/ilk foliküler fazı ilk gününden itibaren hCG uygulamasına kadar günde 0.1mg (kısa protokol) siklus/ilk foliküler fazı ilk gününden itibaren hCG uygulamasına kadar üç gün 0.1mg'dır (çok kısa protokol). **SAKLAMA KOŞULLARI:** Decapeptyl® 0.1mg buzdolabında (2-8°C) saklanmalıdır. Tek kullanımlık enjektörler ambalajı içinde ve ışıktan korunarak saklanmalıdır. **TİCARİ TAKDİM ŞEKLİ ve AMBALAJ MUHTEVASİ:** Decapeptyl® 0.l mg: 1 ml solüsyon içeren, kullanıma hazır 7 şırıngalık kutularda **RUHSAT SAHİBİ:** FERRING İlaç San. Tic. Ltd. Şti. Büyükdere Cad. Nurol Plaza, No: 71 A Blok Kat 13, Maslak / İstanbul **RUHSAT TARİHİ ve NO:** 02.11.2006 ve 121/7 **KDV DAHİL PERAKENDE SATIŞ FİYATI:** 119,90 TL (Temmuz 2010 itibariyle). **ÜRETİM YERİ:** Ferring GmbH Kiel, Almanya REÇETE İLE SATILIR. Ayrıntılı bilgi için lütfen firmamıza başvurunuz.

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MENOPUR® Ürün Kısa Prospektüs Bilgisi

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 ereklerde kısırlık tedavisinde (HCG ile birlikte, spermatojenezin 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, uterusta, overde ve memede tümör. Ereklerde; 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 taşırlar, Pelvik muayeneden kaçınılmalı veya muayene dikkatle yapılmalıdır, Böyle bir risk mevcut iken cinsel ilişkiden kaçınılmalıdır, Tedavi sırasında hastanın yakın takibi şarttır, İstemeden 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 irritasyon, 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. Ereklerde: Menopur® tedavisi sırasında bazen jinekomasti, göğüste ağrı, mastit, bulantı, anormal lipoprotein fraksiyonu, anormal SGOT ve SGPT oluşabilir. 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 rüptüre olarak karın içi kanamalara neden olur. Buna ek olarak, karın boşluğunda sıvı birikimi (asit), göğüs boşluğunda sıvı birikimi (hidrotoraks), idrarda azalma (oliguri), kan basıncında düşme (hipotansiyon) ve kan pıhtısıyla kan damarlarının tıkanması (tromboembolik olay) olabilir. Aşırı uyarılmanın ilk belirtileri ortaya çıkağında tedavi hemen durdurulmalıdır. Gebelikle beraber bu yan etkiler şiddetlenebilir ve uzun süre devam eder; hayatı tehdit edecek nitelikte olabilir. HMG ile tedavi sırasında istenmediği halde birden çok gebelik olabilir. Çok ender olarak uzun süreli tedavi, antikor oluşumuna neden olarak tedaviyi etkisiz kılabilmektedir. **BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. İLAÇ ETKİLEŞİMLERİ:** Başka ilaçlarla etkileşimi bilinmemektedir. Kısır ereklerde HMG, hCG ile bir arada enjekte edilebilir. **KULLANIM ŞEKLİ VE DOZU:** Ambalajın içindeki çözücü ile çözdükten sonra I.M. ya da S.C. olarak uygulanır. Hekim tarafından başka türlü tavsiye edilmedikçe, aşağıdaki dozlarda uygulanır: Kadınlarda Kısırlık: Normo veya hipogonadotropik kadınlarda follikullerin 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 follikullerde 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 itibariyle). 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Editorial

Dear Colleagues,

It is a great pleasure to be introducing the final issue of our journal in 2010. Many interesting articles are submitted in this issue from Turkey and other countries. We are proud that the number of citations from our journal is increasing day by day and this will help our journal to be indexed by many internationally accepted databases. One of the new ideas of our editorial staff is to be sending our journal to our readers as an e-journal for the new issues. This will lead JTGGA (Journal of Turkish German Gynecology Association) to reach more readers in our field. Therefore, our journal will be followed by more domestic and international readers which will raise the citation of manuscripts of Turkish scientists by more foreign authors.

The 17th annual meeting of the MEFS (Middle East Fertility Society) was held in Damascus, Syria in October. The meeting was very successful and it strengthened the collaboration of our societies. The other substantial meeting that we have participated was the 4th Congress of TSRM (Turkish Society of Reproductive Medicine) which was held in Antalya. Our booth at the congress was shown high interest by our colleagues.

We are working hard for the organization of our 9th congress as the beginning date approaches. The scientific committee of the congress works hard to finalize the scientific program and it will be announced very soon. More than 40 well known international speakers have already accepted our invitation to join our congress as members of the international faculty. The abstract submission system is active on the web site of the congress, www.tajev2011.org . Several abstracts have already been submitted from Turkey and other countries and we are looking forward to the submission of the new abstracts by the young researchers. We are also delighted with the support of the high interest from the sponsors. Leading companies in our field have already confirmed their attendance and support to our congress.

The social responsibility project called ORReady will be supported by the Turkish German Gynecological Education and Research Foundation. ORReady is a worldwide, multi-Specialty initiative to encourage steps that are known to improve surgical outcomes and save lives. If the suggested guidelines, which include Check Lists, Time Outs and Warm Ups are followed routinely, it is estimated that Six Million patients around the world could have better outcomes. This initiative is founded by Paul Alan Wetter, the chairman of the Society of Laparoendoscopic Surgeons and also the advisory board member of our journal.

We sincerely hope to meet you by the beginning of May in Antalya.

Kind regards,

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

ARVELES®

DEKSKETOPROFEN TROMETAMOL

AMPUL IM/IV TABLET

Hızlı etki başlangıcı[1]

Olumlu **güvenlik** profili[1]

Kanıtlanmış **etkinlik**[1]

Analjezik tedavide

ilk tercih[1]

olarak uygulanmasını desteklemektedir.

REFERANSLAR 1- Barbanoj et al: Dexketoprofen trometamol: clinical evidence supporting its role as a painkiller, Expert Rev. Neurother. 8(11), 1625-1640 (2008)

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FORMÜL: Her bir tablet 25 mg deksketoprofene (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 q.s., enjeksiyonluk su q.s. 2 ml içerir. **FARMAKOLOJİK ÖZELLİKLER:** Deksketoprofen trometamol, steroid olmayan antiinflamatuvar ilaç grubuna dahil analjezik, antiinflamatuvar ve antipiretik bir ilaçtır. **ENDİKASYONLAR: ARVELES®** *25 mg Tablet:* Muskülo-skeletal ağrı, dismenore, diş ağrısı, postoperatif ağrı gibi hafif ve orta şiddetteki ağrıların semptomatik tedavisinde kullanılır. **ARVELES®** *50 mg Ampul:* Oral kullanımın 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 olgularda uygulanmamalıdır: •Dek*sket*oprofene, diğer NSAİİ'lere veya üründeki herhangi bir yardımcı maddeye karşı daha önce duyarlılığı olan hastalar •Benzer etkili (Örn. Aspirin veya diğer NSAİİ'ler) bileşiklerin astım, bronkospazm, akut rinit krizlerine yol açtığı veya nazal polipler, ürtiker veya anjiyonörotik ödeme neden olduğu hastalar •Aktif veya şüpheli gastrointestinal ülseri olan veya gastrointestinal ülser veya kronik dispepsi hikayesi olan hastalar •Gastrointestinal kanama veya diğer aktif kanamaları veya kanama bozukluğu olan hastalar •Crohn hastalığı veya ülseratif koliti olan hastalar • Şiddetli kalp yetmezliği olan hastalar •Orta veya şiddetli böbrek fonksiyon bozukluğu olan hastalar • Şiddetli karaciğer fonksiyon bozukluğu olan hastalar •Hemorajik diatezi veya diğer pıhtılaşma bozukluğu olan veya antikoagülan tedavisi gören hastalar • Bronşiyal astım geçmişi olan hastalar • Gebelik ve laktasyon dönemlerinde •**ARVELES®** Ampul'ün, etanol içermesinden dolayı nöraksial (intratekal veya epidural) yolla alımı kontrendikedir. **ÖZEL UYARILAR ve ÖZEL KULLANIM TEDBİRLERİ:** Çocuklarda kullanım güvenilirliği tespit edilmemiştir. Alerji hikayesi olan hastalarda kullanırken dikkatli olunmalıdır. Deksketoprofen trometamol alan hastalarda ender oluşabilecek gastrointestinal kanama veya ülserasyon durumlarında, tedaviye hemen son verilmelidir. NSAİİ'ler, trombosit agregasyonunu baskılayabilir, kanama süresini uzatabilirler. Kumarin tedavisi alan hastalar dikkatle izlenmelidir. Tüm NSAİİ'ler plazma üre azotunu ve kreatinini artırabilir. Tüm NSAİİ'ler bazı karaciğer parametrelerinde geçici küçük artışlara ve SGOT ve SGPT'de anlamlı artışlara neden olabilir. Bu durumda tedavi sona erdirilmelidir. Karaciğer, böbrek veya kardiyak fonksiyon bozukluğu olan hastalarla, sıvı retansiyonuna neden olan diğer hastalıkları olan hastalarda dikkatli olunmalıdır. Bu hastalarda renal fonksiyonlar kötüleşebilir ve sıvı retansiyonu ile sonuçlanabilir. Nefrotoksisite riskinde artma olması nedeniyle diüretik tedavisi gören hastalar ile hipovolemik olabilecek hastalarda da dikkat gereklidir. Kalp yetmezliğini tetikleme riski artabileceğinden, kalp hastalığı hikayesi bulunan hastalara özel dikkat gösterilmelidir. Tüm NSAİİ'ler infeksiyöz hastalıkların semptomlarını maskeleyebilir. Yaşlı hastalar, istenmeyen etkilere daha fazla duyarlıdır ve sonuçlar daha ciddi olabilir. Yaşlı hastalarda hepatik ve renal fonksiyonlar izlenmelidir. Hemopoietik 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. **ARAÇ ve MAKİNE KULLANMAYA ETKİSİ:** Baş dönmesi ve uyuklama 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 istenmeyen etkiler, bulantı ve/veya kusma, abdominal ağrı, diyare, dispepsi ve Ampul için bulantı, kusma, enjeksiyon yeri ağrısıdır. Sık olmayan (%0,1-1) yan etkiler uyku bozuklukları, anksiyete, baş ağrısı, baş dönmesi, vertigo, palpitasyonlar, gastrit, konstipasyon, ağız kuruluğu, gaz çıkarma, cilt döküntüleri, yorgunluk, sıcak basması, ağrı, asteni, rigorlar, hasta hissetmedir. Ayrıca ender olarak (%0.01-0.1) parestezi, hipertansiyon, periferik ödem, bradipne, peptik ülserasyon, hemoraji veya perforasyon, anoreksi, hepatik enzimlerde artma, ürtiker, akne, terlemede artma, poliüri, dişide menstrüel bozukluklar; erkekte prostatik bozukluklar, srt ağrısı, senkop ve çok ender-izole olarak da (<%0.01) nötropeni, trombositopeni, görme bulanıklığı, tinnitus, taşikardi, hipotansiyon, bronkospazm, dispne, pankreas hasarı, karaciğer hasarı, şiddetli mukokütanöz cilt reaksiyonları (Stevens Johnson, Lyell sendromları), anjiyoödem, dermatolojik reaksiyonlar, fotosensitivite reaksiyonları, prurit, böbrek hasarı (nefrit veya nefrotik sendrom), anaflaksi, fasiyel ödem bildirimleri bulunmaktadır. Belirgin olarak sistemik lupus eritematozus veya karışık bağ dokusu hastalığı olan hastalarda oluşabilen aseptik menenjit ve hematolojik reaksiyonlar (purpura, aplastik ve hemolitik anemi, ve ender olarak agranülositoz ve medüller hiperplazi). BEKLENMEYEN BİR ETKİ GÖRDÜĞÜNÜZDE DOKTORUNUZA BAŞVURUNUZ. **İLAÇ ETKİLEŞMELERİ ve DİĞER ETKİLEŞMELER:** Aşağıdaki etkileşmeler genelde tüm steroid olmayan antiinflamatuar ilaçlar (NSAİİ) için geçerlidir: Önerilmeyen kombinasyonlar: •Salisilatlar, diğer NSAİİ'ler •Oral antikoagülanlar, parenteral heparin ve tiklopidin •Lityum •Metotreksat •Hidantoinler ve sulfonamidler. **KULLANIM ŞEKLİ ve DOZU: ARVELES®** *Tablet:* Genel Popülasyon: Ağrının cinsine ve şiddetine göre önerilen doz genellikle her 4-6 saatte bir 12,5 mg veya 8 saatte bir 25 mg'dır. Postoperatif ağrı tedavisinde önerilen doz her 8 saatte bir 25 mg'dır. Günlük toplam doz 75 mg'yi geçmemelidir. **ARVELES®** *Ampul:* Yetişkinlerde: Tavsiye edilen doz her 8-12 saatte bir 50 mg'dır. Günlük maksimum doz olan 150 mg'yi aşmamak şartıyla, 6 saat arayla uygulanabilir. **ARVELES®** Tablet ve 50 mg/2 ml Enjektabl Çözelti İçeren Ampul, kısa süreli kullanım içindir ve tedavi akut semptomatik dönem ile sınırlandırılmalıdır (Ampul için maksimum 2 gün). **Uygulama Yöntemi:** *IM uygulama:* 1 adet ampul içeriği kas içine derin ve yavaş bir enjeksiyon ile verilmelidir. *IV uygulama: IV infüzyon:* Bir ampul (2 ml) içeriği normal NaCl, glikoz veya ringer laktat solüsyonu ile 30 ila 100 ml'lik hacim oluşturacak şekilde seyreltilmelidir, 10 ile 30 dakika arası bir sürede yavaş bir şekilde damar içine infüzyon ile verilmelidir. Solüsyon daima direkt güneş ışığından korunmalıdır. *IV bolus:* Gerekli ise, bir **ARVELES®** 50 mg/2 ml Enjektabl Çözelti İçeren Ampul içeriği 15 saniyeden uzun bir sürede yavaş **IV** bolus ile verilebilir. **DOZ AŞIMI:** Kazara veya fazla alınımda, acilen semptomatik tedavi uygulanmalı ve gerekiyorsa mide yıkanmalıdır. Deksketoprofen trometamol diyalizle uzaklaştırılabilir. **SAKLAMA KOŞULLARI:** 30°C'nin altında ve oda sıcaklığında, ışıktan korunacak şekilde saklayınız. Çocukların ulaşamayacakları yerlerde ve ambalajında saklayınız. **TİCARİ TAKDİM ŞEKLİ ve AMBALAJ İÇERİĞİ:** 20 film kaplı çentikli tablet. 2 ml Enjektabl çözelti içeren cam ampuller (6 ampul). **RUHSAT SAHİBİNİN İSİM ve ADRESİ:** UFSA İlaç Sanayi Tic. A.Ş., Davutpaşa Cad., No: 12, 34473 Topkapı-İSTANBUL. Tel: (0212) 467 11 11, Faks: (0212) 467 12 12. **RUHSAT TARİHİ ve NUMARASI: ARVELES®** *Tablet:* 30.12.2003-115/18, **ARVELES®** *Ampul:* 29.12.2006-121/57. **KDV DAHİL PERAKENDE SATIŞ FİYATI** (Nisan 2009 itibarıyla): **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 – 67100 L'Aquila-ITALYA. / Laboratorios Menarini SA Alfons XII, 587 08918 Barselona - İspanya. **ARVELES®** *Ampul:* A. Menarini Manufacturing Logistics And Services S.r.l. Via Sette Santi, 3, Floransa–İTALYA. Reçete ile satılır. Ayrıntılı bilgi için prospektüse bakınız. Daha geniş bilgi için firmamıza başvurunuz. **PROSPEKTÜS ONAY TARİHİ: ARVELES®** *Tablet:* 05.07.2005, **ARVELES®** *Ampul:* 14.08.2007

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MENARINI GROUP

Ayrıntılı bilgi için,
Adres: Davutpaşa Caddesi, No: 12, 34473 Topkapı - İstanbul
Telefon: 0 212 467 11 11 **Faks:** 0 212 467 12 12
Web sitesi: www.ieulagay.com.tr **E-posta:** ieulagay@ieulagay.com.tr

Prenatal diagnosis of conjoined twins: Four cases in a prenatal center

Yapışık ikizlerin prenatal tanısı: bir prenatal tanı ünitesinin dört olgusu

Ali Gedikbaşı[1], Gökhan Yıldırım[1], Sezin Saygılı[2], Reshad Ismayilzade[2], Ahmet Gül[1], Yavuz Ceylan[1]

[1] Department of Obstetrics and Gynecology, Perinatology Unit, Istanbul Bakırköy Maternity and Children Diseases Hospital, Istanbul, Turkey

[2] Department of Obstetrics and Gynecology, Istanbul Bakırköy Maternity and Children Diseases Hospital, Istanbul, Turkey

Abstract

Objective: To assess the findings in conjoined twins diagnosed prenatally.

Material and Methods: Between January 2002 and June 2009, we reviewed the database and medical records of 857 twin pregnancies, including 140 monochorionic twins. Nineteen monochorionic-monoamniotic twin pregnancies were detected, four of which were complicated by conjoined twins.

Results: Of these 4 cases, 2 were complicated by thoracopagus and one had thoraco-omphalopagus; these three cases underwent termination at 16, 11, and 19 weeks gestation, respectively. The last case was diagnosed as a pygopagus tetrapus parasitic twin at 28 weeks gestation. The family decided to continue the pregnancy, and achieved a successful outcome with elective surgery postpartum.

Conclusion: Conjoined twins are an uncommon and complex complication of monozygotic gestations, which is associated with high perinatal mortality. The early prenatal diagnosis of conjoined twins allows improved counseling about the management options, including maintenance of pregnancy with surgery after delivery or termination of pregnancy. (J Turkish-German Gynecol Assoc 2010; 11: 174-7)

Key words: Conjoined twins, prenatal diagnosis

Received: 22 December, 2009 **Accepted:** 11 February, 2010

Özet

Amaç: Prenatal olarak tanısı konmuş yapışık ikiz olgularında bulguların değerlendirilmesi.

Gereç ve Yöntemler: Ocak 2002 ile Haziran 2009 tarihleri arasında, 140 monokoryonik ikiz olgusunu da içeren, toplam 857 ikiz olgusunun verileri ve tıbbi kayıtları değerlendirildi. Toplam 19 monokoryonik-monoamniotik ikiz olgusunun dört tanesi yapışık ikiz olarak değerlendirildi.

Bulgular: Bu 4 olgunun ikisi torakopagus ve bir tanesi torako-omfalopagus ile komplike olup, sırası ile 16, 11 ve 19. gebelik haftalarında gebelik sonlandırması uygulanmıştır. Son olgu bir pygopagus tetrapus parazitik ikiz olgusu olup 28. gebelik haftasında tanısı konmuştur. Gebeliğin devamına karar veren ailenin, elektif postpartum cerrahi ile başarılı sonucu alınmıştır.

Sonuç: Yapışık ikizler monozigot ikizlerin ender saptanan komplike bir gelişimi olup, yüksek perinatal mortalite oranları göstermektedir. Yapışık ikizlerin erken tanısı, ebeveynlere gebeliğin devamı ve doğum sonrası cerrahi seçenekleri ile gebeliğin sonlandırılması konusunda erken bilgilendirme olanağı sağlamaktadır.

(J Turkish-German Gynecol Assoc 2010; 11: 174-7)

Anahtar kelimeler: Yapışık ikizler, prenatal tanı

Geliş Tarihi: 22 Aralık 2009 **Kabul Tarihi:** 11 Şubat 2010

Introduction

Conjoined twins are defined by the conjoined body area, and result from incomplete monozygotic twinning. The incidence of conjoined twins is estimated at 1% of monozygotic twinning or 1/200,000 live births (1). Over the last decade, the widespread use of assisted reproductive techniques has decreased the rate of monochorionic twins, and consequently may have changed the prevalence of conjoined twins (2, 3). Approximately 75% of conjoined twins are females (4). Conjoined twins have an anomaly of duplication in single-zygote conceptions which is thought to occur because of splitting and incomplete separation of the inner cell mass at 13-15 days post-fertilization. Forty percent of conjoined twins are stillborn and another 30% die during the 1st day of life (5). The prenatal diagnosis of conjoined twins began in 1976 (6). There is no doubt that the accurate and early diagnosis of fetal malformations will affect management and perinatal outcomes. We present four cases of conjoined twins (thoraco-omphalopagus, thoracopagus, pygopagus tetrapus parasitic twins, and omphalopagus) detected in the first, second, and third trimesters using two-dimensional (2D) color Doppler ultrasound and three-dimensional (3D) ultrasound for the last case. Case 3 has previously been published with the diagnosis of a pygopagus tetrapus parasitic twin (7).

Material and Methods

All twin pregnancies admitted, followed, and delivered in our maternal-fetal medicine unit between January 2002 and June 2009 were recorded in medical charts and our computer database. A careful ultrasound evaluation was performed to identify or verify fetal details. Pregnancy and ultrasonographic findings were also entered into the database.

Twin pregnancies were divided into two groups: dichorionic (DC) and monochorionic (MC) pregnancies. MC

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Ali Gedikbaşı, İstanbul Bakırköy Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, İstanbul, Turkey*
Mobile: +90 532 213 51 40 e.mail: alged_1971@yahoo.com
doi:10.5152/jtgga.2010.32

twins were also sub-grouped as diamniotic and monoamniotic twins. Prenatal sonographic details were evaluated with related abnormalities depending on chorionicity and fetal development. Ultrasonographic examinations were performed transabdominally or transvaginally by one of four experienced maternal-fetal medicine physician sonographers using a Sonoline-G50 (TM-Siemens, multifrequency convex transducer 2.0-7.0 MHz; Issaquah, WA, USA) and Voluson 730 Expert (TM-GE Healthcare, multifrequency convex transducer 2.0-7.0 MHz, a 2-7-MHz convex transducer and a 4-8-MHz micro-4D convex real-time 4D-transducer; Milwaukee, WI, USA).

Results

During the study period, our database consisted of 857 twin pregnancies. We excluded 672 DC pregnancies with 140 MC twins. One hundred and two MC twins had regular development or additional malformations and 32 cases had twin-twin transfusion syndrome (TTTS). Nineteen cases were diagnosed as MC monoamniotic twin pregnancies, four of which were complicated by conjoined twins and two cases had acardiac twin development. Forty-five DC and MC twins were excluded because of an incomplete database.

Case 1

A 27-year-old gravida 1 para 0 was referred at 16 weeks 3 days gestation with a presumptive diagnosis of conjoined twins. On referral,the 2D transabdominal ultrasound demonstrated a monochorionic, monoamniotic twin gestation complicated by thoracopagus. Observations of the thoracic and abdominal cavities in transverse planes clearly demonstrated that the twins were joined over an area that extended from the central abdomen (omphalopagus) to the lower aspect of the thorax (thoracopagus). In view of the poor fetal prognosis, the family opted for pregnancy termination.

Case 2

A 19-year-old gravida 1 para 0 at 19 weeks gestation was registered for care in our prenatal clinic in the second trimester. Sonography revealed the presence of a monochorionic, monoamniotic twin pregnancy. The twins, facing each other, were joined at the thoracic level with a final diagnosis of thoracopagus (Figure 1). An elective abortion was performed after counseling.

Case 3

A 30-year-old multigravida was referred to our maternal-fetal unit for evaluation of polyhydramnios at 28 weeks gestation. A sonographic examination revealed a single fetus and polyhydramnios with an amniotic fluid index of 30 cm. The fetus had a normal head, spine, thorax, abdomen, two upper and two lower limbs, and two relatively well developed rudimentary parasitic lower limbs in the sacral region. The lower limbs of the autosite moved freely, but no movement was detected in the parasite. The parasite contained irregular lower limbs and a left foot with three toes. Short and deformed long bones were also present in the parasitic limbs. A cesarean section was performed at 38 weeks gestation. A live female infant weighing 3600 g was delivered. The parasitic lower limbs were totally excised. The final diagnosis was a pygopagus tetrapus parasitic twin (Figure 2). The post-operative period was uneventful and the newborn was discharged in healthy condition. Postnatal follow-up was uneventful after 9 months (7).

Case 4

A 25 year-old gravida 1 para 0 was referred to our perinatology clinic because of a monochorionic, monoamniotic twin pregnancy. An ultrasound examination revealed conjoined twins, each with a crown-rump length of 44 mm, consistent with 11 weeks 3 days gestation. The twins were joined at the abdomen. An omphalopagus conjoined twin pregnancy was diagnosed with 3D ultrasound (Figure 3). After counseling, the family opted for an elective abortion.

Discussion

Classically, conjoined twins have been reported to arise at around 12-13 days post-conception from a single blastocyst

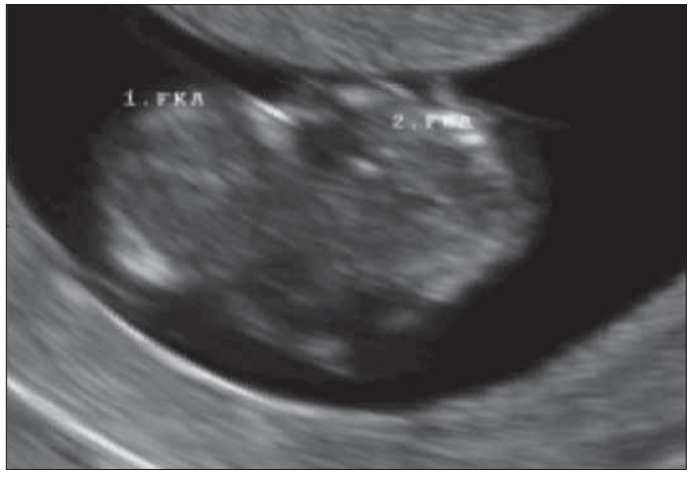

Figure 1. Diagnosis of case 2 with thoracopagus

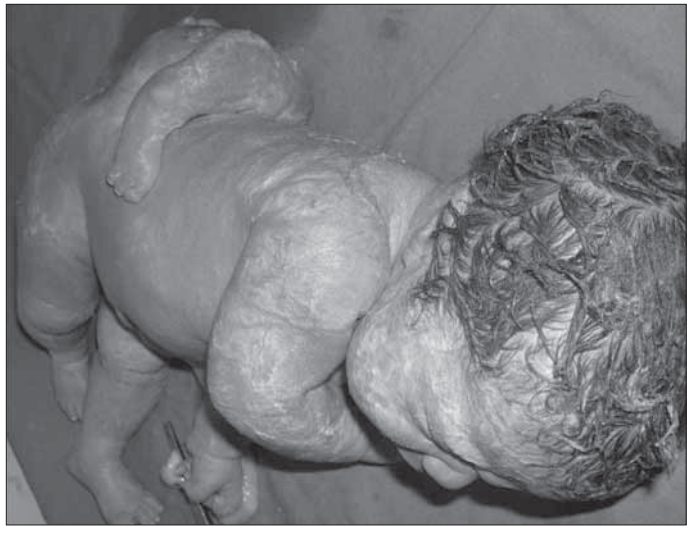

Figure 2. Postnatal final diagnosis of case 3 as pygopagus tetrapus parasitic twin

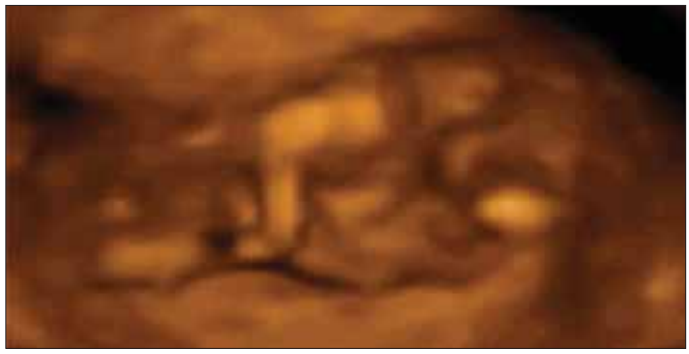

Figure 3. 3D image of case 3 with omphalopagus

that had undergone incomplete division of the embryonic cell mass (4). Embryologic studies have shown that this extraordinary anomaly could develop from fusion of the two separate embryonic discs. Conjoined twins are classified according to the site of fusion and are always joined at identical anatomic points (Table 1). The combination of different types can occur, but the most frequently seen types include thoracopagus (20-40%), omphalopagus (18-33%), and parapagus (28%). Rachipagus is the rarest type of conjoined twins with an incidence of approximately 2% (8, 9).

The sonographic diagnosis of conjoined twins was first reported by Wilson et al. (6). Conjoined twins have been diagnosed in the first trimester with both transabdominal and transvaginal sonography (10, 11). According to Hill (12), the earliest prenatal suspicion of conjoined twins can arise at 7 weeks gestation. Because all conjoined twins are monochorionic and monoamniotic, the level of suspicion should increase when only one yolk sac is noted alongside two embryos in very early pregnancies or there are separating membranes not seen by ultrasound examination at any stage of pregnancy.

Non-operative management in cases with complex cardiac union, and emergency separation in cases with cardiac instability or additional structural anomalies warranting immediate surgical intervention and planned elective separation are ideally carried out between 2 and 4 months of age. Emergency separation carries a mortality rate of 71%, whereas the survival rate for elective separation is 80% (13). In cases with extensive cardiac or cerebral fusion, or when the anticipated severity of deformity following separation is unacceptable, the parents may desire to terminate the pregnancy (14). Although our cases with the diagnosis of separated hearts and thoracopagus and/or omphalopagus (cases 1, 2, and 4) had a better prognosis, the parents elected termination.

Although the prognosis for all types of conjoined twins is extremely poor, a careful anatomic and vascular mapping to determine the extent of organ sharing is of vital importance (15). First-trimester transvaginal ultrasonography in combination with color Doppler and 3D ultrasound are important advances that allow for the early diagnosis of conjoined twins. The data obtained by combining these complementary modalities may also be of prognostic value (16). Additionally, the accurate prenatal diagnosis of conjoined twins can be performed with these modalities as early as 10 weeks gestation (17, 18). Cases with false-positive diagnoses in the first trimester have been documented; therefore, an exact diagnosis should be made with caution (19). This technique may also provide images that are easier for parents to understand, which can help in decision making (20, 21).

Parasitic twins are a rare form of conjoined twins and consist of an incomplete twin (parasite) attached to the fully developed body of the co-twin (autosite). Parasitic twins are classified (22) as (a) an externally attached parasitic twin, (b) an enclosed fetus *in fetu*, (c) an internal teratoma, or (d) an acardiac twin connected via the placenta. This was the only surviving case (case 3) in our study in which the parents made the decision to continue the pregnancy and a successful result was achieved.

Table 1. Classification of conjoined twins with incidence

Classification	Incidence (%)
Ventral union	
Cephalopagus. Fusion from top of head to umbilicus. Each twin has 2 extremities and lower abdomen and pelvis are separated.	11
Thoracopagus. Twins are located face to face, with fused thoraces and shared heart or single interatrial vessel.	20-40
Omphalopagus. Twins have similar fusion to thoracopagus without shared heart or interatrial vessel.	18-33
Ischiopagus. These twins share a large conjoined pelvis and are more commonly joined end to end. External genitalia and anus are always shared.	6-11
Dorsal union	
Craniopagus. Twins are joined by any portion of the skull except the face and foramen magnum. The bony cranium, meninges and brain are shared.	2
Pygopagus. Twins have fused sacrococcygeal and perineal regions, typically with shared anus but separate rectums.The spinal cord may be shared.	18-28
Rachipagus. Twins have dorsal fusion above the sacrum.	Rare
Lateral union	
Parapagus. Twins have side-by-side connection with shared pelvis and variable cephalad sharing defined as follows: - *Dithoracic parapagus:* separate thoraces and heads. - *Dicephalic parapagus:* separate heads with fused thoraces. - *Diprosopus parapagus:* 2 faces on the same side of single head.	28

From Winkler et al. (9)

Conflict of interest

No conflict of interest is declared by authors.

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Comparison of the efficacy of intrauterine lidocaine, paracervical block and oral etodolac for decreasing pain in endometrial biopsy

İntrautein lidokain, paraservikal blok ve oral etodolak uygulamalarının endometrial biopside ağrıyı azaltmadaki etkinliklerinin karşılaştırılması

Ayşe Güler[1], H. Güler Şahin[1], Zehra Küçükaydın[1], Evrim Erdemoğlu[2]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey

[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey

Abstract

Objective: To compare the effectiveness of paracervical block, intrauterine lidocaine and oral etodolac in decreasing the pain caused by pipelle endometrial sampling. A secondary goal of this study was to determine the adverse effects and compare possible effects of these methods on pulse and blood pressure.

Material and Methods: The study was performed between April 2006 and October 2006 in the Obstetrics and Gynecology Department of Van Yüzüncü Yıl University Research Hospital. One-hundred twenty patients were randomized into four groups: 1. Group: Paracervical block was performed with 3 ml 2% prilocaine solution. 2. Group: Five ml of 2% lidocaine solution was instilled through the endocervix into the uterine cavity. 3. Group: Subjects received 400 mg oral etodolac tablet 1-1.5 hour before the procedure. 4. Group: No method of anesthesia was used in the control group. Endometrial sampling was performed with pipelle. Severity of pain during the procedure was scored by the subjects according to the "6-point Verbal Rating Scale (VRS)". Blood pressure and pulse rate were measured before, during and 30 minutes after the procedure.

Results: Pain scores in intrauterine lidocaine group (2nd group) were found statistically significantly lower than the other three groups ($p<0.05$).

Conclusion: Intrauterine lidocaine anesthesia technique decreases pain in endometrial sampling with pipelle more efficiently than paracervical block or oral etodolac. While indication of menorrhagia and endometrial thickness more than 5 mm increased pain scores, intrauterine lidocaine application or paracervical block decreased the scores significantly ($p<0.05$).

(J Turkish-German Gynecol Assoc 2010; 11: 178-81)

Key words: Anesthesia, lidocaine, pain

Received: 9 October, 2010 **Accepted:** 14 November, 2010

Özet

Amaç: Endometrial biopsi alınmasında Pipelle kullanımının neden olduğu ağrıyı azaltmada praservikal blok, intrauterin lidokain ve oral etodolakın etkinliklerinin karşılaştırılması. Bu çalışmada ikincil olarak bu yöntemlerin yan etkileri ile nabız ve kan basıncı üzerindeki olası etkilerinin belirlenmesi ve karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışma Nisan 2006 ve Ekim 2006 tarihleri arasında Yüzüncü Yıl Üniversitesi Arastırma Hastanesi Kadın Hastalıkları ve Dogum kliniğinde gerçekleştirildi. Yüz yirmi hasta 4 gruba randomize edildi. Birinci gruba; 3 ml %2'lik prilokain ile paraservikal blok yapıldı. İkinci gruba; intrauterin olarak 5 ml %2'lik lidokain uygulandı. Üçüncü grubtaki olgulara işlemden 1-1.5 saat önce oral olarak 400 mg etodolak verildi. Dördüncü gruba ise herhangi bir yöntem uygulanmadı. Endometrial örnekleme pipelle endometrial örnekleme aleti ile yapıldı. İşlem esnasında duyulan ağrının şiddeti olgular tarafından "6-Nokta VRS (Verbal Rating Scale)" ye göre derecelendirildi. Kan basıncı ve nabız işlemden önce, işlem esnasında ve işlemden 30 dk sonra ölçüldü.

Bulgular: İntrauterin lidokain grubunun (2. grup) ağrı skorları diger 3 grubun ağrı skorlarından istatistiksel olarak anlamlı şekilde daha düşük bulundu ($p>0.05$).

Sonuç: Pipelle ile endometrial biopsi alınmasında intrauterin lidokain anestezisi, ağrıyı paraservikal blok veya oral etodolaktan daha etkin biçimde azaltmaktadır. Biopsi endikasyonunun menoraji olması ve endometrium kalınlığının 5 mm'den fazla olması ağrı skorlarını yükseltirken, intrauterin lidokain veya paraservikal blok uygulamaları skorları belirgin şekilde azaltmaktadır ($p<0.05$).

(J Turkish-German Gynecol Assoc 2010; 11: 178-81)

Anahtar kelimeler: Anestezi, lidokain, ağrı

Geliş Tarihi: 09 Ekim 2010 **Kabul Tarihi:** 14 Kasım, 2010

Endometrial sampling is a diagnostic tool that is frequently applied in outpatient clinics for many disorders, including abnormal uterine bleeding, abnormal cytology, postmenopausal bleeding, hormone therapy monitoring and infertility. Today, although sonographic evaluation of the endometrium is the first step, pathological examination is still "the gold standard" in the diagnostic pathway. Traditionally, the standard method of assessing the endometrium has been dilatation of the cervix and curettage (D&C) of the uterine cavity. Recently, simple, quick, safe and inexpensive methods such as Pipelle, Vabra and Z-sampler have superceded this technique. Pipelle is the most popular of these sampling devices (1, 2).

Although pipelle is known to be painless or to cause less pain than conventional methods of endometrial sampling, nearly half of the patients experience moderate-to-severe pain during the procedure (3). Nevertheless, there are only a few studies that have evaluated possible methods of pain-relief during endometrial biopsy using a pipelle (4).

Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Ayşe Güler, Yüzüncü Yıl Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Van, Turkey*
Mobile: +90 533 334 71 04 e.mail: doctorayseguler@yahoo.com.tr
doi:10.5152/jtgga.2010.33

Paracervical block is the most common anesthetic technique which has been used for minor gynecological procedures since 1925. It has been suggested that paracervical block may reduce pain, but the evidence is not strong. The risk of anesthetic intravasation is its main disadvantage (5).

Nonsteroidal antiinflammatory drugs block prostaglandin synthesis and have been shown to be effective in the relief of mild-to-moderate pain related to various obstetrical and gynecological syndromes and procedures, such as dysmenorrhea, intrauterine device insertion, suction curettage, postpartum pain, gynecologic surgery and menorrhagia (6, 7).

Recent studies have investigated the use of local anesthetics (i.e., lidocaine, mepivacaine) to lessen the pain experienced during minor gynecological procedures such as endometrial biopsy and office hysteroscopy. Most, but not all, of these studies reported reduced pain during the procedure (8-10).

The main objective of the present study was to compare the effectiveness of paracervical block, intrauterine lidocaine and oral etodolac in decreasing pain caused by endometrial sampling. A secondary goal of this study was to determine the adverse effects and compare possible effects of these methods on pulse and blood pressure.

Material and Methods

The study was performed between April and October 2006 in the Obstetrics and Gynecology department of Yuzuncu Yıl University Research Hospital. One-hundred twenty patients who fulfilled the inclusion criteria and required endometrial biopsy to be taken for various indications were enrolled in the study. Subjects were randomized for paracervical block (1st group), intrauterine lidocaine (2nd group), etodolac (3rd group) and control (4th group) groups. In the 1st group, paracervical block was performed with 3 ml 2% prilocaine (Citanest flacon; AstraZeneca, İstanbul, Türkiye) solution. In the 2nd group, a blue colored feeding catheter (2.70 mm in diameter) was shortened with a sterile scalpel to about 20 cm in length and its tip was inserted into the endometrial cavity up to 2-3 cm distal to the endocervix. Five ml of 2% lidocaine solution were instilled slowly through the catheter into the uterine cavity and the catheter was withdrawn after 3 minutes. In the 3rd group, subjects received 400 mg oral etodolac tablet 1-1.5 hour before the procedure. In the 4th group no methods of anesthesia was used. Endometrial sampling of all subjects was performed by the same person using the pipelle endometrial sampling device. After completion of the procedure, but before the speculum was taken out, all patients were asked to score the severity of pain they had felt during the procedure according to the "6-point Verbal Rating Scale (VRS)". Blood pressures and pulse rates of all subjects were measured before, during and 30 minutes after the procedure. All subjects were observed in the clinic during the first hour after the procedure and were asked at the end of this time if they needed additional analgesia. Endometrial tissue samples were examined in the pathology laboratory of Yuzuncu Yil University Research Hospital.

Statistical analysis of data was performed using SPSS 13.0 for Windows package programme with Student's-*t* test, Post-hoc LSD test, Chi-square test, One-way ANOVA and Spearman correlation analysis tests.

Results

In Table 1, demographic characteristics of the subjects are demonstrated. Ages of 120 subjects included in the study were between 20-67 years and mean age was 46.1±9.3 years. Of the 120 subjects, 92 (77%) were premenopausal and 28 (13%) were postmenopausal. There were no statistically significant differences in age, gravidity, parity, number of living children or menopausal status of the groups ($p>0.05$). Mean systolic blood pressure of the subjects measured before, during and 30 minutes after the procedure were 125.3±11.7 mmHg, 123.9±11.6 mmHg and 123.2±9.9 mmHg, respectively. Mean diastolic blood pressures were 79.9±7.4 mmHg, 80.6±7.6 mmHg, 78.7±9.3 mmHg, and mean pulse rates were 83.9±7.1 beat/minute, 82.8±5.2 beat/minute and 83.8±4.2 beat/minute, respectively. No statistically significant differences among groups were found in terms of blood pressures and pulse rates ($p>0.05$). For blood pressures and pulse rates, there were also no clinically significant differences between measurements before and during or after the procedure ($p>0.05$).

In Table 2, dispersion of the pain scores of four groups are showed. When pain scores of groups were compared (Table 3), scores in the intrauterine lidocaine group (2nd group) were found statistically significantly lower than in the other three groups ($p<0.05$).

Table 1. Demographic characteristics of the groups

	1. Group (n=30)	2. Group (n=30)	3. Group (n=30)	4. Group (n=30)	p
Age (year)*	43.3±10.4	44.8±8.8	48.5±8.3	47.8±9.2	p=0.099
Gravidity*	8.7±4.1	7.4±3.6	8.7±3.5	7.6±4.4	p=0.364
Parity*	7.0±3.3	6.2±3.4	7.7±3.3	6.6±3.5	p=0.362
Abortion*	0.6±1.0	0.9±1.6	0.5±0.6	0.7±1.3	p=0.552
Live child*	5.9±3.1	5.1± 2.6	6.6±2.3 5.	6±2.9	p=0.163
Menopausal status					
Premenopausal (%)	23 (76.7)	23 (76.7)	23 (76.7)	23 (76.7)	p=1.000
Postmenopausal (%)	7 (23.3)	7 (23.3)	7 (23.3)	7 (23.3)	p=1.000

*Mean±SD

Table 2. Distribution of patients in groups according to the pain scores

Groups	PAIN SCORE						Total
	0	1	2	3	4	5	
Paracervical block	8	15	0	5	1	1	30
Intrauterine lidocaine	13	8	8	0	0	1	30
Oral Etodolac	3	12	7	4	3	1	30
Control	2	9	11	4	3	1	30
Total	26	44	26	13	7	4	120

0: No pain, 1: Mild pain, 2: Moderately severe pain, 3: Severe pain, 4: Very severe pain, 5: Unbearable pain

Table 3. Comparison of groups for pain scores

GROUPS COMPARED	P VALUES
Group 1-Group 2	**p=0.004**
Group 1-Group 4	**p=0.004**
Group 1-Group 3	p=0.057
Group 2-Group 3	**p=0.015**
Group 2-Group 4	**p=0.008**
Group 3-Group 4	p=0.911

While the difference between pain scores of paracervical block (1st group) and etodolac (3rd group) groups, and between pain scores of etodolac and control (4th group) groups were not statistically significant (p>0.05), the difference between the scores of paracervical block (1st group) and control (4th group) groups was statistically significant (p=0.004).

In ordinal regression analysis, predictors which probably affect pain scores (menopausal status, parity, endometrial thickness, indication for biopsy and type of anesthesia applied) were examined. Of these predictors, indication for endometrial biopsy, thickness of endometrium being less or more than 5 mm and the method of anesthesia/analgesia were all the factors which affected the pain scores. While the indication of menorrhagia (p=0.02) and endometrial thickness more than 5 mm (p=0.03) increased pain scores, intrauterine lidocaine application and paracervical block decreased the scores significantly (p<0.05).

There was no statistically significant difference among groups in terms of additional analgesia requirement (p>0.05). No complications occurred in any of the subjects either during or one hour after the procedure.

Discussion

In many gynecologic examinations, assessment of the endometrium is required. Traditionally, this used to be achieved by dilatation and curettage (D&C) (1, 2). D&C, which had gained wide acceptance by the end of the 1950's, has begun to be questioned after awareness of evidence-based medicine. As a result, many investigators were forced to find alternative methods.

Since this relatively expensive method, D&C, is not excellent in diagnosis and treatment and also has some complications and problems in its acceptability by patients, many investigators tended to search for alternative methods (11-15). Pipelle is a relatively painless method that does not require dilatation and has low morbidity and 97.5% sensitivity for cancer (16). Many recent studies revealed that pipelle was preferred because of its low cost, easy transport, suitability for peripheral usage and causing less pain. We also preferred pipelle for taking endometrial biopsy in our study.

At the end of the study, a statistically significant difference was determined among groups in terms of pain scores. Although pipelle has been defined as a painless method, in a study by Trolice et al, a moderate degree of pain was reported to be felt by the patients when anesthesia was not applied during pipelle endometrial biopsy (4). Intrauterine anesthesia is a method that have been tried in different gynecologic procedures by some investigators and various data on its effectiveness have been reported. In the study by Guney et al. published in 2006, it was reported that intrauterine lidocaine could be an effective anesthetic method for removing lost IUD's (17). In their 40-patient-study, Edelman et al. reported that 5 ml of 4% lidocaine injected into the endometrial cavity after giving a standard paracervical block decreased the pain significantly more than a placebo in dilatation and curettage of first trimester elective abortions (18). Although these studies are different from ours in terms of material and method, they are significant as they showed that intrauterine anesthesia decreased pain in many gynecologic procedures.

A limited number of studies on intrauterine topical anesthesia is available in literature and in most of these studies, the effectiveness of intrauterine anesthesia was investigated either in hysteroscopy or in hysteroscopy combined with endometrial biopsy (5, 8-10, 17). Endometrial biopsy taken during hysteroscopy is more invasive and potentially more disturbing than only endometrial biopsy. Pain and disturbance caused by uterine distension during hysteroscopy are less responsive to the topical anesthesia (10). Considering that endometrial biopsy alone is simpler and less painful than hysteroscopy, intrauterine lidocaine is expected to prevent pain in endometrial biopsy according to these studies. In our study also, this anesthetic method was found effective.

In two different studies by Cicinelli et al., the effectiveness of intrauterine anesthesia in postmenopausal patients was investigated during diagnostic hysteroscopy and endometrial biopsy. In the first (19) of those studies, no statistically significant difference was found between intrauterine anesthesia and placebo. However in the second, which was performed with a larger number of subjects, more effective anesthesia was achieved with application of intrauterine anesthesia and this was statistically significant (10). Although both pre- and post-menopausal patients were included in our study, the second study by Cicinelli et al. supports our results.

In the study by Zupi et al., it was reported that 5 ml 2% mepivacaine applied into the uterus, as in our study, effectively decreased pain in an endometrial biopsy taken during hysteroscopy (9). Chanrachakul et al. also reported that intrauterine lidocaine decreased pain in fractionated curettage without causing any complications (20).

Lau et al. reported in two separate studies that neither paracer-

vical block nor intrauterine anesthesia was effective in decreasing pain in hysteroscopy and endometrial biopsy compared to a placebo (5, 8).

Anesthetic methods were not combined in our study and the nonsteroidal antiinflammatory tablet did not provide sufficient analgesia by itself. Pain scores were similar in the etodolac tablet group and the control group where no form of anesthesia was applied.

In the study by Dogan et al., the pain decreasing effects of intrauterine lidocaine and oral naproxen sodium in endometrial biopsy with pipelle were compared with each other and with their combined usage. Pain caused by pipelle biopsy was evaluated with the10 cm visual analog scale. They found that intrauterine lidocaine application combined with naproxen sodium given 1 hour before the procedure statistically significantly decreased pain. When applied separately, naproxen sodium and intrauterine lidocaine each decreased pain equally compared to the placebo, but this decrease was not significant statistically. However, when applied together, intrauterine lidocaine and naproxen sodium statistically significantly decreased pain more compared to placebo and to each of them separately (3).

Instead of naproxen, which has been tried before, we aimed to investigate the effectivness of etodolac, also a nonsteroidal antiinflammatory drug that has not been previously tried for use in endometrial biopsy with pipelle, and had a pain decreasing effect comparable to naproxen. In our study, we did not find a significant difference between the group given nonsteroidal antiinflamatory drug 1 hour before the procedure and the control group to whom no anesthetic or analgesic methods was applied. In Dogan et al.'s study also, no significant diferences was determined between the naproxen and placebo groups. Also in that study, in contrast to our findings, intrauterine lidocaine application itself was not found more effective than placebo or naproxen sodium application. However, in our study, intrauterine lidocaine in the same doses were determined to provide significant pain decrease compared to paracervical block and etodolac.

In conclusion; intrauterine lidocaine anesthesia is the anesthesia of choice for pipelle endometrial biopsy, being easily applied without pain and can provide sufficient anesthesia without causing serious complications. Intrauterine lidocaine anesthesia may be an effective method that is safely used mainly for endometrial sampling and also for various other gynecological and obstetrical procedures. It is clear that further clinical studies with larger numbers of patients are required in order to obtain more scientific data on this issue.

Conflict of interest

No conflict of interest is declared by authors.

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Association between the extent of DNA damage in the spermatozoa, fertilization and developmental competence in preimplantation stage embryos

Spermatozoada DNA hasarının boyutu ile fertilizasyon ve implantasyon öncesi embriyoların gelişimsel kompetansı arasındaki ilişki

Dinesh Upadhya[1], Guruprasad Kalthur[1], Pratap Kumar[1], Bola S. Rao[2], Satish K. Adiga[1]

[1]*Clinical Embryology, Division of Reproductive Medicine, Department of Obstetrics and Gynecology, Kasturba Medical College, Manipal University, Manipal, India*

[2]*Department of Radiobiology and Toxicology, Manipal Life Science Centre, Manipal University, Manipal, India*

Abstract

Objective: To examine the fertilizing ability and DNA damage response of preimplantation stage embryos derived from the γ-irradiated mouse sperm carrying varying amounts of DNA strand-breaks.

Material and Methods: The DNA damage in the sperm was induced by exposing the testicular area to different doses of γ-radiation. After mating with healthy female mice, sperm zona binding, fertilizing ability of DNA damaged sperm and developmental competence of embryos derived from the DNA damaged sperm were assessed.

Results: The *in vivo* zona binding ability and fertilizing ability of DNA damaged sperm was significantly affected in the 5.0 and 10.0 Gy sperm irradiation groups. Although the development of the embryos derived from the DNA damaged sperm was not significantly affected until day 2.5 post-coitus, further development was significantly altered, as evidenced by the total cell number in the embryos.

Conclusion: The sperm carrying DNA strand breaks still has the ability to fertilize the oocyte normally. However, the events like zona-binding and successful fertilization depend on the extent of sperm DNA fragmentation. The study has also showed a great heterogeneity in embryonic development at peri-implantation period with respect to the degree of sperm DNA damage.

(J Turkish-German Gynecol Assoc 2010; 11: 182-6)

Key words: Sperm DNA damage, fertilization, preimplantation development

Received: 1 July, 2010 **Accepted:** 24 August, 2010

Özet

Amaç: Gama ışınları ile ışınlanmış ve değişen miktarda DNA zincir kırığı taşıyan fare sperminin dölleme yeteneğini ve bu spermlerden oluşan implantasyon öncesi embriyoların DNA hasarı yanıtını incelemek.

Gereç ve Yöntemler: Spermde DNA hasarı, testiküler bölgenin farklı dozlarda gama ışınlarına maruz bırakılmasıyla indüklendi. Sağlıklı dişi fareler ile çiftleşmeden sonra, sperm-zona bağlanması, DNA hasarlı spermin dölleme yeteneği ve DNA hasarlı spermden oluşan embriyoların gelişimsel kompetansı değerlendirildi.

Bulgular: 5.0 ve 10.0 Gy ışın uygulanan gruplarda, DNA hasarlı spermin *in vivo* zona bağlanma yeteneği ve dölleme yeteneği anlamlı olarak etkilendi. DNA hasarlı spermden oluşan embriyoların gelişimi koitus sonrası 2.5 güne kadar anlamlı ölçüde etkilenmemekle beraber, sonraki gelişim embriyolardaki toplam hücre sayısından anlaşılacağı gibi anlamlı olarak değişti.

Sonuç: DNA zincir kırıkları taşıyan sperm hala oositi normal bir şekilde dölleme yeteneğine sahiptir, bununla beraber, zona-bağlanması ve başarılı fertilizasyon gibi olaylar sperm DNA parçalanmasının boyutuna bağlıdır. Çalışma ayrıca peri-implantasyon döneminde embriyonik gelişimde sperm DNA hasarının derecesine ilişkin olarak büyük bir heterojenlik göstermiştir.

(J Turkish-German Gynecol Assoc 2010; 11: 182-6)

Anahtar kelimeler: Sperm DNA hasarı, fertilizasyon, implantasyon öncesi gelişim

Geliş Tarihi: 01 Temmuz 2010 **Kabul Tarihi:** 24 Ağustos 2010

Introduction

Ionizing radiation induces DNA double-strand breaks (DSB) and inflicts a variety of DNA damage responses which include induction of cell cycle checkpoint and apoptosis (1). Paternal irradiation in experimental animals sometimes induces genomic instability in somatic and germ cells, which is detected in the offspring (2). Female mammals undergo a cycle of oogenesis once in their lifetime. In contrast, cycles of spermatogenesis persist throughout the life of sexually mature males. Therefore, males are more convenient for analyzing the effect of radiation at various stages of spermatogenesis (3).

Although the chromatin is highly condensed in the mature spermatozoa, it is susceptible to various genetic insults, producing large numbers of single and double strand breaks (4). The DNA lesion carried by the sperm induces a series of damage responses in the zygotes and in developing embryos (5-7). However, none of these studies have addressed the response in early embryos with respect to the extent of DNA strand breaks in the spermatozoa present at the time of ferti-

Address for Correspondence / Yazışma Adresi: *Satish Kumar Adiga, Ph.D., Clinical Embryology, Division of Reproductive Medicine, Kasturba Medical College, Manipal University, Manipal-576 104, India Phone: 91-820-29-22027 Fax: 91-820-25-71934 e.mail: satish.adiga@manipal.edu*

doi:10.5152/jtgga.2010.34

lization. Hence, in this study, an attempt was made to quantify the degree of DNA strand breaks in γ-irradiated spermatozoa and then assess fertilization and subsequent pre-implantation developmental potential of the embryos using a mouse model.

Material and Methods

Animals and irradiation

Eight to twelve week old healthy male and female Swiss Albino mice were used for the experiments. The DNA damage to the spermatozoa was introduced by partial body irradiation (0, 2.5, 5.0 and 10.0 Gy) to the testicular area of males using ^{60}Co teletherapy unit.

Sperm extraction and quantification of DNA strand breaks

Eighteen hours after irradiation, animals were sacrificed and spermatozoa were extracted from the caudae epididymis in one milliliter of pre-warmed Earle's Balanced Salt Solution (EBSS). The sperm suspension was analyzed for DNA integrity by alkaline comet assay as described by Singh *et al*. (8), with minor modifications. Briefly, 10μl of sperm suspension was mixed with 200μl of 0.8% low melting agarose and layered on a slide precoated with 1% normal agarose. A third coat of 0.8% agarose was layered over the second layer, followed by overnight incubation in lysing solution (2.5M NaCl, 100mM disodium EDTA, 10mM Trizma base, pH 10, 1% Triton X-100, 10mM GSH and 100μM heparin) under alkaline conditions (pH 10) at 4°C. After allowing the sperm DNA to unwind in electrophoresis buffer (300mM NaOH, 1mM EDTA, pH >13) for 20 minutes, electrophoresis was carried out at 25V for 20min. The slides were stained with ethidium bromide (2μg/ml) and observed under a fluorescent microscope (Imager-A1, Zeiss, Germany). The comet evaluation of the captured images was done using Kinetic Imaging software (Komet 5.5, UK). The percent tail DNA was calculated in at least 50 spermatozoa per slide and a minimum of five animals were used per data point.

Assessment of sperm zona binding

The irradiated male mice were mated with normally cycling healthy female mice for one hour. The successful mating was confirmed by the presence of vaginal plug. The oocytes collected at 10h after mating were washed using M16 medium, placed onto clean glass slides and observed using a 40X objective. The data on the number of sperm bound to zona in the different radiation groups was collected. To test the *in vitro* sperm binding ability to zona pelluicida, oocytes with a intact cumulus were inseminated in 100μl sperm suspension containing 1x10^6 motile spermatozoa/ml incubated at 37°C and 5% CO_2. After 2 hours, oocytes were denuded and observed under the 40X objective for the evaluation of the number of sperm bound to the zona pellucida.

Evaluation of fertilization

The oocytes were collected at 10 hours after mating and successful fertilization was confirmed by the appearance of two pronuclei and two polar bodies.

Assessment of embryonic development potential

Preimplantation embryos were collected from the oviduct on day 1.0, 1.5, 2.0 and 2.5 and from the uterine horn on day 3.0 and 3.5 by gentle flushing with EBSS under the stereomicroscope (Nikon SMZ-10, Japan) and examined under the phase contrast microscope (Olympus IX70, Japan) for morphological assessment. Cell numbers were counted under a fluorescent microscope after treating the embryos with 0.9% trisodium citrate for 15 min, followed by fixation in Carnoy's fixative, and staining with propidium iodide (0.1mg/ml) on a clean glass slide.

Statistical analysis

The results were expressed as mean±SEM. The level of significance was determined by. One Way Analysis of Variance (ANOVA) and Unpaired 't' test using Graph pad software Inc. USA.

Results

Successful induction of DNA breaks by γ-radiation

The percent tail DNA in spermatozoa exposed to the lowest dose of radiation (2.5Gy) was 7.95±0.42, which was significantly ($P<0.01$) higher than the control group (5.44±0.35). Approximately 1.8 and 2.2 fold increase in percent tail DNA was observed in 5 and 10.0Gy group respectively in comparison to the control group. An attempt was made to analyze the distribution of DNA damaged sperm in relation to the tail DNA and the amount of radiation dose received. The number of DNA strand breaks induced by γ-radiation consistently increased with higher doses of radiation. In the control group, the majority of spermatozoa had intact DNA (0-5% tail DNA) and less than 5% were severely damaged. However, in the case of irradiated spermatozoa, the percentage of spermatozoa with intact DNA sharply decreased with a concomitant increase in the spermatozoa with moderate (5-15% tail DNA), high (15-20% tail DNA) and severe (>20% tail DNA) damage.

Sperm-zona binding

The mean number of spermatozoa attached to the zona pellucida in the control group was approximately 1.2. The number of spermatozoa bound to zona pellucida in different sperm irradiated groups was reduced in a dose-dependent manner. Even though no significant decline was observed in the 2.5.0Gy group, 5.0 and 10.0Gy groups exhibited a significant decline in the number of spermatozoa bound to the zona pellucida compared to the control group ($p<0.05$ and $p<0.001$ respectively). In addition, the number of sperm bound in 2.5.0Gy and 10.0Gy groups were significantly different ($p<0.001$) (Fig 1A). When the number of spermatozoa bound to the zona pellucida of fertilized oocytes and unfertilized oocytes were compared, no significant difference was observed in the control and 2.5.0Gy groups. However, in the the 5.0Gy and 10.0Gy groups, the spermatozoa bound to unfertilized oocytes were almost 50% of the spermatozoa that were bound to fertilized oocytes. The ability of sperm binding to zona *in vitro* did not show any significant difference (Fig 1B).

Influence of sperm DNA fragmentation on fertilization

The assessment of fertilization was made in the oocytes collected from the normally cycling healthy females mated with irradiated males. A minimum of 50 oocytes were assessed for each data point. The fertilization rate observed in the control group was approximately 95%, whereas an inverse relationship was observed between the dose of sperm irradiation and fertilization rate. Although, the fertilization rate in the 2.5.0Gy

group was not significantly affected, 5.0Gy sperm irradiation had a significantly reduced fertilization rate ($p<0.01$). Further, in the 10.0Gy group, approximately 50% of the oocytes failed to demonstrate successful fertilization ($p<0.001$) (Fig 2A, Table 1).

Influence of sperm DNA fragmentation on pre-implantation development

The first cleavage of sperm-irradiated embryos (embryos derived from the irradiated sperm) was not affected except in the 10.0Gy group, where approximately 42% embryos showed delayed development. In addition, the embryonic fragmentation was evident in approximately 14% of the 10Gy sperm-irradiated, delayed embryos on day-1 of development. On day-1.5 the embryo fragmentation rate in this group was further increased to 27% (Fig 3 upper panel). The cleavage rate was further reduced in the 10.0Gy group on day-2 of development where only 71% embryos successfully completed two cleavage divisions and the remaining embryos were arrested at 2-3 cell stage. On day-3 of development, the cleavage delay was also evident in 10.0Gy as well as in 5.0Gy sperm-irradiated embryos. Approximately 40% of 5.0Gy sperm-irradiated embryos and 50% of the 10.0Gy group failed to complete compaction, which was significantly lower than the control group ($p<0.05$). However, on day-3.0, no morphological abnormalities were detected in the sperm-irradiated embryos of all the groups. On day-3.5, approximately 65% and 35% embryos reached blastocyst stage in the 5Gy and 10Gy groups respectively, whereas in the control group, all the embryos successfully reached blastocyst stage (Fig 3 lower panel).

Total cell number in preimplantation stage embryos:

The TCN in the sperm-irradiated embryos was not significantly different on day 1.0 and 1.5. However, on day-2.5, embryos derived from 5.0Gy sperm irradiation demonstrated a significant decline in TCN, which was approximately 9% compared to the control group ($p<0.05$). Although TCN in this group increased during subsequent developmental periods, it was approximately 23% and 25% lower than control group on day-3.0 and 3.5 respectively. However, 10.0Gy sperm irradiation resulted in lower TCN as early as on day-2.0 of development, which subsequently resulted in the significant decline of TCN throughout their pre-implantation development ($p<0.05$-0.001). This decline in TCN was approximately 12%, 25% and 32% on day 2.0, 2.5 and 3.0 respectively. On day-3.5, the reduction in TCN in this group was approximately 50% compared to the control group (Fig 2B).

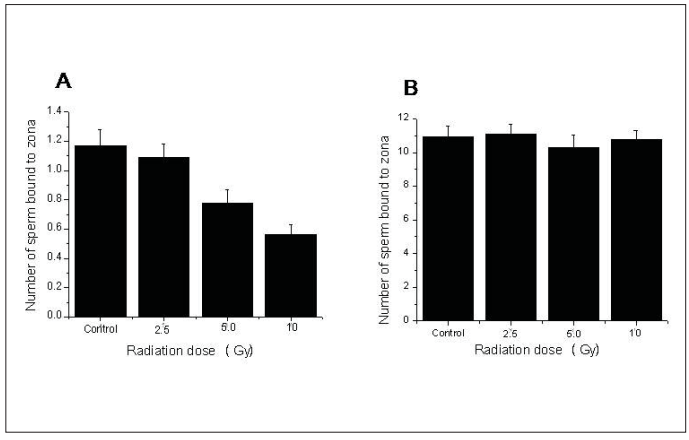

Figure 1. A. *In vivo* zona binding ability of male mice exposed to different doses of γ-radiation (the data includes both fertilized and unfertilized oocytes). $p<0.05$ for 5.0Gy v/s control; $p<0.001$ for 10.0Gy v/s control and 2.5.0Gy B. *In vitro* zona binding ability of epididymal sperm collected 18h after exposure to different doses of γ-radiation. The data were indicative of three independent experiments. A minimum of 50 oocytes were assessed in each group to determine the sperm-zona binding

Discussion

The present study clearly demonstrated that sperm carrying varying levels of DNA strand breaks still has the ability to fertilize the oocyte normally. However, successful fertilization depends on the extent of DNA strand breaks in the sperm at the time of fertilization. In addition, the study has also shown that development of the sperm-irradiated embryos exhibit great heterogeneity at the peri-implantation period with respect to the degree of sperm DNA damage. This work also demonstrate the fact that the effects of sperm DNA fragmentation are apparently visible only when embryonic genome becomes completely functional at the peri-implantation period of development.

Several *in vitro* studies demonstrated the decline in fertilization rate with increasing amounts of sperm DNA damage (9, 10). In contrast, other *in vitro* studies in human (11, 12), bovine (13), and mice (5) found no decline in fertilization rates. However, the novel observation in our *in vivo* study has demonstrated that spermatozoa carrying a high level of DNA strand breaks still has the ability to reach the oviduct and fertilize the oocyte successfully. It is possible that a significant number of DNA fragmented spermatozoa might have been retained/removed prior to/during the oviductal passage. This was supported by the fact that the number of spermatozoa bound to the zona pellucida

Table 1. Comet analysis showing the distribution of DNA fragmented spermatozoa exposed to various doses of γ-radiation

Group	Spermatoza	Distribution of spermatozoa with respect to percent tail DNA (Mean±SEM)				
	evaluated	0-5	5-10	10-15	15-20	>20
Control	274	62.54±2.7	17.6±3.0	14.38±1.9	3.5±1.8	1.96±0.6
2.5Gy	275	44.53±3.5	24.75±5.0	14.98±2.8	8.46±0.4	7.27±1.2
5.0Gy	262	32.06±2.2	25.64±2.1	19.46±3.5	13.06±2.1	9.76±2.9
10.0Gy	271	27.18±4.6	21.96±2.5	19.92±2.5	13.7±2.0	17.26±3.3

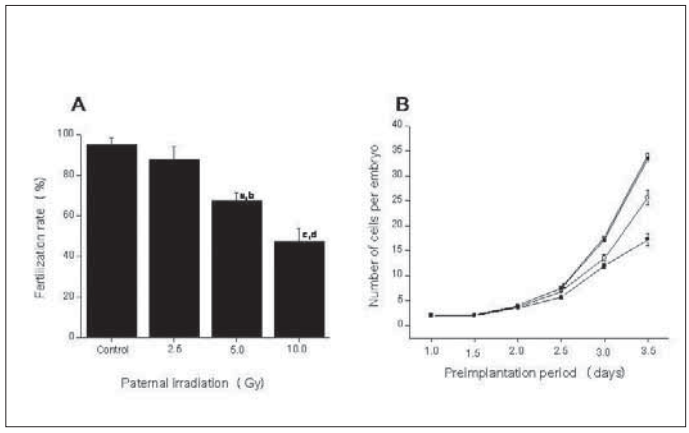

Figure 2. A. Fertilizing ability of sperm exposed to different doses of γ-radiation. [a]p < 0.001 for 5.0Gy v/s control; [b]p < 0.05 for 5.0Gy v/s 2.5.0Gy; [c]p < 0.001 for 10.0Gy v/s control, and 2.5.0Gy; [d]p < 0.05 for 10.0Gy v/s 5.0Gy. B) Total cell numbers (number of cells/embryo) in sperm irradiated embryos at different preimplantation days (□ Control; ■ 2.5.0Gy; ○ 5.0Gy; ● 10.0Gy). P < 0.001 for 10.0Gy v/s control, and 2.5.0Gy on day 2.0; 10.0Gy v/s control, 2.5.0Gy, and 5.0Gy on day 2.5; 5.0Gy v/s control, and 2.5.0Gy on day 3.0; 10.0Gy v/s control, and 2.5.0Gy on day 3.0; 5.0Gy v/s control, and 2.5.0Gy on day 3.5; 10.0Gy v/s control, 2.5.0Gy, and 5.0Gy on day 3.5 p < 0.05 for 10.0Gy v/s 5.0Gy on day 2.0; 5.0Gy v/s control on day 2.5

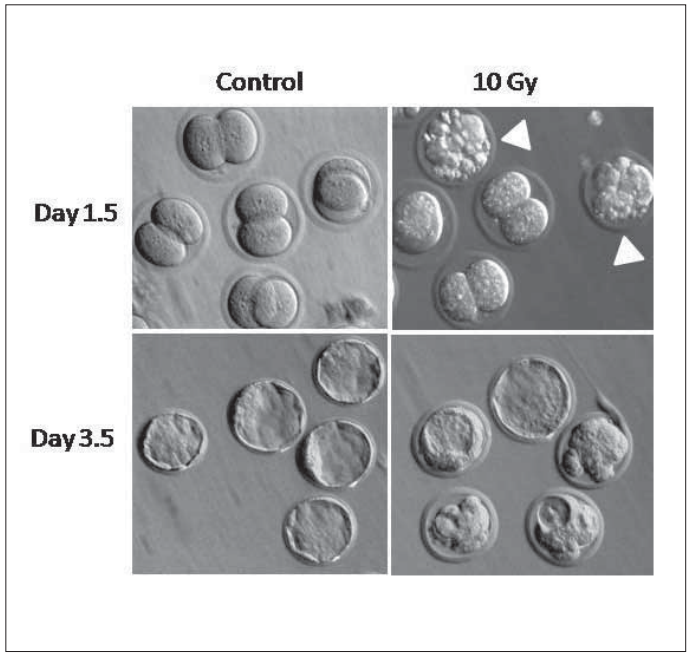

Figure 3. Developmental potential of the sperm irradiated embryos (10.0Gy) and control on day 1.5 and 3.5. Arrowhead in day 1.5 indicates fragmented one-cell embryos and arrowhead in day 3.5 shows cleavage stage embryos in 10.0Gy group

in the 10Gy sperm irradiation group was significantly lower. In addition, the number of spermatozoa bound to unfertilized oocytes was low in the 10.0Gy sperm irradiation group, indicating that a significant number of spermatozoa failed to reach the oocyte. Earlier, it was shown that human spermatozoa bound to oviduct cells had better DNA integrity than those of unbound sperm, suggesting that sperm selection may occur during sperm transportation in the female reproductive tract *in vivo* (14). This indicates that mostly defective spermatozoa were withheld in the uterus or uterotubal junction and such males showed drastically reduced fertility (15). Thirdly, there might be a decline in zona binding ability of the DNA damaged spermatozoa since it has been shown that sperm with single stranded or denatured DNA generally do not bind to the zona pellucida (16). However, the present study demonstrated no significant difference in zona-binding ability of the spermatozoa with varying levels of DNA strand breaks, when inseminated *in vitro*. This suggests that DNA fragmentation in sperm does not impair the zona binding ability. However, a significant number of damaged sperm are eliminated during their passage in the reproductive tract, which eventually resulted in the reduced number of sperm available for zona binding at the site of fertilization.

The reduced fertilization rate observed in the present study could be possibly due to one of the following factors. Primarily, a high incidence of fragmented oocytes was observed in the 5.0 and 10.0Gy groups. Fertilization with DNA damaged sperm leading to failed sperm head decondensation and pronuclear formation might have resulted in subsequent fragmentation. This is supported by an earlier study where the high incidence of fragmented oocytes resulted from mutagen treated spermatozoa, which is considered to be due to a result of fertilization with highly DNA damaged sperm (17). Thus, decline in fertilization rate is possibly associated with fragmentation caused by fertilization with DNA damaged sperm. Further, reduced oocyte availability in this group could be ruled out since the sum of the fertilized and fragmented oocytes in the 5.0Gy and 10.0Gy groups was almost similar to fertilized oocytes in the control group, indicating that an equal number of oocytes was available for fertilization in all the groups. Thus, the decline in fertilization rate might be either due to the high incidence of oocyte fragmentation caused by DNA damaged sperm which reached the oocyte after escaping the barriers of female reproductive tract, or a decreased number of spermatozoa reaching the oocyte due to selective barriers of the female reproductive tract or a collective defect. In addition, there is a possibility that spermatozoa with gross damage might have been retained while those with unidentified damage might have reached the oocyte since motility of the DNA damaged spermatozoa is not altered. However, the mechanism behind this phenomenon is not known.

The effects of sperm DNA integrity are apparent on the cleavage stage embryos when the paternal genome becomes activated and its transcriptional activity begin to play a contributory role in embryo function (18). It has been found in various animal studies that the damage response in early embryos is stage specific (7, 19). Xenopus embryogenesis has been characterized by a period called midblastula transition in which a burst of transcription takes place concomitant with prolongation of cell cycle time (20). A similar transition period is widespread among many metazoan species. In mice, even though mouse embryonic gene transcription starts at the late one-cell stage, the apparent effects become visible during the midblastula transition period, which corresponds to the morula-blastocyst stage when a burst of transcription takes place (21). In the present study, while developmental abnormalities were observed on day 2.0 onwards, it was marked after day 3.0, which corresponds to the morula blastocyst transition stage.

Hence, the embryonic response to genetic insult introduced by the sperm is stage specific, which is possibly associated with changes in chromatin conformation or activation of the embryonic genome (22). Further studies are required to elucidate the mechanism associated with sperm DNA damage response during embryonic genome activation.

Acknowledgement
This work has been supported by the Indian Council of Medical Research in the form of senior research fellowship to DU (IRISID-No. 2006-01640). The Authors are greatful to the Department of Radiotherapy, S.S. Cancer Hospital for providing radiation facility.

Conflict of interest
No conflict of interest is declared by authors.

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Comparison of the ultrashort gonadotropin-releasing hormone agonist-antagonist protocol with microdose flare -up protocol in poor responders: a preliminary study

Zayıf over cevaplı hastalarda ultra kısa GnRH agonist/antagonist protokolünün mikrodoz flare up protokolü ile karşılaştırılması

Bülent Berker[1], Candan İltemir Duvan[2], Cemil Kaya[3], Ruşen Aytaç[1], Hakan Şatıroğlu[1]

[1]*Centre of Artificial Reproduction, Ankara University, Ankara, Turkey*

[2]*Centre of Artificial Reproduction, Fatih University, Ankara, Turkey*

[3]*Department of Obstetrics and Gynecology, Ufuk University, Ankara, Turkey*

Abstract

Objective: To determine the potential effect of the ultrashort gonadotropin-releasing hormone (GnRH) agonist/GnRH antagonist protocol versus the microdose GnRH agonist protocol in poor responders undergoing intracytoplasmic sperm injection (ICSI).

Material and Methods: The patients in the Agonist-Antagonist Group (n=41) were administered the ultrashort GnRH-agonist/ antagonist protocol, while the patients in the Microdose Group (n=41) were stimulated according to the microdose flare-up protocol. The mean number of mature oocytes retrieved was the primary outcome measure. Fertilization rate, implantation rate per embryo and clinical pregnancy rates were secondary outcome measures.

Results: There was no differenc between the mean number of mature oocytes retrieved in the two groups. There were also no statistical differences between the two groups in terms of peak serum E_2 level, canceled cycles, endometrial thickness on hCG day, number of 2 pronucleus and number of embryos transferred. However, the total gonadotropin consumption and duration of stimulation were significantly higher with the Agonist-Antagonist Group compared with the Microdose Group. The implantation and clinical pregnancy rates were similar between the two groups.

Conclusion: Despite the high dose of gonadotropin consumption and longer duration of stimulation with the ultrashort GnRH agonist/ antagonist protocol, it seems that the Agonist-Antagonist Protocol is not inferior to the microdose protocol in poor responders undergoing ICSI.

(J Turkish-German Gynecol Assoc 2010; 11: 187-93)

Key words: Poor responder, mature oocytes, Agonist-Antagonist protocol, microdose flare-up protocol

Received: 11 August, 2010 **Accepted:** 19 November, 2010

Özet

Amaç: ICSI uygulanan zayıf over cevaplı hastalarda ultra kısa GnRH agonist/GnRH antagonist protokolünün mikrodoz GnRH agonist protokolüne karşı potansiyel etkisini belirlemek.

Gereç ve Yöntemler: Mikrodoz grubundaki (n=41) hastalar mikrodoz flare up protokolüne uygun olarak stimüle edilirken Agonist-Antagonist grubundaki (n=41) hastalara da ultra kısa GnRH-agonist/ antagonist protokolü uygulandı. Bu çalışmanın primer sonuç değeri toplanan ortalama matür oosit sayısı iken, fertilizasyon oranı, embryo başına implantasyon oranı ve klinik gebelik oranı da sekonder sonuç değerleriydi.

Bulgular: İki grup arasındaki toplanan ortalama matür oosit sayıları arasında fark yoktu. Serum E_2 düzeyleri, iptal edilen sikluslar, hCG günü endometrial kalınlığı, 2 pronukleus sayıları ve transfer edilen embryo sayılarında da iki grup arasında istatistiksel farklılıklar yoktu. Bununla birlikte Agonist-Antagonist grubunda total gonadotropin tüketimi ve stimülasyon süresi Mikrodoz grubuyla karşılaştırıldığında belirgin olarak daha yüksekti. İki grup arasındaki implantasyon ve klinik gebelik oranları ise birbirine benzerdi.

Sonuç: Ultra kısa GnRH agonist/ antagonist protokolü ile yüksek doz gonadotropin tüketimi ve daha uzun süreli stimülasyona rağmen ICSI uygulanan zayıf over cevaplı hastalarda Agonist-Antagonist Protokolünün mikrodoz protokolünden daha az etkili olmadığı görülmektedir.

(J Turkish-German Gynecol Assoc 2010; 11: 187-93)

Anahtar kelimeler: Zayıf over cevaplı, matür oositler, Agonist-Antagonist protokol, mikrodoz flare-up protokol

Geliş Tarihi: 11 Ağustos 2010 **Kabul Tarihi:** 19 Kasım 2010

Introduction

The management of the poor-responder patients still presents a challenging and frustrating problem in assisted reproductive technologies (ART). Poor ovarian response is unfortunately associated with a high rate of cycle cancellation and decreased pregnancy rates (1, 2). Although there is no universally accepted definition for poor responders, a poor response to controlled ovarian hyperstimulation (COH) might occur in a significant number of women undergoing ART, with a percentage ranging between 10% and 25% (2, 3). The ideal approach to patients who respond poorly to traditional COH

Address for Correspondence / Yazışma Adresi: *Ass. Prof. Dr. Candan İltemir Duvan, Fatih University, Centre of Artificial Reproduction, Hosdere Cad. No: 145 P.K. 06540 Y. Ayrancı, Ankara, Turkey Phone: +90 312 409 88 88 Fax: +90 312 441 54 98 e.mail: candanduvan@yahoo.com*

doi:10.5152/jtgga.2010.35

regimens in preparation for ART has not been clearly defined. Different treatment interventions have been proposed for these women to overcome the poor ovarian response during COH. These options consisted of pituitary down-regulation protocols as gonadotropin-releasing hormone agonist (GnRH-a) stop protocols, microdose GnRH-a flare-up protocols or GnRH antagonists protocols and also adjuvant therapy regimes including growth hormone and letrazol (4, 5).

The most prevalent approaches for treating poor responder patients are microdose GnRH-a ''flare'' (6, 7) and GnRH antagonist protocol (8, 9). According to several studies, microdose GnRH-a flare-up regimes seem to be more successful in terms of ovarian response and/or pregnancy rates (4, 10). The basic hypothesis of this approach is the administration of the minimal dose of GnRH-a necessary to induce gonadotropin release while minimizing premature ovulation. The other attractive treatment option for poor responders is the GnRH antagonist protocol. These agents act to block the pituitary gonadotrop receptors rapidly without any associated stimulatory effects. As the initiations of the GnRH-antagonists occur after the beginning of gonadotropin stimulation, their impact on early follicular recruitment is minimal (8).

Even in the original manuscript of Surrey describing the microdose flare protocol, no change in follicular phase testosterone, LH, and progesterone levels were reported, but there are still some concerns about these issues (7, 11, 11-13). In a similar fashion, the GnRH antagonist protocol exposes the maturing oocytes to the patient's own endogenous androgen production, which is detrimental during the 6th to 7th days of stimulation before development of a mature follicle (14). In addition, the impact of these protocols on endometrial receptivity also remains controversial (15, 16). As a result, neither of these protocols has been effective in improving ART outcomes in this subgroup of patients (7, 17, 18).

The idea of the combination of the microdose GnRH-a flare-up and GnRH antagonist protocol to minimize these detrimental effects and to combine the beneficial effects of these two stimulation protocols for poor responders was first presented by Berger et al. as a novel protocol - the "Agonist-Antagonist Protocol (AAP)" (19).

Up tol date, there have been no randomized, prospective published data comparing the novel AAP and microdose GnRH-flare-up protocols in poor responders undergoing intracytoplasmic sperm injection (ICSI). Therefore, in this randomized prospective study, we aim to compare the efficacy of the ovarian stimulation by ultrashort GnRH agonist-antagonist with microdose flare-up protocol in poor responders undergoing ICSI.

Material and Methods

Patients and study design

Between September 2006 and April 2008, a total of 82 poor responder patients who underwent intracytoplasmic sperm injection cycles (ICSI) were included. All patients underwent precycle ovarian reserve testing, which included an assessment of cycle day 3 serum follicle-stimulating hormone (FSH) and E_2 levels and a measurement of ovarian volume and number of antral follicles counting by transvaginal ultrasound during the follicular phase. Criteria for classification as a poor responder included at least one of the following: day 3 serum FSH level >10 mIU/mL, <6 total antral follicles, prior cycle cancellation, prior poor response to COH (peak E_2 <500 pg/mL and/or <6 oocytes retrieved), and age >41 (18). The study was approved by the Institutional Review Board of the University. All patients received adequate counseling regarding the stimulation regimens and signed informed consent forms.

Patients were excluded from the study if they had only one ovary, a body mass index higher than 30, polycystic ovary syndrome, stage III–IVendometriosis, endocrine or metabolic disease, chromosomal disorders and patients whose partners were azospermic.

A method of computer-generated block randomization using sealed envelopes was employed. Patients were assigned in a 1:1 ratio to either an ultrashort GnRH agonist/GnRH antagonist group or microdose flare up protocol. Sealed envelopes with treatment allocation instructions were opened on the day of stimulation initiation by a nurse who assigned participants to their groups and was responsible for coding protection.

Treatment protocols

The patients in theultrashort GnRH agonist/GnRH antagonist group (n=41) were administered the ultrashort GnRH-agonist/ GnRH antagonist protocol. The ultrashort GnRH-agonist/ GnRH antagonist protocol entailed the administration of leuprolide acetate (LA, Lucrin; Abbott, Cedex, France) at 40 microg sc/ bid, started on the second day of menses and continued for 3 consecutive days, followed by gonadotropins, which were initiated on the last day of LA administration with maximal doses continuing until hCG day**.** Once the leading follicle had reached a size of 14 mm, cotreatment was initiated with the GnRH-antagonist cetrorelix (Cetrotide; Serono, Turkey) at 0.25 mg/day, which was continued up to hCG injection. A schematic for this protocol is provided in Figure 1.

The patients in the Microdose Group (n=41), who started to use 40 microg sc/bid LA on the second day of menses and two days after initiation of GnRH-a, gonadotropin stimulation was initiated and continued until hCG day. A schematic representation for this protocol is provided in Figure 2. In general, the starting dose of recombinant FSH (Gonal-F; Serono, Istanbul, Turkey) was determined depending on the age, body mass index and ovarian response to previous cycle (if present) and increased to a maximum of 450 IU/day depending on the ovarian response. The dosage of gonadotrophins was individualized after day 5 according to ultrasonographic and hormonal follow-ups of the follicular growth. Once at least three follicles >17 mm in diameter were achieved, 10,000 IU of human chorionic gonadotrophin (Choragon, Ferring, Kiel, Germany) were administered and transvaginal ultrasound guided oocyte recovery was scheduled for 35.5 h later.

Embryo culture and transfer

Standard intracytoplasmic sperm injection (ICSI) was performed as clinically appropriate. Gametes and embryos were cultured in a sequential G medium (Vitrolife, Englewood, CO) and incubated in 6% CO2, 5% O2, and 89% N2. Embryo transfer was performed on day 3 after oocyte collections. Embryo transfers were performed under ultrasound guidance using a Wallace catheter (Marlow, Willoughby, OK). Luteal support was given by daily vaginal progesterone (crinone %8 gel, Serono). Luteal support was initiated on the day of oocyte retrieval and continued

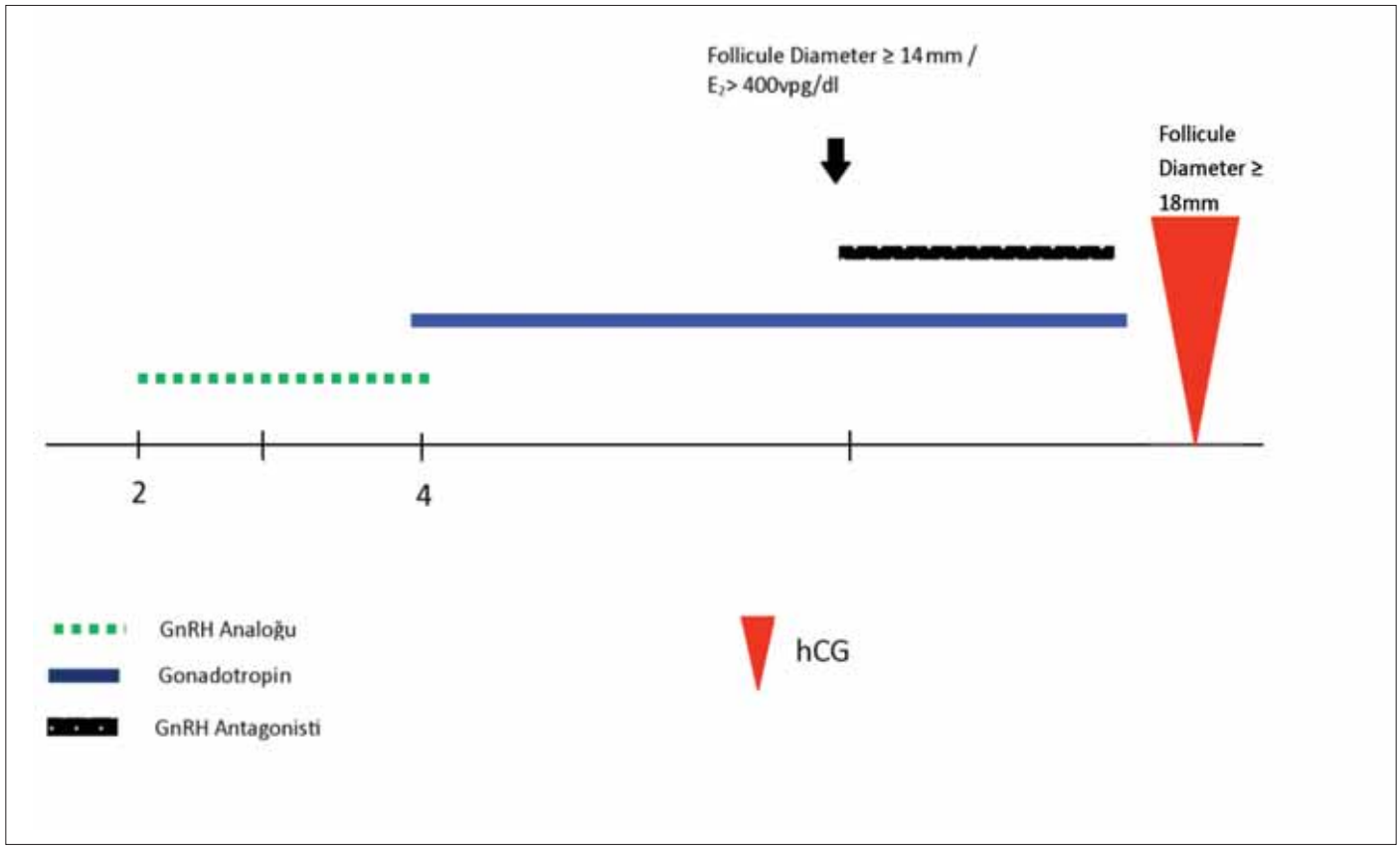

Figure 1. Schematic representation of the Agonist-Antagonist Protocol

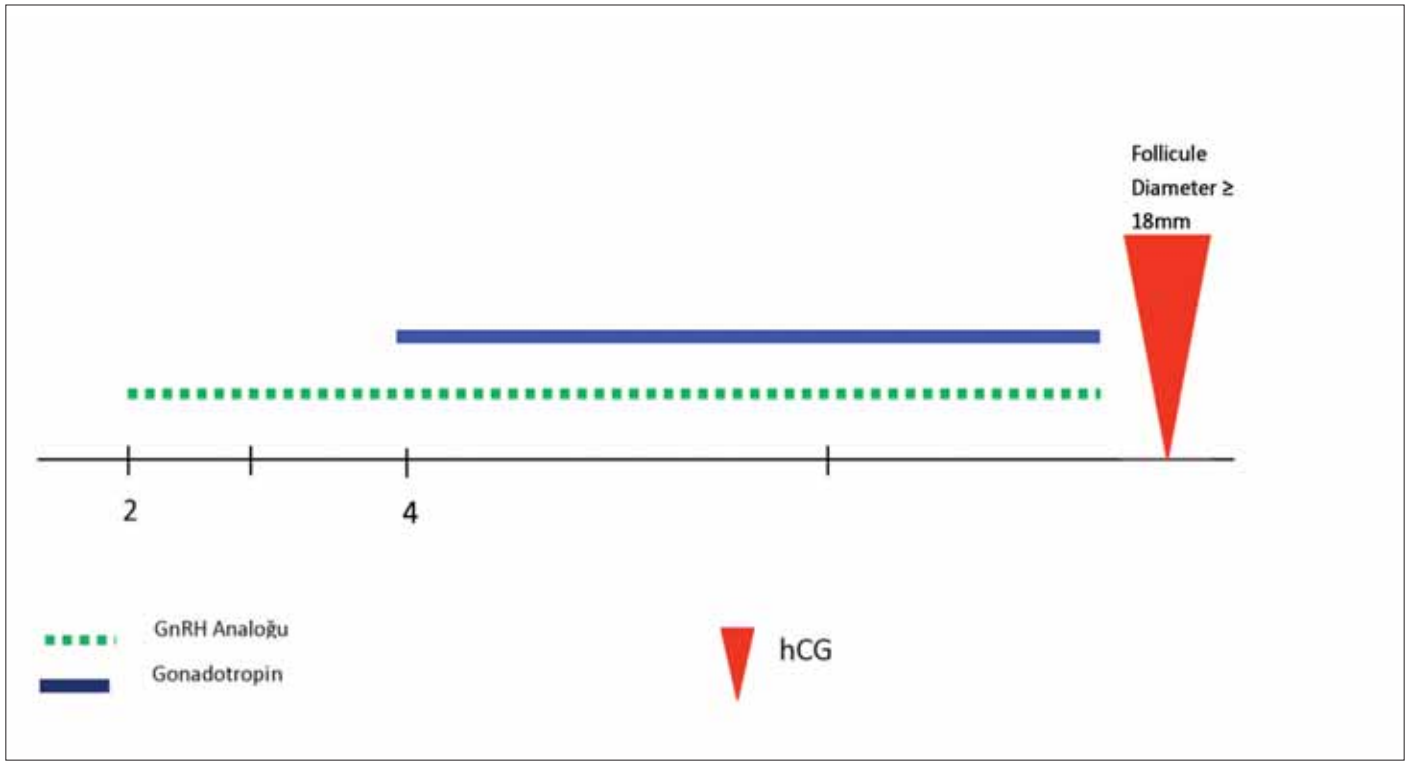

Figure 2. Schematic representation of the Microdose GnRH-a flare-up protocol

until the day of pregnancy testing and if the test was positive, progesterone treatment was continued up to 12 gestational weeks. Pregnancy tests were performed 14 days after oocyte retrieval. Clinical pregnancies were confirmed by transvaginal ultrasound examination at 4.5 weeks from oocyte retrieval with the number of gestational sacs and cardiac activity noted.
FSH was measured by a chemiluminescent immunometric assay with Immulite One, Bio-DPC, Siemens, USA. Analytical sensitivity: 0.1 mIU/ml. The inter assay and intra assay coefficients of variation were 5.6% and 3.1%.

Statistical analysis

Although the primary aim of this study was to compare the overall pregnancy rate per groups, to assess a difference in pregnancy rates between the protocols, a prior power calculation estimated that any sample size of between 160 and 348 would show a 10% difference with 80% power (α=0.05). Considering the rare occurrence of poor responders, it should take a considerably long time to be able to collect large samples in this subject, so we preferred to focus on oocyte numbers as a main outcome measure. The primary aim of this study was to compare by means of the number of mature oocytes A total sample size of 54 cases (27 for Agonist-Antagonist Group, 27 for Microdose Group) was required to detect a difference in means of 1.0 (SD=1.58) with a power of 80% at the 5% significance level using a two-sided Mann-Whitney test, assuming that the actual distribution is double exponention.
Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Whether the continuous variables were normally distributed or not were determined by using Shapiro Wilk test. Continuous variables were expressed as mean±standard deviation or median (minimum-maximum), where applicable. Nominal data were presented as the number of cases and (%). Whereas the differences between groups regarding normally distributed data were tested by Student's t test, non-normally distributed data were evaluated by Mann Whitney U test. Nominal data were analyzed by Pearson Chi-square test. A p value less than 0.05 was considered as statistically significant.

Results

A total of 82 poor responder patients underwent 78 COH-ICSI cycles. Of these patients, 41 received the ultrashort GnRH agonist/GnRH antagonist protocol and 41 received the microdose flare-up protocol. The cycle cancellation was done for two patients in the AAP (n=39) group (one due to poor folliculogenesis, and one to fertilization failure), two patients in the Microdose Group (n=39, one cycle owing to premature LH surge, one cycle owing to poor folliculogenesis). Cycle cancellation rates were similar in the groups.
The mean number of mature oocytes retrieved was similar in the two groups (7.1±4.9 in AAP Group; 7.4±6.0 in Microdose Group; p>0.05). There were no statistical differences in age, BMI, day 3 FSH and estradiol levels between the two groups. Demographic data of the patients are displayed in Table 1. There were also no statistical differences between the two groups in terms of peak E_2 level, endometrial thickness on hCG day, number of 2PN and number of embryos transferred. However, the duration of stimulation (10.51±2.4 vs. 9.05±2.61, respectively) and total consumption of the gonadoptrophin doses (3365.93±1627.59 v. 2327.02±929.46; p=0.004) were significantly higher in the AAP Group (Table 2). The rate of top-quality embryo (Grade A; at least seven cells and <10% fragmentation on day 3) transferred, fertilization rate and implantation rate per embryo were similar between the groups (Table 3). However, pregnancy rate was higher in the microdose GnRH-a flare-up protocol than in AAP, but it did not reach the significant level (19.5% vs 26.3%, respectively).

Discussion

To the best of our knowledge, this is the first study comparing the AAP with the microdose GnRH-a flare-up protocol in poor responders. In the current study, we showed that the mean number of mature oocytes retrieved were similar between two groups. The results of our study further indicated that clinical pregnancy rates were also similar between the groups.
The idea of minimizing the dose of the GnRH agonist agents created the so-called `mini' and `micro' dose flare-up GnRH

Table 1. Demographic characteristics of the patients in both groups

	Agonist-Antagonist	Microdose flare-up	p
Number of patients (n)	41	41	
Number of cycles (n)	39	39	
Age (years)	35.21±6.07	35.81±4.84	0.63
Number of patients aged >35(years)	18	21	0.39
BMI (kg/m^2)	26.69±4.20	25.93±4.53	0.52
Infertility period (years)	9.1±5.68	9.28±6.39	0.98
Day 3 FSH (mIU/mL)	10.03±8.05	7.32±2.95	0.09
Number of patients >FSH 10 (n)	13	12	0.56
Day 3 Estradiol (pgmol/L)	51.5±27.45	47.48±21.07	0.37
Cycle number	1.71±0.94	1.57±0.82	0.54

*Statistical significance was defined as p<0.05. Data were shown as mean±SD. Groups were compared using Student's t or Mann Whitney U test, where appropriate

Table 2. The ovarian stimulation cycle characteristics in both groups

Parameter	Agonist-Antagonist	Microdose flare-up	p
Days of stimulation (n)	10.51 ± 2.4	9.05 ± 2.61	< 0.05
Gonadotropin administrated (IU)	3365.93 ± 1627.59	2327.02 ± 929.46	< 0.05
Canceled cycle (n)	2	2	NS
Peak estradiol (pg/ml) on hCG day	1370.86 ± 718.64	2029.57 ± 1365.78	NS
Endometrial thickness on hCG day (mm)	9.68 ± 1.43	9.83 ± 2.47	NS
Number of oocytes retrieved (n)	7.82 ± 5.24	8.52 ± 6.38	NS
Number of mature oocytes (n)	7.16 ± 4.94	7.4 ± 6	NS
Number of 2PN	3.54 ± 3.39	4.17 ± 4.2	NS

*NS, Not significant. Statistical significance was defined as p < 0.05. Data were shown as mean ± SD. Groups were compared using Student's t or Mann Whitney U test, where appropriate

Table 3. Clinical pregnancy and implantation rates in groups

Parameter	Agonist-Antagonist	Microdose flare-up	p
Fertilization rate (%)	54	62	NS
Grade A embryo (%)	66	59	NS
Number of embryos transferred (n)	2.62 ± 1.37	3.05 ± 1.55	NS
Implantation rate (%)	7.6	8.6	NS
Clinical Pregnancy rate /cycle(%)	19.5 (8/41)	26.3 (10/38)	NS

*NS, Not significant. Statistical significance was defined as p < 0.05. Groups were compared using Student's t or Mann Whitney U test, where appropriate

agonist regimens. A microdose flare-up regimen has been proposed and used successfully in poor responders. The basic hypothesis of this approach is the administration of the minimal dose of GnRH-a necessary to induce gonadotropin release while minimizing premature ovulation. This approach takes advantage of the initial release of endogenous gonadotropins induced by low-dose GnRH-a administration in the early follicular phase, in an effort to enhance response to the subsequent administration of exogenous gonadotropins (7, 18, 20). Although this flare effect enhances follicular recruitment, it can result in premature luteinization and thus compromise the cycle (21). This approach has also some disadvantages such as increased serum LH levels, with a concomitant increase in serum progesterone and testosterone levels during the early follicular maturation (i.e., flare effect), which in turn may affect oocyte quality (11-13).

The incorporation of GnRH antagonists represents an appealing alternative to agonists in the management of the poor responder. The addition of the GnRH antagonist to stimulation protocols prevents premature LH surges, without causing suppression in the early follicular phase, a crucial time for poor-responder patients (22). The results of GnRH antagonists for poor responders indicate the possibility of reducing the amount of gonadotropins, the length of stimulation, the number of cancelled cycles, and the overall cost normally associated with the long protocol (23-27). However, the issue of the reported lower clinical pregnancy and implantation rates in the earlier studies comparing antagonist and agonist protocols is still not resolved. In the literature, there are several controlled studies comparing microdose flare and antagonist protocols and antagonist plus letrosole in the recent literature. For example, Demirol et. al. reported that the microdose flare-up protocol seems to have a better outcome in poor-responder patients, with a significantly higher mean number of mature oocytes retrieved and higher implantation rate. (28). In another study, Malmusi et al. also reported that, in terms of mature oocytes retrieved, fertilization rate, and top-quality embryos transferred in poor-responder patients, the flare-up protocol appears to be more effective than the GnRH-antagonist protocol (29). On the other hand, Kahraman et al. found that the microdose GnRH-a flare-up protocol and multiple dose GnRH antagonist protocol seem to have similar efficacy in improving treatment outcomes of poor responder patients (30).

Schoolcraft et al. also compared the efficacy of a microdose GnRH agonist flare (ML) with a GnRH antagonist/letrozole (AL) protocol in poor responders, and reported that stimulation between the microdese and antagonist-letrazol protocols were equivalent, with the exception of peak E_2 levels. However, the higher ongoing pregnancy rates and trend toward superior implantation rates would suggest that microdose represents a preferred approach for the poor responder (4). However, in another study from Yarali et al. İt was reported that, in terms of the high fertilization rate and the rate of at least one top-quality embryo transferred in the GnRH antagonist/letrozole protocol, compared with the mirodose protocol the GnRH antagonist/letrozole protocol is an effective protocol that may be used in poor ovarian responders for ICSI (31).

Although as in the above studies, several trials investigated the microdose flare and antagonist protocols or antagonist plus

letrozole protocol in poor responders, only a limited number of studies in the literature investigated combining the ultrashort GnRH agonist-antagonist protocols in poor responders (17, 19, 32). The report by Berger et al. (19), which is the first report dealing with the AAP protocol, was presented only as a meeting abstract, so no data exists concerning the stimulation characteristics of the control cycles. Similarly, Orvieto et al. (17) evaluated the role of the ultrashort GnRH-agonist flare protocol combined with the flexible multidose GnRH-antagonist protocol in patients who had responded poorly to a previous IVF attempt. In contrast to our study, their AAP protocol entailed depot analog (triptorelin 0.1 mg/day) as a GnRH-a. In addition, they did not report any information regarding the patients' previous stimulation protocols. In 2005, Erden et al. in their retrospective study, compared the Agonist-Antagonist Protocol and microdose flare-up protocols in poor responder IVF patients (32). They reported that there were higher peak estradiol levels, more mature and fertilized oocytes and higher clinical pregnancy rates in the Agonist-Antagonist Protocol. Unfortunately, this study was presented only as an oral presentation. All the above studies had found statistically significantly higher numbers of oocytes retrieved and embryos transferred in the ultrashort GnRH agonist-antagonist group. In contrast to previous studies, we did not detect any differences in terms of stimulation and reproductive outcome parameters. The small number of patients in the studies with differences in the treatment period and in different antagonist protocols may explain these discrepancies. In addition, one of the difficulties in critically evaluating various COH protocols is the lack of a single universally accepted definition of 'poor responder' (5). A variety of criteria have been used alone or in combination as inclusion criteria for proposed protocols. In our study, in contrast to the previous studies, not only the previous IVF failure but other poor response markers were also used as inclusion criteria. It is possible that results may differ with the application of more strict criteria for this patient group. However, the definitions for poor responders employed in this trial are consistent with those employed in Schoolcraft et al.'s previously published evaluation of a microdose flare-up regime (18).

In this study, the women in the ultrashort GnRH agonist/GnRH antagonist protocol had a longer treatment duration and required significantly more gonadotropin, but had the same mean number of metaphase II oocytes retrieved as did women in the microdose flare-up protocol. Thus, the follicular response was slower in the ultrashort GnRH agonist/GnRH antagonist group. Prolongation of the follicular phase in patients stimulated with rec-FSH and GnRH antagonist for IVF does not affect oocyte or embryo quality (33). In our results, the implantation and clinical pregnancy rate per cycle were also similar between groups. Differences of our study from other microdose protocols may include not using oral contraceptive (OC) pretreatment during GnRHa in the flare-up protocol. As in our previous published study, which reported that OC pretreatment plus microdose GnRHa in the flare-up protocol does not offer advantages over non-OC microdose GnRHa in the flare-up protocol among poor responder ICSI patients, we also did not use oral contraception in the microdose protocol. In our previous study, we found no significant differences between groups in the number of oocytes, peak estradiol levels, endometrial thicknesses, fertilization rates and embryo qualities. Furthermore, implantations and pregnancy rates per embryo transfer were similar. As a result of our previous study, we thought that this preference should not affect the outcomes of the microdose protocol negatively (34).

The major weakness of our study is the limited number of couples undergoing the ICSI procedures investigated. Thus, we consider that the results of this study could be significant if the number of patients per group were increased.

In conclusion, the most convenient COH protocol for poor responder patients is still unclear. According to our preliminary study, in terms of primary outcome measure, this protocol seems to be equal to the microdose protocol, but in terms of secondary outcome measures there are statistically significant differences in terms of gonadotropin consumption and duration of stimualtion in favor of the microdose flare protocol. Hence, we may consider that, in the event of high doses of gonadotrophin consumption and long duration of stimulation, AAP protocols seem to be valuable alternatives for poor responders. , This novel protocol may be offered especially to patients with a history of a failure with the microdose flare-up protocol. However, before making any recommendations; further large prospective randomized studies are needed to elucidate the exact role of the Agonist-Antagonist Protocols in poor responders.

Conflict of interest

No conflict of interest is declared by authors.

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The assessment of nuchal translucency and serum markers for down syndrome screening with ductus venosus Doppler measurements in the first trimester

Down sendromu taramasında birinci trimester nukal kalınlık ve serum belirteçlerinin duktus venozus doppler ölçümü ile değerlendirilmesi

Özlem Özer, Cenk N. Sayın, Füsun G. Varol

Department of Obstetrics and Gynecology, Faculty of Medicine, Trakya University, Edirne, Turkey

Abstract

Objective: The aim of the study was to improve nuchal translucency (NT) and serum marker Down syndrome (Tri21) screening methods by including fetal ductus venosus (DV) Doppler measurements.

Material and Methods: A total of 213 pregnant women were screened consecutively by combining maternal age, fetal NT and maternal serum pregnancy associated plasma protein A (PAPP-A) and free β-human chorionic gonadotropin (f β-HCG) values at 11-14 weeks of gestation. Also, a DV Doppler analysis was performed for the contribution to the screening for Tri21 and other fetal anomalies or adverse pregnancy outcomes.

Results: Twelve fetuses had DV PI measurements above the 95th percentile and two (17%) developed intrauterine growth retardation. DV PI values negatively correlated with birth weight ($p=0.013$, $r=0.171$). Two patients had T 21 among the study group (0.9%) with abnormal biochemical screening results. In these with Tri21, the combined test risk was above the suggested limit (>1/250). PAPP-A was <0.4 MoM in 23, and f β-HCG was >1.91 MoM in 49 patients. The rates of false positivity were 10% for PAPP-A and 22% for f β-HCG. The sensitivity, specificity, positive and negative predictive values of the combined test was 100%, 95%, 20% and 100%, respectively.

Conclusion: The combined test has high sensitivity and specificity for Tri21 detection. The addition of DV Doppler ultrasound in the first trimester might have the advantage of predicting some adverse pregnancy outcomes. However, in the Turkish population, further studies with larger numbers of patients will be needed to establish the usefulness of DV for the detection of Tri21 or the prediction of some major cardiac anomalies. (J Turkish-German Gynecol Assoc 2010; 11: 194-8)

Key words: Turkish population, Down syndrome, combined test, ductus venosus

Received: 16 October, 2010 **Accepted:** 23 October, 2010

Özet

Amaç: Down sendromu (Tri21) taramasında kullanılan nukal kalınlık (NT) ve serum belirteçlerine fetal ductus venozus (DV) Doppler ölçümü eklenmesinin katkısını incelemek.

Gereç ve Yöntemler: Antenatal muayene için başvuran 11-14 haftalık 213 ardışık gebe anne yaşı, fetal NT, anne serum "pregnancy associated plasma protein A" (PAPP-A) ve serbest beta-human koryonik gonadotropin (s β-HCG) değerleri ile tarandı. Bu gebelere ayrıca Tri21, diğer fetal anomaliler ve olumsuz perinatal sonuçların taraması amacıyla DV Doppler analizi de gerçekleştirildi.

Bulgular: On iki fetusta DV PI ölçümü hesaplanan 95. persantilin üzerindeydi ve 2 tanesinde (%17) intrauterin gelişme geriliği gelişti. DV PI değerleri doğum ağırlığı ile negatif yönde ilişkili bulundu ($p=0.013$, $r=0.171$). Çalışmadaki 213 hastadan ikisinde Tri21 saptandı. Tri21 saptanan bu hastalarda kombine test sonucu riskli (>1/250) olarak saptandı. PAPP-A 23 hastada <0.4 MoM ve s β-HCG 49 hastada >1.91 MoM olarak bulundu. PAPP-A için yanlış pozitiflik oranı %10, s β-HCG için ise %22 bulundu. Kombine testin duyarlılık, seçicilik, olumlu ve olumsuz öngörü değerleri sırasıyla %100, %95, %20 ve %100 oranında saptandı.

Sonuç: Tri21 belirlenmesinde kombine test yüksek duyarlılık ve seçiciliğe sahiptir. Birinci trimesterde DV Doppler ultrasonografisi eklenmesi bazı olumsuz gebelik sonuçlarının öngörüsünde faydalı olabilir. Ancak Türk toplumunda DV incelemesinin Tri21 belirlenmesi ve bazı kalp anomalilerinin öngörüsünde yararını ortaya koymak için daha geniş serili çalışmalara ihtiyaç vardır.

(J Turkish-German Gynecol Assoc 2010; 11: 194-8)

Anahtar kelimeler: Türk toplumu, Down sendromu, kombine test, ductus venozus

Geliş Tarihi: 16 Ekim 2010 **Kabul Tarihi:** 23 Ekim 2010

Introduction

Prenatal screening for Down syndrome (Tri21) was developed by the introduction of nuchal translucency (NT) and ultrasound to the first trimester of pregnancy. In pregnancies with fetal Tri21, low maternal serum pregnancy associated plasma protein A (PAPP-A) and elevated free β-human chorionic gonadotropin (f β-HCG) values were observed by the 1990s (1, 2). Screening for Tri21 by combining maternal age, fetal NT thickness and maternal serum f β-HCG and PAPP-A at 11-13 weeks was associated with a detection rate of about 90% for a false-positive rate of 5% (3, 4). However, since measurements of NT varied considerably between centers and clinicians, the sensitivity can be as low as 31%, thus it could hardly be reliably incorporated into the test (5). Doppler ultrasound of the ductus venosus (DV) has also been added to expert antenatal screening programs for chromo-

Address for Correspondence / Yazışma Adresi: *Doç. Dr. Cenk N. Sayın, Trakya Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, 22030 Edirne, Turkey*
Phone: +90 284 235 76 42-43008 e.mail: ncsayin@yahoo.com
doi:10.5152/jtgga.2010.36

somal abnormalities. An association between abnormal flow in the DV and fetal aneuploidy has been introduced. The use of DV velocimetry in combination with NT has been asserted as better than either test alone, since it increased the sensitivity in the detection of Tri21 (6-11). In fetuses with cardiac defects or fetal hypoxia some abnormal patterns of the "a" wave on DV, which represents atrial contraction, can be observed (12). Matias et al. analyzed fetuses at 10-14 weeks of gestation with increased NT and found that 57 of 63 had chromosomal defects, whereas only 13 out of 423 with normal chromosome had abnormal DV flow patterns (13). Likewise, in fetuses with Tri21, absence of flow or reverse flow of the "a" wave can be observed (14).
In this study, our aim was to improve Tri21 screening methods based on NT and serum markers by including fetal DV Doppler measurements.

Materials and Methods

The study was performed in Trakya University Faculty of Medicine, Department of Obstetrics&Gynecology, on 213 consecutive pregnant women aged between 18 and 43 years admitted for antenatal care at 11-14 weeks of gestation. Twins or higher order pregnancies, pregnancies ending in spontaneous abortion or with congenital anomalies detected at the first trimester and patients that did not deliver in our clinic or were lost during follow-up were excluded from the study. All patients were delivered in our department and the newborns were examined after birth for possible anomalies. in the Neonatology Department by a pediatrician The study was approved by the Ethics Committee for Human research at Trakya University, Turkey, and informed consent was obtained from the patients. The study population consisted of Turkish women living in the Trakya Region of Turkey. Gestational age was based on the last menstrual period and according to a reliable menstrual history confirmed by ultrasonography.
Age, maternal smoking habit, previous fetuses with anomalies, presence of diabetes were noted, height and weight were obtained and body mass index calculated from all women. A detailed structural survey by ultrasound (Shimadzu SDU-2200, Japan) was performed on each fetus with a 3.5 MHz transabdominal transducer. Crown rump length (CRL), NT and DV flow patterns were measured by the same clinician (OY) during periods without uterine contractions and in the absence of fetal body movements. Three measurements for NT were obtained and the highest was accepted for calculation of risk for the combined test.
The pulsatility (PI) of DV was estimated from the Doppler waveforms. The mean value assessed from five consecutive waveforms was analyzed. Color Doppler imaging was used to optimize placement of the pulsed wave Doppler gate by adjusting the velocity scale to identify area and direction of maximum blood flow. The size of the sample gate was enlarged to encompass the entire vessel, and transducer position was adjusted to eliminate aliasing, in order to minimize the Doppler angle. All measurements were obtained from the sagittal plane of the fetus. DV was identified from where it appeared from the umbilical vein and all measurements were taken from the beginning of the vessel since the flow pattern changes from the beginning to the end of DV.
Blood samples were obtained from the subjects through venipuncture to perform the PAPP-A and f β-HCG assays. Samples were assayed immediately. Serum concentrations of PAPP-A and f β-HCG levels were all analyzed by chemiluminescent immunometric assays (Immulite 2000, Diagnostic Products Co., LA, USA), following the instructions of the manufacturers. All values were calculated by multiples of median (MoM) according to gestational age. Risk analysis for trisomies was made by the computer program PRISCA version 3.4. In this first trimester biochemical tests, values <0.4 MoM for PAPP-A, and >1.91 MoM for f β-HCG were accepted as high risk for Tri21 as suggested (15). 'Screen-positive' risk for Tri21, based on combined PAPP-A, f β-HCG and NT was accepted with a cut-off ≥ 1 : 250. A second level genetic ultrasound examination was performed on all patients for anomaly screening at 18 - 23 weeks. Amniocentesis for chromosomal anomalies was carried out in women who had a high risk according to the first trimester screening or had anomalies in genetic ultrasound, as suggested (16, 17).
Data were stored and analyzed by SPSS program (Statistical Package for Social Science, release11.0; SPSS, Chicago, IL) for Windows. Kruskal-Wallis test was used for inter-group comparisons of non-normally distributed variables. Continuous variables were analyzed with student *t*-test if distributional assumptions were consistent with normality. Otherwise, we performed Mann-Whitney U tests for the parameters that were not normally distributed. Spearman and Pearson correlation analysis was used for linear correlations. A *P* value less than 0.05 was considered statistically significant.

Results

Mean±SD age, gestational age at admittance, and gestational age at delivery were 27.8±4.9 years, 12.4±0.72 and 38.1±1.5 weeks, respectively. Only 20 (9.4%) women were older than 35 years. Twenty-four women (11%) were smokers. Mean weight at delivery was 3278±445 (min. 1090, max. 4260) gr., of which 117 (56%) were boys (3345±443 gr.) and 94 (44%) were girls (3199±435 gr.). Birth weight was significantly higher in boys ($p=0.017$). Ten amniocenteses were performed in women ≥ 35 years ($n=20$) and no Tri21 syndrome was detected.
Mean CRL, NT, DV PI values were 58.5 9.1 mm, 1.16±0.3 mm and 1.05±0.13, respectively. Fetal heart rate measurements significantly changed (162±8 to 164±7.4 beats/min., $p<0.01$, $r=0.869$) after Doppler analysis. NT and DV PI measurements according to gestational age were shown in Table 1. The 95th percentile was high in 13-13.4 weeks, because there was a fetus with Tri21 with a NT value of 3.6 mm in that group. NT measurement increased significantly with the CRL value ($p<0.001$, $r=0.457$). DV PI values showed a plateau during 11th and 14th weeks of gestation ($p>0.05$, $r=0.009$). Twelve fetuses had DV PI measurements above the 95th percentile and two (2/12, 17%) developed intrauterine growth retardation (IUGR) in the third trimester. Also, DV PI values negatively correlated with birth weight ($p=0.013$, $r=0.171$). Of 213 women detected, 2 had Tri21 (Table 2). In these pregnancies with Tri21, the combined test risk was above the suggested limit (>1/250). In the first , no absence or reversal of flow during atrial contraction was observed, but DV PI measurement could not be obtained in the second case.
In all patients, mean±SD values for PAPP-A and f β-HCG were 0.82±0.41 (min.:0.18, max.: 2.4) MoM and 1.61±1.31 (min.:0.11, max.: 8.74) MoM, respectively. PAPP-A values decreased ($p>0.05$, $r=0.032$) and f β-HCG increased ($p>0.05$, $r=0.003$)

nonsignificantly with the development of pregnancy (Table 3). Ten women had PAPP-A values under the 5th percentile, whereas 9 had f β-HCG above the 95th percentile. Smoking habits and sex did not correlate with PAPP-A and f β-HCG values (p>0.05). PAPP-A was <0.4 MoM in 23, and f β-HCG was >1.91 MoM in 49 patients. The rates of false positivity were 10% for PAPP-A and 22% for f β-HCG. In patients who had PAPP-A <0.4 MoM, 2 had Tri21 syndrome detected by amniocentesis and were terminated, whereas 17 (74%) had uneventful pregnancy outcomes. One patient had pericentric translocation on the 9th chromosome which had no effect on phenotype, 2 had IUGR and one developed gestational hypertension. However, in another 5 patients who developed IUGR, PAPP-A values were >0.4 MoM. In patients who had f β-HCG >1.91 MoM, one had had Tri21 and was terminated, 37 (75%) had uneventful pregnancy outcomes.

Table 1. Percentiles for fetal nuchal translucency and for ductus venosus pulsatility index

Gestational weeks	NT				DV		
	N	5th p	50th p	95th p	5th p	50th p	95th p
11-11.4	22	0.72	0.83	1.56	0.66	1.02	1.27
11.5-11.9	37	0.73	1.04	1.50	0.78	1.08	1.23
12-12.4	53	0.76	1.10	1.48	0.83	1.03	1.26
12.5-12.9	61	0.91	1.25	1.64	0.79	1.06	1.26
13-13.4	27	0.85	1.29	2.80	0.88	1.13	1.28
13.5-14	13	0.86	1.42	1.64	0.77	1.08	1.26

DV: Ductus venosus; NT: Nuchal translucency; p: Percentile

Table 2. Calculated parameters in pregnancies with Down syndrome

Case	Age	CRL (mm)	NT (mm)	PAPP-A (MoM)	f β-HCG (MoM)	DV PI	Combined test risk
1	27	66.9	3.6	0.39	2.31	0.98	1/50
2	26	66.7	1.6	0.2	1.7	-	1/114

CRL: Cranium rump length; DV PI: Ductus venosus pulsatility index; f β-HCG: free β human chorionic gonadotropin; NT: Nuchal translucency; PAPP-A: Pregnancy associated protein A

Table 3. Calculated multiples of median (MoM) values for pregnancy associated protein A (PAPP-A) and free β human chorionic gonadotropin (f β-HCG) in the whole group

Gestational weeks	PAPP-A				f β-HCG		
	N	5th p	50th p	95th p	5th p	50th p	95th p
11-11.4	22	0.42	0.87	2.16	0.26	1.22	5.04
11.5-11.9	37	0.31	0.88	1.79	0.41	1.14	6.88
12-12.4	53	0.34	0.75	1.55	0.48	1.33	3.15
12.5-12.9	61	0.22	0.70	1.91	0.52	1.35	5.61
13-13.4	27	0.24	0.66	1.25	0.55	1.28	5.09
13.5-14	13	0.29	0.60	1.33	0.67	1.22	2.81

f β-HCG: free β human chorionic gonadotropin; PAPP-A: Pregnancy associated protein A; p: Percentile

Five (10%) had IUGR (one of which had also PAPP-A <0.4 MoM), one had coarctation of the aorta, 2 developed gestational diabetes, 1 preeclampsia, 2 threatened preterm labor.

Ten patients (4.7%) had ahigh risk for Tri21 according to the combined test (risk ≥1/250) and 2 fetuses had Tri21 detected by amniocentesis. Two women had a high risk on combined test, but did not accept amniocentesis. However, neither had adverse pregnancy outcomes nor any fetal anomaly detected at birth. The sensitivity, specificity, positive and negative predictive values of the combined test was 100%, 95%, 20% and 100%, respectively.

Amniocentesis was performed in 21 patients (9.8%). Indications were maternal age (n=10), high risk in screening test (n=8), findings on genetic ultrasound (n=2) and history of recurrent abortion (n=1).

Two cardiac anomalies were observed in the study group. One had coarctation of the aorta and the other had secundum type atrial septal defect with duodenal atresia. Both fetuses had normal phenotype and normal NT, PAPP-A and DV PI values, whereas one had a f β-HCG level above the 95th percentile. However, these two abnormalities could not be detected by the II. level ultrasound.

Discussion

The most sensitive method for Tri21 screening was introduced as the combination of maternal age, serum screening for PAPP-A, f β-HCG with fetal NT with 90% detection and 5% false positive rate (18). Nearly 70% of fetuses with Tri21 are born of mothers <35 years-old (19). Similarly, our two patients with Tri21 fetuses were below age 35. Also, not only did the amniocentesis reveal no Tri21, no case was found in patients who did not accept amniocentesis in women >35 years in our study. In a study evaluating NT in a low risk population of 1473 women, only 67% of fetuses with Tri21 would have been detected with a 24% invasive testing rate, if the only screening criteria was maternal age. If NT measurement had been added to the screening policy, the sensitivity would have been 100% with a 19.1% invasive testing rate (20). In the study by Snijders et al. (3) the estimated Tri21 risk, from maternal age and fetal NT, was 1 in ≥ 300 in 7907 (8.3%) of 95476 normal pregnancies, but in 268 (82.2%) of 326 with Tri21. The number of invasive procedures performed to detect one Tri21 was calculated as 30. In line with that study, others observed that the main benefit of the addition of first trimester NT measurements to the risk screening protocol was a very high detection rate with a moderate false-positive rate (21). Different studies have used the combined test for the screening of chromosomal anomalies in low and high risk populations, or used pooled data with patients with Tri21 and reported a detection rate of about 80% (18, 22-24). The detection rate of Tri 21 with only NT measurement was reported as 77%, with a 5% false positive rate (3). However, biochemistry tests alone, consisting of PAPP-A and f β-HCG, detected about 60% of the cases with 5% false positive rate (5, 24). For screening purposes, a cut-off threshold value for NT of ≥3 mm gave a sensitivity ≥50%, a false positive rate <5% and a positive predictive value >1% for chromosomal anomalies (25). In our study, only one case had NT> 3 mm. If only NT was considered for screening of Tri21, the sensitivity would have been 50%, specificity 100%, positive and negative predic-

tive values 100% and 99%. Likewise, according to our results, the sensitivity, specificity and positive and negative predictive values of the combined test were 100%, 95%, 20% and 100%, respectively However, these high rates seem to result from the limited number of patients in our study.

The effect of smoking on PAPP-A and f β-HCG values has been defined (26). We did not find any effect of smoking on biochemical markers of the combined test. Smoking reduced serum PAPP-A and f β-HCG levels in women who smoked ≥5 cigarettes a day in a Turkish population (27). However, it was demonstrated that the effect of adjusting for smoking on the combined test is small, with an estimate of less than half percentage point increase in the detection rate (28). Smoking decreases trophoblast invasion and proliferation (29, 30). So the clinical effect on placental function may be obvious by IUGR. However, in our study smoking neither decreased PAPP-A nor had a relationship with the development of IUGR. Besides, out of 213 patients, 23 had PAPP-A < 0.4 MoM; 2 had Tri21 and 2 (9.5%) developed IUGR. In the other 5 fetuses that developed IUGR, PAPP-A values were within normal limits. Thus, PAPP-A, the marker for placental function, has not been shown to predict IUGR.

The reference range for DV PI has been shown to have a biphasic pattern; with an initial non-significant increase up to a CRL of 63 mm and a fall thereafter, as in our study (31). Doppler studies of the DV have been applied as an adjunct to NT measurements. In 1998, increased DV PI values above the 95th percentile have been observed in 73% of the fetuses with Tri 21 between the 10th and 18th weeks (14). In a further study, the same investigators found that the median DV PI in Tri21 was 1.70 times higher than in unaffected pregnancies in women between 10 and 14 weeks. Also, the addition of PI to NT alone will increase the detection rate from 76 to 85%, and, combined with serum markers, from 88 to 92% (8). Murta et al. analyzed absent or reversed flow during atrial contraction in 93.1% of chromosomally abnormal fetuses (32). However, abnormal ductal blood flow was observed in 5.2% of euploid fetuses and 70.8% of fetuses with Tri21 (6). Inclusion of DV flow in first-trimester screening by maternal age, fetal NT and maternal serum free β-HCG and PAPP-A would detect about 96% of trisomy 21 fetuses at a false-positive rate of about 2.5% (6). Assessment of DV flow is time consuming and requires appropriately trained sonographers, and sonographers with extensive experience in the first trimester scan require an average of 80 examinations to achieve this level of competence (33). The alternative strategy is to reserve this examination for the subgroup of pregnancies with an intermediate risk (between one in 51 and one in 1000) after combined fetal NT, FHR, free β-HCG and PAPPA screening. Even when NT is normal, reverse flow during atrial contraction in DV has a strong association which predicts adverse outcome such as IUGR, cardiovascular abnormalities and renal abnormalities (34). Although we could not measure the flow pattern in a case with Tri21 in our study, the addition of DV Doppler to the combined test did not improve the detection of Tri21 or the development of IUGR and cardiovascular abnormalities. In line with our results, some authors observed a lack of correlation of DV PI values with NT or with serum markers (8, 10), but the association between reversed a-wave on DV and increased NT may be explained by the coincidence of cardiac defects or transient cardiac dysfunction (6). Abnormal DV flow may result from abnormal cardiac preload, cardiac compliance or afterload. When there is an overlap in the pathophysiology leading to an increased NT and abnormal DV blood flow, their combination improved the sensitivity and specificity of aneuploidy prediction (13).

Matias et al. (13) observed significantly higher DV PI values in Tri21,18,13,Turner syndrome and triploidy, but multivariate regression analysis demonstrated that only the height of the a wave provided a significant independent contribution in distinguishing between the chromosomally normal and abnormal groups. We did not find any absent or reverse flow during atrial contraction on DV Doppler, but 12 fetuses had DV PI >95th percentile and 2 (17%) developed IUGR in the third trimester, while DV PI negatively correlated with birth weight in our study. The first case with Tri21 and the other two cases with cardiac defects without chromosomal anomaly also revealed normal flow patterns. Favre et al. (35) observed abnormal flow and increased NT in 36% of fetuses with a normal chromosome but a major cardiac defect, and the authors have concluded that in chromosomally normal fetuses with increased NT, assessment of DV blood flow velocimetry could improve the predictive capacity for an underlying major cardiac defect. However, we could not find any pathologic pattern of flow in DV in our two cases.

In conclusion, the combined test has a distinctive effect on Down syndrome detection with high sensitivity and specificity. The addition , DV Doppler ultrasound might have the advantage of predicting some adverse pregnancy outcomes. However, further studies in the Turkish population will be needed to rectify these screening tests; in the current study we could not establish the usefulness of DV Doppler analysis for the detection of Tri21 or the prediction of some major cardiac anomalies.

Conflict of interest
None declared.

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Performance of MLPA as a screening method for aneuploidy in uncultured amniocytes

Anöploidilerin kültür edilmemiş amniyositlerde multiplex ligation dependent amplification (MLPA) yöntemi ile saptanması

Hüseyin Yurdakul[1], Beyhan Durak[1], Muhammed Hamza Müslümanoğlu[1], Muhsin Özdemir[1], Oğuz Çilingir[1], Turgay Şener[2], Sevilhan Artan[1]

[1]Department of Medical Genetics, School of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey.

[2]Department of Obstetrics and Gynecology, School of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

Abstract

Objective: To test whether the Multiplex Ligation-dependent Probe Amplification (MLPA) technique can be used as a screening test for rapid diagnosis of aneuploidies in uncultured amniocentesis.

Material and Methods: In this prospective blind study, MLPA with chromosomes 13,18,21,X and Y specific probe mixes was performed in 500 amniotic fluid samples. Chromosome copy numbers were determined by analyzing size and peak area for each MLPA probe. Results were compared with those of karyotyping/FISH.

Results: Conclusive test results were obtained in 98% of the samples, whereas 10 were inconclusive. In all conclusive tests, the MLPA results were concordant with that of cytogenetic and/or FISH analyses. There were no false-positive results. A case with 69,XXX triploidy could not be diagnosed by MLPA. In total, 28 aneuploidies were diagnosed. There were no false-positive results. The performance of each probe was determined.

Conclusion: MLPA is a rapid, simple and reliable assay for aneuploidy screening in uncultured amniocytes.

(J Turkish-German Gynecol Assoc 2010; 11: 199-203)

Key words: MLPA, prenatal screening, common aneuploidies, uncultured amniocytes

Received: 5 November, 2010 **Accepted:** 14 November, 2010

Özet

Amaç: MLPA tekniği ile prenatal dönem anöploidi tanısı yeni, alternatif bir metoddur. Çalışmamızda bu yeni tekniğin prenatal tanı testi olarak rutinde kullanılabilirliğinin sınanması, tekniğin sensivite, spesivite ve test başarısızlık oranlarının saptanması ve bu yeni yöntemin rutinde kullanılan diğer anöploidi tanı yöntemlerine göre avantaj ve dezavantajlarının belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Toplam 500 hastanın amniyon sıvısında MLPA tekniği ile 13., 18., 21., X ve Y kromozomları için doz tayini yapılmıştır. MLPA tekniği ile saptanan sonuçlar, bu hastalara ait diğer rutin yöntemlerle saptanan sonuçlar ile karşılaştırılmıştır.

Bulgular: Tekniğin anöploidi tanısınındaki sensivitesi %100, spesivitesi %100 ve test başarısızlık oranı %4 olarak saptanmıştır. 69,XXX karyotipli örneğimizde MLPA tekniği ile doğru sonuç alınamamıştır.

Sonuç: MLPA te kniği ile prenatal tanıda anöpoidi tayininin pratik, hızlı ve güvenilir şekilde yapılabileceği düşünülmüştür.

(J Turkish-German Gynecol Assoc 2010; 11: 199-203)

Anahtar kelimeler: MLPA, prenatal tanı, anöploidi, kültüre edilmemiş amniyositler

Geliş Tarihi: 05 Kasım 2010 **Kabul Tarihi:** 14 Kasım 2010

Introduction

Prenatal diagnosis for genetic disorders was first carried out in the 1970s, and since then the most common indication for prenatal diagnosis remains an increased risk of having a child with trisomy syndromes of chromosomes 21,13,18 and sex chromosome aneuploidies. They account for 60-80% of abnormal fetal karyotypes detected in amniotic fluid cells (1). Fetal karyotyping has been the gold standard for diagnostic testing for over 30 years and no new technology could be proven usable for the detection of numerical and/or structural abnormalities for all chromosomes. However, a number of molecular methods based on uncultured fetal cells have been developed to reduce the waiting time related with prenatal chromosome analysis. Molecular methods including FISH and multiplex quantitative fluorescence-PCR (QF-PCR) are now in common practice for the rapid prenatal diagnosis of the most prevalent chromosome abnormalities (2, 3). These technologies importantly decrease the reporting times from 2-3 weeks to 1-2 days (4-6). Although they are informative for only commonly seen aneuploidies, such a rapid result is important in cases of abnormal US findings or for obstetric managements, and is valuable for relieving parental stress during the necessary culture period.

Recently, a new technique, Multiplex Ligation dependent Probe Amplification (MLPA), has emerged for the relative quantification of about 40 different DNA sequences in a single reaction. It was first described in 2002 and it has been shown to have many potential applications in diagnostic cytogenetic and molecular genetics (7). A MLPA kit for rapid aneuploidy detection is commercially available. The experiences in prenatal samples using MLPA is promising, but further studies

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Hüseyin Yurdakul, Küçük Ihsaniye Mah. Vatan Cad. No: 45/b 42060 Selçuklu, Konya, Turkey*
Phone: +90 332 321 15 22 e.mail: huseyin.yurdakul@genetikon.com
doi:10.5152/jtgga.2010.37

need to be reported to know the limitations and performance of the MLPA tests. In this prospective blind study, we present the results of 500 consecutive amniocentesis samples analyzed by computer assisted MLPA analysis. The sensitivity and specifity percentages of the technique and each of the probes were addressed in the study.

Materials and Methods

In this prospective blind study, a total of 500 amniotic samples were referred to the cytogenetics section of the Department for karyotyping. Referral reasons covered all the prenatal diagnosis indications including maternal age (≥35), increased Down Syndrome risk based on maternal serum screening and/or nuchal thickness measurement, ultrasound detected abnormalities or anxiety. The first 2ml of amniotic fluid drawn was discarded because of maternal cell contamination. Usually, 15-20 ml of amniotic fluid samples were obtained and 2 ml was taken for MLPA testing. Blood contaminated samples were excluded. Of all samples, 450 (89%) were between 15 and 18 weeks whereas 80 were between 24 and 30 weeks.
G-banding analysis and direct-FISH analysis by using AneuVision Probe Set (Vysis) were carried out by using standard techniques. Since the aim of this study was to test MLPA (SALSA MLPA kit P095 Aneuploidy Lot 0307, 1206, 1106, 0505) analysis prospectively, the MLPA data were interpreted without knowing FISH and/or karyotyping results.

Sample preperation and analysis

DNA from 2 μl amniotic fluid was isolated by using QIAamp kit (Qiagen) according to the manufacturer's instructions. In total, 45-150 ng DNA was used in the MLPA protocol. The MLPA assay was performed according to the manufacturer's protocol with small modifications. Briefly, 5μl of lysate were denaturated for 5 min at 98^{0}C, and then 3 μl probe mix were added and the mix was heated at 950C for 1 min and incubated at 60^{0}C overnight (16 hours). By using mineral oil, the problems arising from evaporation were solved.
The ligation was performed at 540C for 15 min by adding 32μl heat-stable ligase-65 enzyme into the hybridization product. The reaction mix including the 10μl ligation mix was preheated at 950C for one minute, followed by 35 cycles (30 sec at 950C, 30 sec at 60^{0}C and 60 sec at 72^{0}C). A measure of 2 μl PCR product was analyzed by capillary electrophoresis on an ABI Prism 310 Genetic Analyzer with Rox-500 size standards. DNA samples from three males and three females were spontaneously used as external normal controls.

MLPA data analysis

By visual analysis of peak profiles, test results were defined as conclusive if MLPA quality control fragments showing sufficient genomic DNA was present in the mixture. Genescan 3.7 and genotyper 3.6 software were used in the analysis of size and peak area for each MLPA probe and the data were exported to a Microsoft Excel based Coffalyser v1.4 program. For quantification purposes, the relative peak area for each probe was calculated as a fraction of the total sum of peak areas in a given sample. Each autosomal peak fraction was divided by the median peak fractions of that locus for all samples in that reaction.
The relative probe signal values between 0.7 and 1.3 were defined as normal. If the value of target sequence was lower than 0.7, it was defined as monosomy, whereas trisomy was defined if the value is ≥1.3.

Results

The MLPA analyses were performed in 500 amniotic fluid samples. Conclusive test results were obtained in 98% of the samples, whereas 10 samples were "inconclusive". The internal MLPA quality control fragments indicated an insufficient amount of genomic DNA in these 10 samples. However, no correlation was determined between the failure of MLPA analysis and gestational age at sampling. In all conclusive tests, the MLPA test for chromosomes 13, 18 and 21 was concordant with that of cytogenetic and/or FISH analyses. The criterion in the trisomy diagnosis was that at least four of eight chromosome-specific probes should have a relative probe signal higher than 1.3. By using this criterion, autosomal trisomy diagnosis was revealed in 24 samples (trisomy 21: 18 samples, trisomy 18: 4 samples and trisomy 13: 2 samples).
In the fetal sex determination, the presence of relative probe signals for X chromosome and Y chromosome specific probes were diagnosed as male, whereas the samples without Y chromosome specific signal but with X chromosome specific probe signals were diagnosed as female. All fetal sex results were consistent with the karyotyped sexes. In two cases, although there were no Y chromosome specific signals, relative probe signals specific to X chromosome were <1.3 in the range from 0.910 to 1.230. These two cases were diagnosed as monosomy X and the results were confirmed by the cytogenetic analysis. In one case, not only were there higher X chromosome specific signals in the ranges from 1.350 to 2.00, but also all Y chromosome specific signals (1.08-1.100) were seen and therefore the gonosomal chromosome constitution of the case was diagnosed as XXY. The result was in accordance with the fetal karyotype (47, XXY). The diagnosis of the other case was XXX since the relative signal ratio of all eight X chromosome specific probes were ≥ 2.0 (ranges in between 2.00 and 3.170).
Although the sex chromosome constitution of the case was revealed as XX by the MLPA, the karyotype of the fetus was 69, XXX triploidy. The triploidy could not be diagnosed by the MLPA. Neither autosomal nor sex chromosomes specific probes showed higher relative probe signals. As seen in "Table 1", the higher (≥1.3) relative probe signal ratio was only seen in the ABCC4 probe specific to chromosome 13, but no higher ratio was determined in the other 23 autosomal specific probe signals.
In the evaluation of the performance of the MLPA in aneuploidy screening, the sensitivity and specifity of the test were determined as 97% and 100%, respectively on the basis of 490 samples with conclusive results. As seen in "Table 2", in a trisomy diagnosis of either chromosome 13, 18 or 21, almost all chromosome-specific probes have a relative probe signal >1.3. Besides, in the diagnosis of sex chromosome aneuploidies, all eight X chromosome-specific probes and four Y chromosome specific probes allowed a correct diagnosis "Table 3". The sensitivity and false-positive rates for all autosomal trisomy probes were determined on the basis of the 490 samples with conclusive results , "Table 4". While only 8 of 24 autosomal specific

Table 1. Relative probe signals in a case with 69,XXX karyotype

Probe Name	Chromosome	Length PCR	Ratio
SIM2	21q22.2	136	0.840
MADH4	18q21.1	142	0.910
ABCC4	13q32	148	1.390
AR	Xq11.2	154	1.480
SRY	Yp11.3	160	0.000
NCAM2	21q21.1	166	1.14
PMAIP1	18q21	172	1.05
CCNA1	13q12.3	178	0.700
FACL4	Xq23	184	1.660
SRY	Yp11.3	193	0.000
USP25	21q11.2	202	1.080
SS18	18q11.2	211	0.730
RB1	13q14.3	220	0.890
ARX	Xp22.1	229	1.410
UTY	Yq11	238	0.000
STCH	21q11	247	0.870
NFATC1	18q23	256	0.940
DACH	13q21.3	265	1.06
TM4SF2	Xp11.4	274	1.550
ZFY	Yp11.3	283	0.00
SOD1	21q22.1	292	0.950
TYMS	18p11.3	301	0.890
P85SPR	13q34	310	1.010
L1CAM	Xq28	319	1.600
APP	21q21.3	337	1.260
SERPINB2	18q21.3	346	1.12
BRCA2	13q12.3	355	1.16
RPS6KA3	Xp22.2	364	1.210
TFF1	21q22.3	382	1.110
SS18	18q11.2	391	0.780
DLEU1	13q14.3	400	0.82
PDCD8	Xq25	409	1.600
TIAM1	21q22.1	427	1.000
MC2R	18p11.2	436	0.95
ING1	13q34	445	1.210
DMD	Xp21.2	454	1.530

probes have a sensitivity lower than 100%, the false-positive rate for all probes is below 0.1%. The sensitivity percentage of two chromosome 13 specific probes (85SPR and BRCA2) was 50% but their specifity was100%. The highest false-positive rate was seen in ING1 chromosome 13 specific probe, the others were below 0.1%. The sensitivity rates of X chromosome-specific probes were 100%. However, the false-positive percentages of two X chromosome specific probes (AR and L1CAM) were higher compared to that of autosomal probes "Table 4".

Since it is a screening method for the detection of copy number alterations of chromosomes 13, 18, 21, X and Y, the structural aberrations of these chromosomes and aneuploidies other than these chromosomes could not be detected by this approach. In the clinical series of this study, a fetus with a balanced t(21;21) translocation and two fetuses with structural chromosome aberrations could be diagnosed by karyotyping.

Discussion

MLPA is a rapid technique for prenatal aneuploidy detection in a routine diagnostic laboratory. This is the first study in Turkey related to the data of MLPA used in a clinical series of 500 amniocentesis samples. Although the samples obtained from the 15th week to 30th week of gestation were analyzed, conclusive results were obtained in 98% of the samples and therefore the results showed that the MLPA test is usable until late pregnancy. Inconclusive results were obtained in 10 samples because of insufficient amount of DNA. However, no correlation was seen between the failure of MLPA tests and gestational age at sampling, but the cell content of the sample was an important factor for a reliable MLPA test. In six of these samples, the cell content of the fluid was significantly lower and there were some difficulties in karyotyping these samples, as well. The MLPA probe mix used in this study included four DQ (DNA Quantity) control fragments. These short fragments (in range 64-82 nt long) are very informative since they give off a clear warning signal if the amount of sample DNA is lower than the amount of DNA required for a reliable MLPA test (8). The amplification products of the DQ fragments are only visible when little or no DNA is present, and even when the ligation did not occur. Ten samples with inconclusive results in the present study showed the amplified DQ fragments. Our experiences showed that 2ml of amniotic fluid is sufficient to perform a conclusive test, but the cell content of the sample is becoming an important factor in the reliability of the test.

In the present study, the MLPA-diagnosed trisomic fetuses and fetuses with X chromosomal aneuploidies were confirmed by the cytogenetic and/or direct FISH analyses. However, a fetus with triploidy could not be diagnosed by MLPA but was determined by direct-FISH analysis in a 24h duration test. The inability to detectpolyploidy is one of the main limitations of the MLPA assay and this has also been reported previously (9-13).

If the sensitivity and specifity of the probes were evaluated individually, our experiences showed that most of the probes had 100% sensitivity. The lowest sensitivity rate was 50% seen in the P85SPR probe specific to chromosome 13 "Table 4". The probes TYMS and SS18 specific to chromosome 18 had 75% sensitivity. However, the specificity of these probes was 100% on the basis of 490 samples with conclusive result. The false-positive rate of all probes was below 0.1%, but X chromosomal probes AR and L1CAM had higher false-positive rates than the other X-chromosome and autosome specific probes "Table 4". The high false-positive rate for X chromosomal specific probe

Table 2. Relative probe signals in fetuses with trisomy 13, 18 and 21

Tri-13 Probes	1234	1350	Tri-18 probes	1506	1631	1041	1640											
ABCC4	1.620	1.360	MADH4	1.670	1.790	1.370	1.600											
CCNA1	1.640	1.720	PMAIP1	1.50	1.53	1.47	1.38											
RB1	1.640	1.480	SS18	1.40	1.35	1.410	1.360											
DACH	1.36	1.39	NFATC1	1.310	1.350	1.410	1.480											
P 85SPR	1.460	1.290	TYMS	1.05	1.360	1.460	1.360											
BRCA2	1.48	1.284	SERPINB2	1.32	1.43	1.36	1.40											
DLEU1	1.40	1.39	SS18	1.400	1.190	1.310	1.600											
ING1	1.780	1.640	MCZR	1.36	1.31	1.43	1.38											
Tri-21 Probes	**803**	**811**	**1128**	**1415**	**1868**	**1591**	**1770**	**1864**	**1499**	**1948**	**1954**	**1014**	**1316**	**1358**	**1367**	**1527**	**1670**	**1888**
SIM2	1.57	1.420	1.380	1.800	1.340	1.400	1.350	1.340	1.340	1.380	1.40	1.50	1.40	1.42	1.56	1.50	1.40	1.36
NCAM2	1.74	1.47	1.37	1.70	1.92	1.52	1.40	1.42	1.92	1.37	1.82	1.64	1.33	1.59	1.54	1.39	1.46	1.32
4SP25	1.590	1.460	1.360	1.60	1.60	1.360	1.460	1.850	1.600	1.360	1.480	1.430	1.310	1.390	1.340	1.480	1.340	1.310
STCH	1.600	1.290	1.400	1.830	1.32	1.580	1.390	1.420	1.370	1.090	1.370	1.310	1.360	1.420	1.480	1.210	1.340	1.320
SOO1	1.610	1.320	1.420	1.420	1.35	1.500	1.50	1.200	1.560	1.520	1.560	1.830	1.340	1.400	1.340	1.440	1.340	1.460
APP	1.700	1.430	1.330	1.530	1.430	1.350	1.530	1.42	1.340	1.300	1.340	1.620	1.340	1.600	1.260	1.360	1.400	1.380
TFF1	1.870	1.320	1.520	1.420	1.510	1.390	1.450	1.38	1.800	1.420	1.800	1.410	1.480	1.450	1.380	1.40	1.480	1.380
TIAM1	1.450	1.500	1.450	1.450	1.330	1.500	1.530	1.42	1.380	1.420	1.380	1.380	1.390	1.190	1.450	1.520	1.500	1.420

Table 3. Relative probe signals in fetuses with sex chromosomal aneuploidies

		Monosomy X		XXY	XXX
Probes	**Chromosome**	**1788**	**1953**	**1778**	**1003**
AR	Xq11.2	1.030	0.980	1.770	2.140
SRY	Yp11.3	0.000	0.000	1.040	0.000
FACL4	Xq23	1.080	1.027	1.490	3.170
SRY	Yp11.3	0.000	0.000	1.100	0.000
ARX	Xp22.1	1.010	1.070	1.430	3.050
UTY	Yq11	0.000	0.000	1.06	0.000
TM4SF2	Xp11.4	1.230	0.890	2.000	2.570
ZFY	Yp11.3	0.000	0.000	1.08	0.000
L1CAM	Xq28	1.000	1.030	1.760	2.000
RPS6KA3	Xp22.2	0.880	1.040	1.350	2.890
PDCD8	Xq25	0.930	1.000	1.970	2.840
DMD	Xp21.2	0.910	0.920	1.350	2.040

AR has also been reported previously (10). These unexpected false-positive data might be due to recently detected large-scale copy-number variations (LCV) or copy-number polymorphisms (CNP) spanning from several kilobases to megabase pairs of DNA (14-17). However, population–specific variations might also be involved in these false-positive results. Mutations or polymorphisms very close to the probe ligation site may cause a reduced peak area. In MLPA, amplification of probes by PCR depends on the presence of small specific target sequences in the sample. Nucleotide mismatches at the probe binding site prevent probe hybridization and ligation and therefore single base changes may result in deletions (7, 18). Therefore, in these variations, the relative signal ratios of the other probes specific to the related chromosome should be analyzed in detail.

The widely diverging sensitivity of the MLPA probes in aneuploidy screening has been discussed in previous studies (7, 10, 19). Slater et al. (19) reported false-negative results but they did not document the probes, whereas the false-positive rate in the study of Hochstenbach et al. (10) was between 0.0 % and 4.2% and they reported that only a few probes have 100% sensitivity. The differences might also be due to the differences in probe mixtures, since the SALSA P095 probe mix used in this study is an improved version of the old SALSA MLPA P001 probe mix and it has been mentioned in the MRC-Holland page (8) that the new version is less sensitive to variations in the quality of DNA.

In conclusion, the high sensitivity and specifity rates and low failure rate showed that the MLPA assay can be used as a rapid aneuploidy screening test in uncultured amniocytes. The test is inexpensive and the result can be revealed in 2-3 days,,which is very helpful for parental anxiety. However, the inability of the test to detect structural chromosome abnormalities, chromosome aneuploidies other than common chromosome syndromes and the mosaic status of fetus must always be taken into consideration. Because of these limitations, we suggested that the MLPA assay can be performed in clinical diagnostic laboratories together with fetal karyotyping.

Conflict of interest

No conflict of interest is declared by authors.

Table 4. Performance of probes in detection of autosomal and sex chromosomal aneuploidies

Tri-13 Probes	Sensitivity	False-positive	Tri-18 probes	Sensitivity	False-positive	Tri-21 probes	Sensitivity	False-positive
ABCC4	100	0.00	MADH4	100	0.04	SIM2	100	0.01
CCNA1	100	0.07	PMAIP1	100	0.00	NCAM2	100	0.00
RB1	100	0.00	SS18	100	0.08	4SP25	100	0.02
DACH	100	0.1	NFATC1	100	0.02	STCH	85.7	0.06
P85SPR	50	0.00	TYMS	75	0.09	SOO1	95.2	0.00
BRCA2	50	0.00	SERPINB2	100	0.00	APP	95.2	0.08
DLEU1	100	0.00	SS18	75	0.00	TFF1	100	0.00
ING1	100	0.14	MCZR	100	0.00	TIAM1	95.2	0.09
X chromosome Specific Probes	**45,X Sensitivity**	**False-positive**	**XXY Sensitivity**	**False-positive**	**XXX Sensitivity**	**False-positive**		
AR	100	0.00	100	0.02	100	0.5		
FACL4	100	0.08	100	0.00	100	0.00		
ARX	100	0.03	100	0.00	100	0.02		
TM4SF2	100	0.00	100	0.00	100	0.03		
L1CAM	100	0.00	100	0.00	100	0.4		
RPS6KA3	100	0.02	100	0.00	100	0.00		
PDCD8	100	0.00	100	0.00	100	0.00		
DMD	100	0.00	100	0.09	100	0.02		

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Is mifepristone 100mg an effective alternative to standard dose for medical abortion

Tıbbi abortus için 100 mg mifepriston standart doza etkili bir alternatif midir?

Anupama Goel, Sandhya Mittal, Bk Taneja, Manisha Singhal

Department of Gynaecology, Mmimsr, Mullana, Ambala, Haryana, India

Abstract

Objective: To study the efficacy of a low dose of mifepristone (100 mg) in combination with misoprostol, in women undergoing medical termination of pregnancy up to gestation of 49 days.

Material and Methods: A prospective study was performed in 50 women (mean age 26.54 ± 3.68 years) with single intrauterine pregnancy of up to 49 days of gestation, presenting to our institution between November 2007 and October 2009. 100 mg mifepristone was given orally, followed 24 hours later by 400 micrograms misoprostol vaginally. Misoprostol 400 micrograms was repeated vaginally on the third day if indicated. The primary outcome of complete abortion rate and secondary outcomes of induction-abortion interval and adverse effects, especially bleeding, were assessed.

Results: Mean period of gestation was 38.74 ± 3.90 days. None of the women expelled the products of conception before misoprostol insertion. A second dose of misoprostol was needed in four patients. Complete abortion was achieved in 94.00% of patients, incomplete abortion in 4% and missed abortion in 2%. Approximately all the women reported one or more adverse effects but none of them had any serious ones, the most common being pain in 42 (84%) women followed by nausea, vomiting, fever and diarrhoea in 12 (24%), 6 (12%), 4 (8%) and 3 (6%) women respectively. The overall acceptability rate of the dosing regimen in our study was 94%.

Conclusion: A regimen of low dose mifepristone (100 mg) followed 24 hours later by vaginal misoprostol can be safely and effectively used for early abortion. (J Turkish-German Gynecol Assoc 2010; 11: 204-7)

Key words: Mifepristone, misoprostol, medical abortion

Received: 27 August, 2010 **Accepted:** 17 October, 2010

Özet

Amaç: Kırk dokuz güne kadar olan gebeliklerin sonlandırılmasında, düşük doz mifepriston (100 mg) ile misoprostol kombinasyonunun etkinliğini değerlendirmek.

Gereç ve Yöntemler: Kasım 2007 ve Ekim 2009 tarihleri arasında kurumumuza başvuran, en fazla 49 günlük intrauterin tek gebeliği olan 50 kadın ile (ortalama yaş 26,54 ± 3,68 yıl) prospektif bir çalışma yapıldı. 100 mg mifepriston oral yolla verildi, 24 saat sonra bunu 400 μg vajinal misoprostol uygulaması izledi. Endike ise, 400 μg vajinal misoprostol uygulaması üçüncü gün tekrarlandı. Primer sonuç olarak tam düşük (komplet abortus) oranı, sekonder sonuçlar olarak indüksiyon-düşük aralığı ve advers etkiler -özellikle kanama- değerlendirildi.

Bulgular: Ortalama gebelik süresi 38,74 ± 3,90 gündü. Kadınların hiçbirinde misoprostol yerleştirilmeden önce gebelik ürünü atılımı olmadı. Dört hastada ikinci doz misoprostole ihtiyaç duyuldu. Hastaların %94'ünde tam düşük, %4'ünde tam olmayan düşük (inkomplet abortus) ve %2'sinde atlanmış düşük (missed abortus) görüldü. Kadınların hemen hepsi bir veya daha fazla advers etki bildirdi fakat bunların hiçbiri ciddi değildi. En yaygın advers etki ağrı olup 42 kadında (%84) görüldü, bunu bulantı 12 (%24), kusma 6 (%12), ateş 4 (%8) ve diyare 3 (%6) izledi. Çalışmamızda doz rejiminin kabul edilebilirlik oranı %94'dü.

Sonuç: Düşük doz mifepristonu (100 mg) takiben 24 saat sonra uygulanan vajinal misoprostol rejimi erken düşük için güvenli ve etkili bir şekilde kullanılabilir.

(J Turkish-German Gynecol Assoc 2010; 11: 204-7)

Anahtar kelimeler: Mifepriston, misoprostol, tıbbi abortus

Geliş Tarihi: 27 Ağustos 2010 **Kabul Tarihi:** 17 Ekim 2010

Introduction

An estimated 19 million unsafe abortions occur worldwide each year, resulting in the deaths of about 70,000 women (1). According to the World Health Organization (WHO), every 8 minutes a woman in a developing nation will die of complications arising from an unsafe abortion (2). Medical methods are a safe alternative, because their administration requires little training and has a simpler infrastructure compared to surgical procedures (3).

Mifepristone (RU 486) is an orally active, synthetic antiprogestogen that has been primarily used for the termination of pregnancy, usually in combination with a prostaglandin agent administered either simultaneously (4, 5) or at an interval of 4-6 (6), 6-8 (7), 24 (8), 48 (9),or even up to 72 hours (10). It binds to the glucocorticoid receptor (GR), and oral administration of the drug results in a compensatory, dose-dependent activation of the hypothalamic-pituitary-adrenal (HPA) axis (11). However, due to saturation of alpha 1-acid glycoprotein (AAG), the serum binding protein for RU 486, the serum levels remain similar within the dose range of 100- 800 mg of RU 486 (12) and similar efficacy is expected with 100 mg mifepristone in medical abortion regimens (13). On the other hand, the efficacy decreases with further lowering of the mifepristone dose to 50 mg (14).

The use of mifepristone for abortion in high doses is well established. The present study is an attempt to assess the efficacy of 100 mg of mifepristone, in combination with misopro-

Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Anupama Goel, c/o Sham Lal Goel, Street 1/2, shastri nagar, Jagraon 142026 jagraon, Ludhiana, India*
Phone: 09466634677 e.mail: hiyagoel@yahoo.com
doi:10.5152/jtgga.2010.38

stol, in women undergoing medical termination of pregnancy up to a gestation time of 49 days.

Material and Methods

In this prospective observational study, we enrolled 59 women with up to 49 days of gestation and confirmed a single intrauterine pregnancy presenting at our institution for voluntary termination of pregnancy between November 2007 and October 2009.
Both surgical and medical methods of abortion together with their side effects and cost were explained to the patients. Only those patients who were willing to use the medical method, ready for the follow up schedule and agreed to have a surgical abortion if indicated were included in the study.
Women who conceived with an intrauterine contraceptive device (IUCD) in situ and had a history of more than two lower segment caesarean sections (because of uterine rupture risk) were excluded from the study. Other exclusion criteria were patients allergic to either mifepristone or misoprostol, chronic adrenal failure and patients on corticosteroids or anticoagulants. With this selection protocol, 50 women (mean age 26.54±3.68 years) were included in the study, as 6 women refused to participate and 3 women did not meet the inclusion criteria (two had asthma and were on corticosteroid and one had deep vein thrombosis and was on anticoagulants).
All women gave informed written consent and had a medical and gynaecological examination along with the assessment of haemoglobin level, and Rh-antigen status.
Transvaginal ultrasonography was performed to confirm the gestational age and if there was any discrepancy between the gestational age calculated from the last menstrual period (LMP) to that from ultrasonography, the ultrasonologically estimated age was used for further data analysis. The departmental ethical committee approved the study.
Women were instructed to take 100 mg mifepristone (one half tablet of mifepristone 200 mg, Cipla pharmaceuticals) orally on day 1, and to insert 400 micrograms misoprostol (two tablets of 200 micrograms misoprostol, Cipla pharmaceuticals) vaginally at home, 24 hours after taking mifepristone (Day 2). The women were asked to keep a record of the time of onset of bleeding, expulsion of products of conception and number of days of bleeding as well as adverse effects. No routine antibiotic prophylaxis was used.
The first follow up visit was scheduled for 24 hours after misoprostol insertion. At this visit, they were questioned regarding bleeding, expulsion of products of conception and the side effects. If there was no bleeding until 24 hours after administration of the first dose of misoprostol, they were asked to repeat 400 microgram misoprostol vaginally. The second follow-up visit was scheduled on day 14, or earlier if bleeding was excessive, and the women were questioned in detail about the side effects, especially excessive bleeding, abdominal cramps, headache, nausea, fever and dizziness. All women underwent transvaginal ultrasonography at this visit and if the gestational sac was still present, a surgical abortion was performed. If the woman's blood group was Rh-negative, she was also given Rh-immune globulin 50 μg intramuscularly.
The procedure was considered successful if complete expulsion of the products of conception occurred without the need for any surgical procedure. Failure of the procedure was classified as incomplete abortion, missed abortion, and continuing pregnancy and these women were managed with suction and evacuation.
Statistical analysis was done using SPSS software (version 16.0).

Results

The demographic profile of the study group is shown in Tables 1 and 2. The mean age of the women was 26.54±3.68 years. The mean parity was 1.38±0.94. The gestational age was set by the LMP and confirmed by ultrasonography in 43 women. In 7(14%), it was calculated by the ultrasound examination. The mean period of gestation was 38.74±3.90 days. Eighteen (36%) women had a previous history of abortions. Thirteen (26%) women had a history of previous LSCS, with 2 among them having a history of two caesareans.
Four women could be followed-up only by multiple telephone conversations until their three next menstrual cycles. The reported findings were consistent with complete expulsion and there were no signs of continuing pregnancy. These cases were thus included in the successful procedures.
None of the women expelled the products of conception before misoprostol insertion.
At the first follow up visit, four women had only minimal bleeding and they were asked to insert 400 micrograms misoprostol again at home. In the remaining 46 patients, onset of bleeding occurred at 4.90±1.26 hours. 45 women expelled the products

Table 1. Patient Characteristics

Parameter	Number of women	Percentage
Age group (years)		
≤20	2	4.00%
21-25	19	38.00%
26-30	20	40.00%
31-35	8	16.00%
36-40	1	2.00%
Parity		
0	11	22.00%
1	13	26.00%
2	23	46.00%
3	2	4.00%
4	1	2.00%
Previous Abortion	18	36.00%
Previous caesarean section	13	26.00%

Table 2. Distribution of women according to gestational age

Gestational age(days)	Number of women	Percentage (%)
29-35	4	8.00%
36-42	35	70.00%
42-49	11	22.00%

Table 3. Outcome of the regimen used for medical abortion

	Number of women	Percentage
Complete Abortion	47	94.00%
Incomplete Abortion	2	4.00%
Missed Abortion	1	2.00%
Continuing pregnancy	0	0

Table 4. Adverse effects of drugs used

	Number of women	Percentage
Intolerable abdominal pain	3	6.00%
Nausea	12	24.00%
Vomiting	6	12.00%
Fever	4	8.00%
Diarrhoea	3	6.00%
Dizziness	0	0

of conception within 24 hours after misoprostol insertion and suction aspiration had to be performed on day 6 for excessive bleeding in one patient. In this patient, there was a decline of haemoglobin level from 10.9 gm% to 10.0 gm%.

46 women came for a second follow up visit. Out of four women in whom a repeat dose of misoprostol was inserted, two were found to have had a complete abortion, one a missed and one an incomplete abortion. In the remaining 42 women, transvaginal sonography showed the uterine cavity to be empty. Four women were followed by telephone calls for their next three menstrual cycles. Their histories were suggestive of complete abortion. Success rate in our study was 94.00%. There were no continued pregnancies.

The induction-abortion interval in the whole study group was 8.17±1.08 hours. The mean number of days of bleeding was 9.04±2.38 days, with heavy bleeding on day 2, which then decreased steadily. Only one woman reported spotting up to the next menstrual cycle.

All the women tolerated the dose well,but almost all the women (98%) reported at least one adverse event during the study period. 42(84%) women complained of pain, of whom three reported pain of severe intensity.None of them required parenteral analgesics or reported to the hospital. Nausea, vomiting, fever and diarrhea were reported by 12(24%), 6(12%), 4(8%) and 3(6%) women respectively. Serious adverse events were not reported by any patient in our study. None of them had bleeding requiring blood transfusion and none had any signs of pelvic infection.

Despite the failures and adverse events, the majority (94%) of the women in our study reported that they were satisfied with the medical abortion and would like to utilize this method if needed in future (Table 3, 4).

Discussion

Termination of pregnancy has been practiced since antiquity and an estimated 42 million abortions are performed worldwide each year (2). For many years, termination of early pregnancy was done surgically with the risk of complications like incomplete abortion, uterine perforation, and haemorrhage etc. using vacuum aspiration. Currently, however, agents are available which can terminate pregnancy if administered orally, vaginally or parenterally, obviating the need for the surgical procedures, and thus reducing the complications associated with the procedure. Furthermore, the incidence of miscarriage and postpartum haemorrhage has been found to be significantly lower in the pregnancies following a medical abortion (15).

In September 2000, the U.S. Food and Drug Administration (FDA) approved mifepristone (also known as “RU-486”), the first drug specifically designed for use as a method of medical abortion. This drug, in conjunction with misoprostol (originally intended for use to prevent NSAID-induced gastric ulcers), has become established as one of the most effective means for terminating pregnancies (16).

FDA-approved regimen of mifepristone/misoprostol is mifepristone 600 mg orally followed 2 days later by 400 micrograms of misoprostol vaginally (16). Multicenter trials conducted by the WHO have shown the equivalent efficacy of 600 mg dose and 200 mg dose of mifepristone (17). Now trials are on which further lower the dose of mifepristone in order to decrease the cost and adverse effects.

The success rate in our study with a 100 mg dose was 94%, which is comparable to those seen in standard regimens with mifepristone 200mg i.e. 92-98% (8,9,17,18) and 600 mg i.e. 87-97% (19,20), demonstrating the potential efficacy of 100 mg mifepristone for medical abortion. Efficacy of low dose mifepristone was also reported by Jerbi et al (13).

von Hertzen et al, in a large multicentre trial, compared the efficacy of 100mg with 200mg mifepristone and the two intervals of misoprostol administration (800 μg vaginal) i.e. 24 vs 48 hours for medical abortion. They found them to be equally efficacious with the rate of complete abortion of 92.0% for women assigned 100 mg of mifepristone as compared to 93.2% for those assigned 200 mg, and 93.5% for 24-hour interval and 91.7% for the 48-hour interval (8). No studies to date have reported the efficacy of the regimen using 100 mg mifepristone along with 400 microgram vaginal misoprostol at an interval of 24 hours. A 24-hour interval is more convenient than 48-hours and, if found effective with the 100 mg dose, the regimen would be more acceptable and cheaper. This is especially important as the relatively high cost of mifepristone has limited its use as pre-treatment in some countries. Further, the lower dose i.e. 400 microgram of misoprostol has fewer side effects compared with higher doses (21).

The adverse effect profile was quite acceptable. None of the women in our study had reported any serious side effect or needed hospital admission. Schaff et al in their study reported the need for hospitalization in 2 women (0.1%) for treatment with intravenous antibiotics for pelvic infections (22). In another study by Creinin et al, 10 women (0.9%), were diagnosed with acute pelvic infection after the medical abortion but were treated as outpatients (23). None of the women in our study required blood transfusion, whereas Creinin et al. (23) and Ruangchainikhom et al. (24) had reported the need of blood transfusion in 0.4% and 3.2% women respectively. Even though this complication is uncommon, the risk of haemorrhage emphasizes the need for vigilance and ready access to medi-

cal care. There are also limitations to medical terminations, including a longer duration of bleeding, longer waiting period for completion and more office visits.

Congenital anomalies in continuing pregnancy are a concern. In our study, none of the patients had a continuing pregnancy. Creinin et al had found continuing pregnancy in 1% women after medical abortion with 100mg mifepristone and 400 μg oral misoprostol (25).

The acceptability rate of the present dosing regimen in our study has been 94%, which is comparable to other series where medical methods have been found to be acceptable by 91% (9) and 97% (26) women respectively. However, women who had previous surgical abortions were more satisfied with the medical abortion.

Although the small sample size is probably a limitation of our study, the efficacy of the regimen using 100 mg mifepristone along with 400 microgram vaginal misoprostol at an interval of 24 hours has not yet been reported by any other study. However, large randomized controlled trials are required from high volume centres in order to accept this regimen as the standard of care.

Conclusion

The present study demonstrated that the decrease in dose of mifepristone from the usual dose of 200mg to 100mg, when followed 24 hours later by 400 microgram misoprostol, can be safely carried in medical abortion regimens without loss of efficacy.

Conflicts of interest

No conflict of interest is declared by authors.

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Comparison of two different laparoscopic hysterectomies: laparoscopic hysterectomy vs. total laparoscopic hysterectomy

Farklı iki laparoskopik histerektomi tekniğinin karşılaştırılması: laparoskopik histerektomi ve total laparoskopik histerektomi

Mert Göl[1], Ayşen Kızılyar[2]

[1] *Department of Obstetrics and Gynecology, Medical School, Çanakkale Onsekiz Mart University, Çanakkale, Turkey*

[2] *Department of Obstetrics and Gynecology, Gazi Hospital, İzmir, Turkey*

Abstract

Objective: The aim of this study was to compare the efficacy and safety of laparoscopic hysterectomy (LH) and Total Laparoscopic Hysterectomy (TLH).

Methods: Both types of hysterectomy were performed by retroperitoneal uterine artery sealing using LigaSure™ by four-puncture. A total of 45 patients were operated on by LH and 22 by TLH. The mean operation time, amount of intraoperative bleeding, drop in hemoglobin concentration, weight of removed uterus, major and minor per-post operative complications, and rate of conversion to the classical abdominal approach in the two groups were compared.

Results: The mean operation time in TLH (110 min.) was significantly longer than in LH (65 min.). This was mainly due to the shorter mean operating time in the vaginal part of LH group (13 min.) compared to laparoscopic dissection of uterosacral ligaments and vaginal suturing (42 min.) in the TLH group. Median blood loss was also significantly higher in the TLH group (278 ml.) compared to the LH group (110 ml.). There were no significant differences in the mean drop of hemoglobin concentration, uterine weight, major and minor complications and conversion to laparotomy between the groups.

Conclusion: LH seems to be a faster and more demanding method than TLH. With its shorter operation time and less bleeding, LH may be preferred to TLH.

(J Turkish-German Gynecol Assoc 2010; 11: 208-11)

Key words: Laparoscopy, hysterectomy, laparoscopic hysterectomy, total laparoscopic hysterectomy

Received: 15 August, 2010 **Accepted:** 23 October, 2010

Özet

Amaç: Laparoskopik histerektomi (LH) ile Total laparoskopik histerektomi (TLH) tekniklerinin etkinliği ve güvenilirliğini karşılaştırmak.

Gereç ve Yöntemler: Her iki tip laparoskopik histerektomi dört port ve LigaSure™ kullanılarak retroperitoneal uterin arter mühürleme yöntemi ile yapıldı. Toplam 45 hasta LH ile ameliyat edilirken, 22 hasta TLH ile ameliyat oldu. Gruplar arasında ortalama operasyon süresi, intraoperative kanama miktarı, hemoglobin de düşüş, uterus ağırlığı, major ve minor ameliyat komplikasyonları, ve laparotomi konversiyon oranları karşılaştırıldı.

Bulgular: TLH uygulanan grupta ortalama operasyon süresi (110 dk.) LH uygulanan gruba göre (65 dk) anlamlı olarak kısa bulundu. Bu farkın nedeni LH grubundaki vajinal etabın (13 dk.), TLH grubundaki uterosakral, kardinal ligamentlerin disseksiyonu ve laparoskopik vajinal sutur uygulama süresine oranla (42 dk.) anlamlı olarak daha kısa sürmesidir. Ortalama kan kaybı TLH grubunda (278 ml.), LH grubuna gore (110 ml.) anlamlı olarak daha fazla bulunmuştur. Gruplar arasında ortalama hemoglobin düzeyinin düşüşünde, uterus ağırlığında, major ve minör komplikasyonlarda ve laparotomi konversiyon oranlarında anlamlı bir farklılık tespit edilmemiştir.

Sonuç: LH, TLH'ye nazaran daha hızlı ve güvenilir bir cerrahi metod gibi görünmektedir. Özellikle daha kısa ameliyat süresi ve daha az kanama miktarı nedeniyle TLH yerine LH'yi tercih etmeliyiz.

(J Turkish-German Gynecol Assoc 2010; 11: 208-11)

Anahtar kelimeler: Laparoskopi, histerektomi, laparoskopik histerektomi, total laparoscopik histerektomi

Geliş Tarihi: 15 Ağustos 2010 **Kabul Tarihi:** 23 Ekim 2010

Introduction

After cesarean section hysterectomy is the second most common gynecologic operation performed worldwide (1). Although hysterectomy can be conducted by mini-laparotomy, the vast majority are performed by a laparotomy with a 8-10 cm incision which enables the patients to tolerate more pain and discomfort compared with the vaginal or laparoscopic routes (2). It is well known that vaginal hysterectomy should be offered to the patient as the first line surgical method for removing her uterus (3, 4). However, vaginal hysterectomy is performed in 50% of patients even in the hands of experienced surgeons because of the limitations due to a large uterus, no previous vaginal delivery, adnexal mass and a history of previous abdominal operation (5). Laparoscopic hysterectomy (LH) is performed much less frequently.

There are different types of classifications for LH. However, more recently, three sub-categorisations of LH have been described by Reich et al., (6) which are as follows. (i) Laparoscopic assisted vaginal hysterectomy (LAVH), where

Address for Correspondence / Yazışma Adresi: *Mert Göl, M.D., Department of Obstetrics and Gynecology, Medical School, Çanakkale Onsekiz Mart University, Çanakkale, Turkey*
Phone: +90 286 218 00 18 Fax: +90 286 218 03 93 e.mail: mertgol@comu.edu.tr
doi:10.5152/jtgga.2010.39

part of the hysterectomy is performed by laparoscopic surgery and part vaginally, but the laparoscopic component of the operation does not involve division of the uterine vessels.(ii) LH, where the uterine vessels are ligated laparoscopically but part of the operation is performed vaginally. (iii) Total laparoscopic hysterectomy (TLH), where the entire operation (including suturing of the vaginal vault) is performed laparoscopically and there is no vaginal component.

We believe that division of the uterine arteries is the most important part of LH. In a recent study we have shown that, when this step is managed laparoscopically, there is less bleeding and fewer complications (7). According to our experience over 300 laparoscopic hysterectomies in 3 years, we have noticed that there is significant amount of bleeding in the vaginal step of LAVH compared to LH and TLH (unpublished data). Therefore, we suggest that LAVH should be performed by endoscopic surgeons who are inexperienced in laparoscopic hysterectomy and as soon as possible they should progress to LH or TLH. However, it is still not well known whether TLH offers any benefits or disadvantages over LH. This question has not been resolved in recent years and we still do not know which method is best. Accordingly, the aim of the present work was to try to determinel the best method for hysterectomy - laparoscopy, TLH or LH.

Materials and Methods

Intraoperative and postoperative data of both groups were analyzed retrospectively. In time, TLH was performed in all patients instead of LH. Both types of hysterectomy were performed under general anaesthesia with the technique described previously by Köhler et al.,(7). However, in contrast to these authors we used LigaSure™ V 5 mm (Valley lab) to seal and cut the uterine vessels instead of using the bipolar cautery (Fig. 1) and infundibulopelvic ligaments (Fig. 2). In the vaginal step of the LH procedure, Ligasure Vmax was used. In TLH uterosacral and cardinal ligaments were also sealed and cut with the Ligasure followed by a circular incision of the vagina using the hook unipolar cautery. The vagina was also sutured laparoscopically in TLH. All operations were performed in the lithotomy position and the drain was only used when indicated. Total operating time (from the maintainence of pneumoperitoneum to vaginal cuff closure), the duration of the vaginal step in LH and also duration of uterosacral and cardinal ligaments dissection within vaginal cuff closure in TLH, estimated blood loss, mean drop in Hb concentration, uterine weight, rate of intraoperative and post-operative complications, conversion from laparoscopy to the classic abdominal approach, use of blood transfusion and duration of hospital stay were recorded and analyzed. Blood loss was measured by recording the contents of the fluid extraction device. We used the fluid extraction device during the vaginal step, without any surgical pads.

Statistical analysis

Statistical Analysis was performed using the SPSS ver. 11 (Chicago- IL). Median, medium and percentages of the variables were analyzed. The differences between the two groups were analyzed by Chi – Square test or Mann Whitney U test. A p value <0.05 was considered statistically significant.

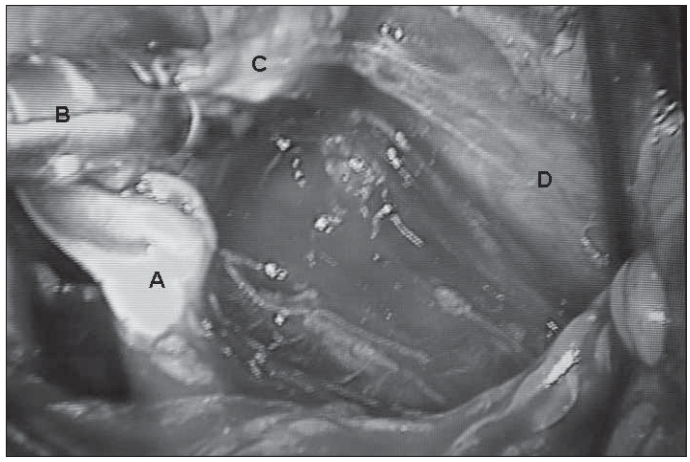

Figure 1. The LigaSure™ V 5 mm (B) is grasping the uterine artery (C) between the internal iliac artery (A) and ureter (D). Note that the suction device is pulling the ureter medially to prevent any damage during sealing

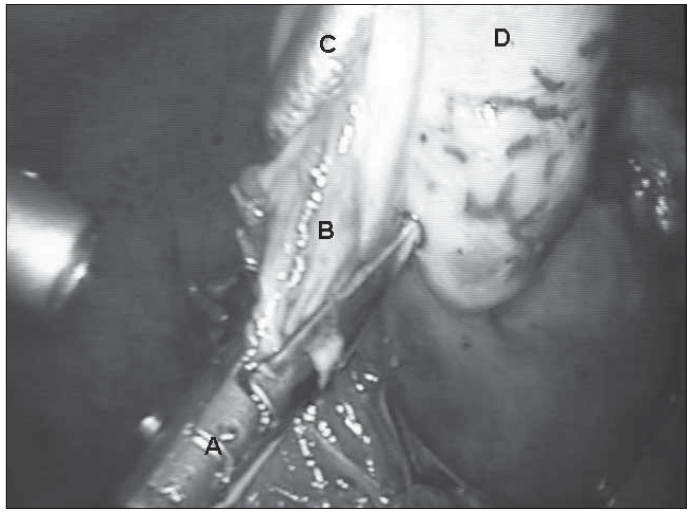

Figure 1. Traction of the infundibulopelvic ligament (B) and ovary (D) upwards by the grasping forceps (C) should be performed for safe, efficient sealing and dissection by the Ligasure (A)

Results

All operations were performed by the same surgeon (MG). Between February 2006 and March 2007, a total of 116 LH and TLH were performed. Of these, 85 were LH and 31 were TLH. To ensure similar demographic characteristics between the groups, patients with one previous abdominal surgery and with a uterine size smaller than 12 gestational weeks were included. Accordingly, 45 patients in the LH group and 22 in the TLH group were eligible for the inclusion criteria.

Table 1 illustrates the demographic characteristics of patients in both groups. There were no significant differences between the variables. The most common indication for LH and TLH was an uterine fibroid. As seen in Table 2, there were no significant differences in operation indications between the two groups. Table 3 depicts intraoperative variables in both groups. Total operation time was significantly longer in the TLH group (110 min.) com-

Table 1. Demographic characteristics of both groups

	TLH (n=22)	LH (n=45)	p value
Age (years)[x]	46 (34-62)	48 (37-57)	0.78
Body Mass Index (kg/m^2)[x]	25 (22-29)	25 (22-28)	0.74
Parity[x]	2 (0-5)	2 (0-4)	0.71
Previous caesarean section[&]	6 (27.2%)	11 (24.4%)	0.31
Previous lower abdominal-pelvic surgery[&]	4 (18.1%)	9 (20%)	0.37

[x]Mann - Whitney U test, [&]Chi-Square test

Table 2. Hysterectomy indications

	TLH (n=22)	LH (n=45)	p
Uterine fibroid	15 (68%)	32 (71%)	<0.05
Endometrial hyperplasia	3 (13.6%)	5 (11.1)	<0.05
Ovarian tumor	2 (9.1%)	3 (6.6%)	<0.05
Pelvic endometriosis	1 (4.5%)	-	0.03
Adenomyosis	1 (4.5%)	1 (2.2%)	<0.05
Cervical intraepithelial neoplasia	2 (9.1%)	3 (6.6)	<0.05
Postmenopausal bleeding	1 (4.5%)	-	0.03
Menorrhagia	-	1 (2.2)	0.03

Table 3. Operative data

	TLH (n=15)	LH (n=15)	p value
Total operating time (min)[&]	110 (80-170)	65 (45-85	0.001
Vaginal step (min)[&]	-	13 (5-22)	
Uterosacral and cardinal lig. dissection and vaginal cuff closure (min)[&]	44 (25-72)	-	0.001
Median blood loss (ml)[&]	278 (110-420)	110 (50-240)	0.042
Median Hb drop (mg/dl)[&]	2.1 (0.4-3)	1.6 (0.6-2.3)	0.76
Median uterine weight (grams)[&]	110 (60-150)	140 (110-220)	0.83
Major Complications[*]	1	1	0.17
Minor Complications[*]	3	2	0.92
Conversion to laparotomy[*]	1	1	0.17

Percent and range in blanket, [&]Mann-Whitney U test, [*]Chi-Square test

pared to the LH group (65 min) (p=0.001). This was due to the longer duration in dissecting uterosacral and cardinal ligaments and cuff closure in TLH compared to the vaginal approach to these steps in LH. Intraoperative blood loss was also significantly higher in TLH (278 ml.) compared to LH (110 ml.) (p=0.004). There were no significant differences in the mean drop of Hb concentration, uterine weight, rate of intraoperative and postoperative complications and conversion from laparoscopy to the classic abdominal approach between the groups.

Blood transfusion was unnecessary in the two groups. All patients except two with cystotomies were discharged on the first postoperative day. One patient in the TLH group had a cystotomy due to difficulty in dissecting severe adhesions in the vesicovaginal fold becuase of a previous cesarean section. This was repaired laparoscopically and subsequently she developed a vesico-vaginal fistula. The other cystotomy was made in the LH group during the vaginal procedure because of inadequate dissection of the bladder from the vagina. This was repaired vaginally. Only one patient converted to laparotomy in the LH group because of severe bowel adhesions due to rectovaginal endometriosis. Two patients had urinary tract infections and one patient had fever in the TLH group and two patients had fever in the LH group. There were no other minor complications.

Discussion

During the early years of laparoscopic hysterectomy, LAVH was the main technique performed by endoscopists. However, with time it was noticed that laparoscopic management of uterine arterial pedicles results in less bleeding compared to the vaginal approach in LAVH (8). Furthermore, surgical experience advanced through the years and new techniques in LH emerged. Experienced surgeons attempted more steps laparoscopically and ultimately they developed the TLH approach. Every laparoscopist has his/her own technique in LH which is most familiar to him/her. Therefore some may advocate performing LAVH whereas others may prefer to perform LH or TLH. However, to date, most authors have examined the efficiency of one type of LH and reported their outcomes. In addition, the vast majority were multicenter studies that were biased by different expertise of the surgeons (9-13). A recent multicenter study by Leung WS et al., (14) reported that TLH resulted in longer operating times compared to LH, as was confirmed in our study. Interestingly, these authors reported more intraoperative blood loss in LH than in TLH. However, in our study we showed that the amount of intraoperative bleeding was significantly less in the LH group compared to that of the TLH.group This could be due to use of Ligasure [tm] in the present study. Another interesting outcome in the study of Leung WS et al., (14) was that patients in the LH group had higher vaginal cuff hematoma incidence compared to patients in the TLH group. In our study, we did not see a single case of postoperative vaginal cuff hematoma in either group. We again assume that this high incidence of vaginal cuff hematoma could be due to the multicenter nature of their study.

Our technique was first described by Köhler et al., (7) in Germany. However, to date, no study has compared retroperitoenal uterine artery ligation with LigaSure™ in LH with TLH. In the present study we have shown that LH could be the better technique because of its shorter operation time and less intraoperative bleeding. Patient recovery is rapid, as all were discharged on the subsequent postoperative day. None had any significant complaints and there were no minor long-term postoperative complications, such as urinary tract and wound infections. During laparoscopic hysterectomy, complications should

be avoided, and preservation of the integrity of the ureter is a major goal when handling the uterine vessel. Although we saw no ureter complications in the present study, we consider that ureteric damage could be much more frequent in TLH than in LH as the surgeon gets much closer to the ureter after the uterine artery step in TLH.

Our study is a case control study, therefore randomized studies are needed to reveal the best method in laparoscopic hysterectomy. Although we obtained statistical significance, there are only a few patients in each group, which could affect the outcomes of some parameters. Accordingly, future randomized studies comparing both methods with anadequate number of patients are needed. However, we suggest that these studies should be performed in a single center and surgeons performing these operations should have similar surgical experience in laparoscopic hysterectomy.

In conclusion, LH seems to be a faster and more demanding method than TLH. With its shorter operation time and less bleeding, LH may be preferable to performing TLH.

Conflicts of interest

No conflict of interest is declared by authors.

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The correlation of the antral follicle count and Serum anti-mullerian hormone

Serum anti-mülleryan hormon ve antral folikül sayısı ilişkisi

Behiye Pınar Göksedef, Nurettin Idiş, Hüsnü Görgen, Yaprak Rüstemoğlu Asma, Murat Api, Ahmet Çetin

Haseki Teaching and Research Hospital, Obstetrics and Gynecology, Istanbul, Turkey

Abstract

Objective: To compare the value of the basal serum anti-Müllerian hormone (AMH) level with most of the established ovarian reserve tests.

Material and Methods: A total of 141 infertile women was studied prospectively. On cycle day 3, serum levels of AMH, inhibin B, estradiol (E), FSH and LH levels were measured, and the number of early antral follicles (2-6 mm in diameter) estimated at ultrasound scanning to compare the strengths of hormonal-follicular correlations.

Results: The mean age of the participants was 29.18±5.54. The mean AMH and total AFC on day 3 were 2.23±1.90 ng/ml and 8.35±2.83, respectively. Serum AMH levels were more tightly correlated ($p<0.001$) with number of the early antral follicle count ($r=0.467$, $p<0.0001$) than age and serum levels of FSH ($r=-0.400$, $p<0.001$; $r=-0.299$, $p<0.001$ respectively). No correlation was detected between serum levels of inhibin B, E_2, and LH ($r=0.154$, $p=0.06$; $p=0.31$; $r=–0.085$ and $r=0.067$, $p=0.42$) and AFC.

Conclusion: Serum AMH levels showed a strong correlation with AFC, and also this correlation is stronger than the other ovarian reserve parameters. (J Turkish-German Gynecol Assoc 2010; 11: 212-5)

Key words: Anti-mullerian hormone; ovarian reserve; antral follicle count

Received: 9 October, 2010 **Accepted:** 22 November, 2010

Özet

Amaç: Bu çalışmada basal serum bazal anti-Müllerian hormone (AMH) seviyesinin diğer sık kullanılan over rezerv testleri ile karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Toplam 141 infertil kadın çalışmaya alındı. Üçüncü gün serum AMH, inhibin B, östradiol (E_2), FSH ve LH seviyeleri ölçümü ve ultrasonografik olarak erken antral folikül (2-6 mm çaplı) sayımı yapılarak hormonal-foliküler korelasyon değerlendirildi.

Bulgular: Olguların ortalama yaşı 29.18±5.54 idi. Ortalama AMH ve total AFC sırasıyla 2.23±1.90 ng/ml ve 8.35±2.83 olarak saptandı. Serum AMH seviyesi ile erken antral folikül sayısı arasındaki korelasyon ($r=0.467$, $p<0.0001$), yaş ve serum FSH düzeyileri ile erken antral folikül sayısı arasındaki korelasyondan (sırasıyla; $r=-0.400$, $p<0.001$; $r=0.299$, $p<0.001$) daha güçlü idi ($p<0.001$). Serum inhibin B, E_2, ve LH seviyeleri ile AFC arasında korelasyon saptanmadı ($r=0.154$, $p=0.06$; $p=0.31$; $r=–0.085$ and $r=0.067$, $p=0.42$).

Sonuç: Serum AMH seviyesi, AFC ile sıkı bir biçimde ilişkilidir ve aynı zamanda bu ilişki diğer over rezervi değerlendirme parametrelerinden daha güçlüdür. (J Turkish-German Gynecol Assoc 2010; 11: 212-5)

Anahtar kelimeler: Anti-mülleryan hormon; over reservi; antral folikül sayısı

Geliş Tarihi: 09 Ekim 2010 **Kabul Tarihi:** 22 Kasım 2010

Introduction

Ovarian reserve is described as the quantity of the ovarian follicular cohort and quality of the oocytes (1). The assessment of the ovarian reserve needs for identification of the response of controlled ovarian stimulation (COH). This assessment facilitates appropriate pretreatment counseling and modification of an individual›s treatment protocol in an attempt to maximize their potential response. Assessing an individual's ovarian reserve includes age, estradiol (E_2) and basal follicle-stimulating hormone (FSH) levels. Antral follicle count, serum inhibin B levels, ovarian volume, and vascular resistance have also been studied as markers of ovarian reserve. The antral follicle count (AFC) have been widely used as the ovarian reserve test, due to convenience of the ultrasonographic tools usage. Follicle counts can be performed easily with the help of the high quality resolution of the sonographic systems (2-10). Although there are well-known difficulties to obtain correct AFC such as high inter-observer differences and anatomical variations (3), it has been suggested that the ability of AFC to predict poor response might be significantly better than basal FSH. Thus, AFC has been considered the "test of first choice" by some investigators (2, 11).

Recently; serum anti-Mullerian hormone (AMH) has been commonly studied as a potential new test for ovarian reserve. AMH, also known as Mullerian-inhibiting substance, is a dimeric glycoprotein that belongs to the transforming growth factor-β family (12-15). Antimullerian hormone is secreted by small antral follicles and in reproductive-aged women and it is expressed by granulosa cells of the ovary (16). In the ovary, AMH inhibits initial primordial follicles recruitment and decreases the sensitivity of preantral and small antral follicles to FSH and hence suggesting its role in intrafollicular and interfollicular coordination of follicle development (17, 18). Recently it has been shown that the higher AMH levels were associated with the greater numbers of retrieved oocytes and improved embryo morphology in the IVF cycles (10, 15, 19, 20). There has been a controversary between the corelation of

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Behiye Pınar Göksedef, Haseki Eğitim ve Araştırma Hastanesi, Kadın Doğum Kliniği, 34394 Aksaray, İstanbul, Turkey*
Phone: +90 212 529 44 00 e.mail: bpgoksedef@yahoo.com
doi:10.5152/jtgga.2010.40

the AFC and the other ovarian reserve tests such as age, AMH, basal FSH, E_2 and inhibin-B. Therefore, the aim of this study is to investigate the correlation between AFC and age, AMH, basal FSH, Estradiol (E_2), LH and inhibin-B levels in a selected population of women who were referred for the fertility treatment.

Materials and Methods

A total of 141 patients who were evaluated prior to their first treatment cycle were prospectively included into our study based on the following criteria: regular menstrual cycles (21-35 days), presence of both ovaries, age less than 45 years. Subjects were excluded if they had abnormal uterine bleeding, evidence of endocrine disorders (normal thyroid stimulating hormone, prolactin, testosterone and androstenedione), suboptimal visualization of the ovary by transvaginal ultrasonography, an ovarian cyst or follicle measuring 20 mm or more in diameter and a history of ovarian surgery. The Institutional Review Board approval and written informed consent were achieved for this study. On the third day of the spontaneous cycle, all patients had a transvaginal scan by the same investigator (N.I) using a GE General logiq 400 pro (GE medical systems, Korea CO., LTD. Sungdam Shi, KS) 5MHZ ultrasound probe to assess the number of antral follicles, measuring 2-6 mm, as described previously (3). Each ovary was measured in three planes and ovarian volume was calculated using the prolate ellipsoid formula (V=D1xD2xD3x0.523). D1, D2 and D3 are being the three maximal longitudinal, antero-posterior and transverse diameters, respectively (21). On the same day, a venous blood sample was obtained for the measurement of AMH, FSH, LH, E_2 and inhibin B.

Measurement of serum AMH levels was performed using the MIS/AMH enzyme-linked immunosorbent assay kit DSL (diagnostic systems laboratories, Inc./USA). Inhibin B was measured using the Inhibin B enzyme-linked immunosorbent assay kit (Diagnostic System Lab, Inc./USA). FSH, LH and E_2 levels were assessed in plasma with the AxSYM immunoanalyser (Abbott Laboratories, Abbott Park, IL, USA).

Statistical analysis was performed using SPSS (version 13.0; SPSS, Inc., Chicago, IL). The data was expressed by means and the standard deviations. Relationship between two different continuous variables was assessed by Pearson Correlation. The Fisher r to z-test was used to determine if the coefficient of correlation (r) was significantly different from zero. A $p<0.05$ was considered as statistically significant.

Results

The mean age of the participants was 29.18±5.54 (range 23-44) and 69.5% (n=98) of the patients had primary infertility. The mean AMH and total AFC on day 3 were 2.23±1.90 and 8.35±2.83, respectively. Table 1 summarizes age, BMI mean of the FSH, LH, E_2, AMH, inhibin B and total AFC and the mean ovarian volume of the participants.

Correlations of the number of antral follicles, the mean ovarian volume, AMH and the others ovarian reserve parameters are shown in Table 2. Unlike, inhibin B, serum levels of E_2 and LH ($r=0.154$, $p=0.06$; $p=0.31$; $r=-0.085$ and $r=0.067$, $p=0.42$), those of age, AMH, and FSH were significantly correlated with the number of early antral follicles on cycle day 3.

It is noteworthy that the correlation between number of early antral follicles and serum AMH levels ($r=0.467$, $p<0.0001$) was significantly stronger ($p<0.0001$) than age and serum levels of FSH ($r=-0.400$, $p<0.001$; $r=-0.299$, $p<0.001$ respectively). In addition to this, serum AMH levels showed a stronger correlation ($p<0.001$) with the mean ovarian volume ($r=0.373$, $p<0.0001$) than did those of age ($r=-0.182$, $p=0.03$), inhibin B ($r=0.180$, $p=0.03$), E_2 ($r=0.079$, $p=$NS), FSH ($r=-0.276$, $p=0.001$) and LH ($r=-0.005$, $p=$NS). Incidentally, serum AMH levels were significantly correlated with those of age ($r=-182$, $p=0.03$), inhibin B ($r=0.259$, $p=0.002$) and FSH ($r=-0.290$, $p<0.001$), but not with those of E_2 and LH.

Table 1. The demographics and FSH, LH, E_2, AMH, Inhibin B, and AFC and the mean ovarian volume on day 3 of the participants

n=141	Mean	±SD
Age (years)	29.18	5.54
BMI (kg/m²)	24.76	3.90
FSH (IU/L)	6.81	3.35
LH (IU/L)	3.77	2.10
E_2 (pg/ml)	41.28	21.29
Inhibin B (pg/ml)	53.87	40.02
AMH (ng/ml)	2.23	1.90
Total AFC (n)	8.35	2.83
Mean ovarian volume	5.44	2.31

Table 2. Correlations of the number of antral follicles, the mean ovarian volume, AMH and the others ovarian reserve parameters

Parameters	AFC		The Mean Ovarian Volume		AMH	
	r	p	r	p	r	p
Age (years)	-0.40	<0.0001**	-0.18	0.03*	-0.18	0.03*
FSH (IU/L)	-0.29	<0.0001**	-0.27	0.001**	-0.29	<0.001**
LH (IU/L)	0.06	0.42	-0.05	0.94	0.13	0.11
E_2 (pg/ml)	-0.08	0.31	0.07	0.34	-0.42	0.62
Inhibin B (pg/ml)	0.15	0.06	0.18	0.03*	0.25	0.002**
AMH (ng/ml)	0.46	<0.0001**	0.37	<0.0001**	1	

Discussion

The count of the number of antral follicles by ultrasonography is the best predictor for the quantitative aspect of ovarian reserve (22). There is no consensus on identification of the antral follicles (2), however several evidence based studies suggested to select the follicles as antral follicles based on a diameter measurement as 2 to 10 mm. (3-10). It has been reported that human antral follicles measuring < 6 mm express the greatest amount of AMH, and that levels decline with antral follicles increase in size (23). Two to six mm antral follicles were defined as AFC in our study. We observed that serum AMH levels are strongly related to early AFC, with a significance that was remarkably stronger than age, serum levels of inhibin B, E_2, FSH and LH. Similar results were found by the previous published studies about the relationship between AMH and antral follicle count and the coefficients of correlation were reported as stronger (0.71-0.74) than present study (0.46) (24, 25). The correlation of AMH and the different sizes of antral follicle was studied previously; the best correlation was found between AMH and >5 to 6 mm size of AFC and correlation coefficient (r) was reported as low as 0.41. These different results may be explained by the lack of an international assay standard for AMH measurements.

In our results; a negative relationship was observed between FSH and total AFC and the ovarian volume. These data confirms the hypothesis of a stimulating role of FSH on granulosa cells on the antral follicle, caused by the dependency of FSH levels on the negative feedback from E_2 and possible different regulation of AMH as compared with other hormonal parameters. Although little is known about FSH effects on AMH expression during the early follicular phase, it can be presumed that this hormone is less FSH-sensitive than inhibin B and E_2.

On the contrary of previous reports; no correlations were detected between total AFC and inhibin B and E_2 levels in this study. This result could be explained by the modulator role of FSH for inhibin B and E_2. During the luteal-follicular transition, the secretion of inhibin B and E_2 by the early antral follicles modulates their own stimulation by FSH (26, 27). This implies that inhibin B and E_2 levels depend not only on the bulk of active granulosa cells available, as represented by follicular number and sizes, but also on their stimulation by FSH. There are potential advantages of using AMH over AFC or the other parameters because AMH can be measured throughout the cycle, in contrast to the other parameters, which can only be determined in the early follicular phase (28, 29). Therefore, AMH may represent a more independent and reliable marker of early antral follicle activity than inhibin B and E_2, and FSH on cycle day 3.

As a conclusion, our results indicate that serum AMH levels are strongly related with ovarian follicular status during the early follicular phase, and also this relationship is more significant than other ovarian reserve parameters. These results also indicate that, serum AMH measurement is better predictor for the number of early antral follicles than conventional hormone measurements. This point may be helpful to refine future clinical applications of AMH measurements in routine infertility work-up for evaluating the fertility potential and monitoring infertility treatments.

Conflicts of interest

No conflict of interest is declared by authors.

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Posterior Reversible Encephalopathy Syndrome in severe preeclampsia: case report and literature review

Ağır preeklampside Posterior Reverzibl Ensefalopati Sendromu: olgu sunumu ve literatürün gözden geçirilmesi

Banu Kumbak Aygün[1], Yakup Baykuş[1], Said Berilgen[2], Burçin Kavak[1], Hüsnü Çelik[1], Bilgin Gürateş[1]

[1] Department of Obstetrics and Gynecology, Medical School, Fırat University, Elazıg, Turkey

[2] Department of Neurology, Medical School, Fırat University, Elazıg, Turkey

Abstract

We describe a 23 year old primigravid patient with severe preeclampsia complicated by posterior reversible encephalopathy syndrome (PRES), who presented with sensory and motor deficits and amnesia in the postpartum period Cranial magnetic resonance imaging (MRI) showed abnormal areas in the white matter of bilateral parieto-occipital lobes, indicating brain edema which disappeared completely on the follow-up scan taken four weeks after delivery together with complete symptom regression. The development of PRES in preeclampsia is discussed and the importance of prompt postpartum blood pressure control is emphasized.

(J Turkish-German Gynecol Assoc 2010; 11: 216-9)

Key words: Posterior reversible encephalopathy syndrome (PRES), preeclampsia, pregnancy

Received: 5 February, 2010 **Accepted:** 29 March, 2010

Özet

Bu yazıda 23 yaşında, ilk gebeliği olan şiddetli preeklamptik bir hastada postpartum dönemde duyusal ve motor sinir bulguları ve unutkanlık ile ortaya çıkan bir posterior reverzibl ensefalopati sendromu (PRES) sunulmuştur. Kranyal manyetik rezonans görüntüleme (MRI) ile bilateral parieto-occipital loblarda beyin ödemine işaret eden anormal alanlar görülmüş olup, doğumdan dört hafta sonra kontrol amaçlı yapılan görüntüleme testi ile bu lezyonların tamamen kaybolduğu ve semptomların da gerilediği tespit edilmiştir. Preeklampside PRES gelişimi tartışılarak, bu hastalarda postpartum kan basıncı kontrolünün önemi vurgulanmıştır.

(J Turkish-German Gynecol Assoc 2010; 11: 216-9)

Anahtar kelimeler: Posterior reverzibl ensefalopati sendromu (PRES), preeklampsi, gebelik

Geliş Tarihi: 05 Şubat 2010 **Kabul Tarihi:** 29 Mart 2010

Introduction

Posterior reversible encephalopathy syndrome (PRES), also termed reversible posterior leukoencephalopathy syndrome, is a newly recognized syndrome affecting predominantly the white matter of the posterior cerebral hemispheres (1). Preeclampsia/eclampsia and HELLP syndrome are the obstetric pathologies most related to PRES (1-4). Other associated conditions are hypertensive encephalopathy, renal failure with hypertension, following immunosuppressive or anticancer treatment, autoimmune connective tissue diseases, thrombotic thrombocytopenic purpura, HIV syndrome, acute intermittant porphyria, organ transplantatio and hypercalcemia (1, 5, 6). The triggering event for this syndrome seems to be an abrupt increase in blood pressure leading to an acute disruption of the blood-brain barrier. However, cases in normotensive patients have also been reported (6, 7). This syndrome is characterized by symptoms such as acute-onset headache, altered consciousness, visual disturbances, seizures and occasionally focal neurologic signs (1, 7, 8). Cranial magnetic resonance imaging (MRI) and computerized tomography (CT) show diffuse abnormalities due to vasogenic edema predominantly within the territories of the posterior circulation and primarily affecting the subcortical white matter of the parieto-occipital lobes (1). This pathology was reported to be mostly reversible, however, in cases of delayed treatment, permanent cerebral injury might occur (1, 5-7).

In this paper, we report the case of a severe preeclamptic patient who had postpartum PRES with atypical symptoms of numbness and weakness in the upper extremity, inability to walk by herself and amnesia. This case is important as it illustrates that the symptoms might be varied and atypical in PRES. The neuroimaging findings, management and follow-up examinations in the patient were presented together with a literature review.

Case Report

Mrs. G.C., a 23-year-old primigravida presented with increased blood pressure and vaginal fluid leakage at the 36th gestational week. She stated that she did not come regularly for routine antenatal examinations. Her blood pressure on admission was 140/80 mmHg and initial laboratory tests were normal except for mild proteinuria (1+). As the amniotic

Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Banu Kumbak Aygün, Department of Obstetrics and Gynecology, Medical School, Fırat University, Elazıg, Turkey Mobile: +90 532 396 19 76 e.mail: bkumbak@yahoo.com*

doi:10.5152/jtgga.2010.41

fluid volume was observed to be significantly decreased on ultrasound and the fetal biometric values were compatible with 32 gestational weeks, labor was induced. During labor, the blood pressure began to show elevations up to 160/110 mmHg values. When the body temperature increased (39°C) together with leukocytosis (22.500/mm^3) and blood pressure values of ≥160/110 mmHg,the decision to deliver by cesarean section was taken. She delivered a baby boy with 1 and 5 minute apgar scores of 5 and 8, weighing 2300 gr. No problem occurred during the cesarean section. On the first postpartum day, blood pressure values of 160/110 mmHg were seen occasionally and treatment with nifedipine was given. Although typical HELLP did not develop, mild decreases and elevations were seen in some of the blood tests; her platelet values decreased to 150.000/mm^3, aspartate aminotransferase (AST) increased to 51 U/L, and lactate dehydrogenase (LDH) increased to 393 U/L. Magnesium sulphate i.v. infusion therapy at 2 g/hour for eclampsia prophylaxis was started during labor and continued in the postpartum period for 24 hours. Fever did not continue in the postpartum period. About 30 hours after delivery by cesarean section, the patient complained of sudden weakness and numbness in the left upper extremity. A neurological problem was suspected and a neurology consultant physician was called. The consultant ordered a cranial MRI which showed T1-weighted hypointense and T2-weighted hyperintense areas in the bilateral parieto-occipital lobes indicating brain edema (Figure 1a). Visual evoked potentials were evaluated which were found to be normal. MR venography was also performed which revealed no pathology. Treatment with i.v. 20% mannitol 4x100cc/day and i.m. dexamethasone 4x2mg/day were started. On the second postpartum day, blood pressure values were around 140/80 mmHg and platelets increased, and AST and LDH values decreased. However, the patient's complaints increased, she stated that she could not comb her hair, and on the next day amnesia developed together with inability to walk by herself. A cranial CT scan performed on the fourth postpartum day showed bilateral low-density areas involving the white matter of the posterior parietal lobe, being more prominent on the right. Cerebral ischemia with subacute infarction was the diagnosis. Low molecular weight heparin 2x0.4 cc/day and aspirin 100 mg/day were added to dexamethasone treatment and mannitol was stopped. Her weakness and numbness resolved two weeks after delivery and she was discharged with acetylsalicylic acid 300 mg daily treatment. The follow-up cranial MRI obtained four weeks after delivery revealed almost complete resolution of the lesions (Figure 1b). On neurological examination four weeks after delivery, she had neither motor nor sensory deficit but complained of intermittent amnesia.

Discussion

We describe the case of severe preeclampsia complicated by clinical and neuroradiological findings consistent with PRES. The cause of PRES is multifactorial, but common precipitants in obstetrics are acute elevation of blood pressure and fluid retention. The mechanism of PRES is probably a brain-capillary leak syndrome related to hypertension, fluid retention, and damage to vascular endothelium. PRES has been described as a puerperal clinicoradiologic entity. Prompt diagnosis of PRES is important, as rapid blood pressure reduction resolves clinical and imaging findings in that pathology.

Hypertension associated with fluid overload in patients with an altered blood-brain barrier best explains the acute, reversible white-matter changes that characterize PRES. In a healthy subject, cerebral autoregulatory mechanisms that have both myogenic and neurogenic components maintain constant brain perfusion (9). The effectiveness of the neurogenic component of autoregulation is directly proportional to the degree of sympathetic innervation. To maintain constant cerebral blood flow, cerebral vasoconstriction occurs in response to hypertension,

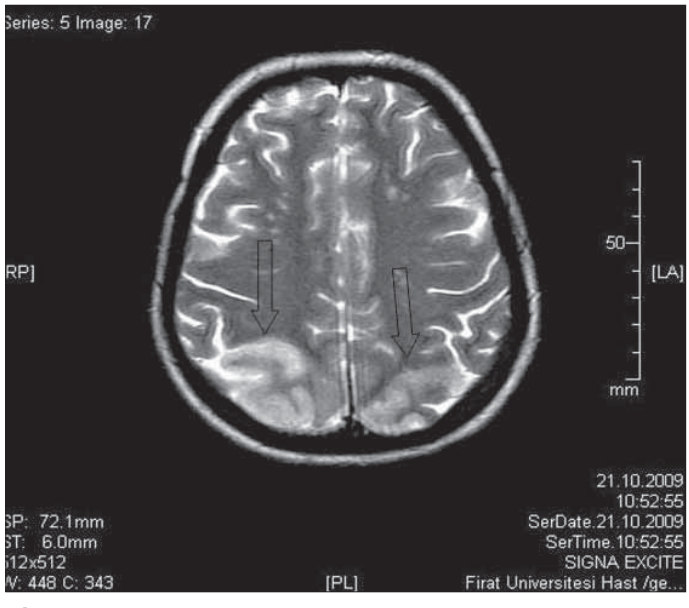

Figure 1a. **Shows areas of high signal intensity bilaterally in the parieto-occipital white matter which are consistent with vasogenic edema (arrows)**

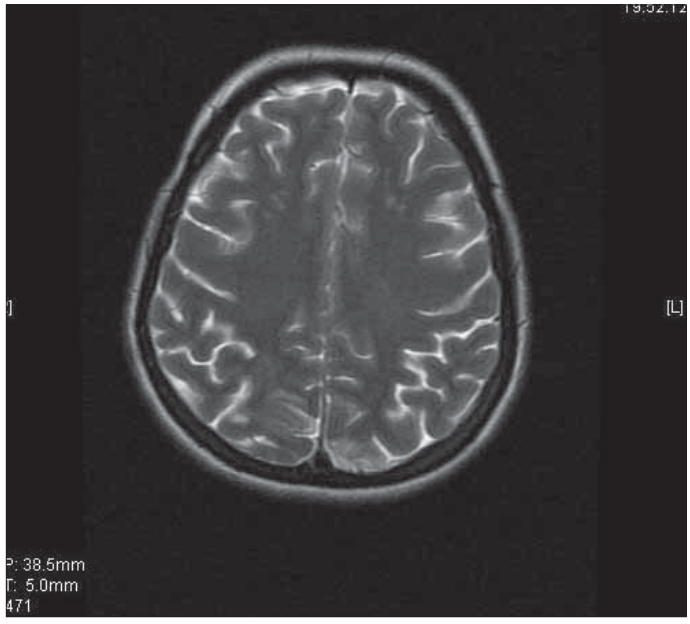

Figure 1b. **The follow-up image obtained four weeks after delivery which shows that the abnormalities have disappeared**

normally via sympathetic innervation. In patients with PRES, sudden elevations in blood pressure overcome the autoregulatory capability of the brain vasculature, leading to abrupt dilatation of cerebral arterioles with resultant hyperperfusion. This event also causes breakdown of the blood-brain barrier with focal transudation of fluid into the interstitium and petechial hemorrhages, which is detected as vasogenic edema (8-10). This vasogenic edema is mainly observed in the white matter of the parieto-occipital regions (1). This preference for the posterior brain regions was proposed to be the result of relatively reduced sympathetic innervation of the vertebrobasilar circulation (8, 11). However, in some cases the protective sympathetic mechanism of the anterior cerebral vessels may also be overcome (12).

The most common abnormality on neuroimaging in PRES was edema involving the white matter, especially in the parieto-occipital regions. In a recent study, vasogenic edema was reported to be seen in the parietal or occipital regions in 92% of the 136 patients, but involvement of other brain regions in patients with PRES, such as the temporal lobes, brain stem, cerebellum, basal ganglia, and frontal lobes, has also been reported (13, 14). Therefore awareness of variations is important to recognize PRES. In the present case, abnormal signal intensity areas in the bilateral parieto-occipital regions, which are the most commonly involved areas of the brain, were seen on both MRI and CT scans.

PRES is a remarkably heterogeneous disorder, the symptoms and signs of which depend on the involved area of the brain, together with the severity and extent of involvement. Among various symptoms and signs, the most common ones are headache, altered alertness, seizures, confusion, and abnormalities of visual perception. The mental functions might be slowed, spontaneity decreased, and responses slowed. Although severe amnesia is unusual, memory and the ability to concentrate might be impaired,. Some patients have weakness and incoordination of the limbs. Similarly, in this case, numbness, weakness, inability to walk and amnesia developed in the postpartum period. Cases of PRES in the postpartum period with different syptomatology have been reported in the literature. Striano et al. (2) reported two patients with PRES during the postpartum period who had eclampsia and chronic epilepsy which developed as a sequel (2). In another paper, two patients were described who experienced PRES in the late postpartum period without classical preeclamptic signs but with impairment of consciousness and epileptic seizures (15). PRES should be considered in the differential diagnosis of postpartum seizures (16). In our case no seizure or loss of consciousness occurred. Sudden weakness and numbness in the left upper extremity appeared initially. Therefore this case is important as it illustrates atypical symptoms in PRES and also emphasizes the importance of cranial MRI in preeclamptic patients with neurological signs and symptoms.

Most authors believe that hypertensive encephalopathy and eclampsia share similar pathophysiologic mechanisms (17-19). The imaging findings and clinical features of postpartum eclampsia are identical to those of hypertensive encephalopathy. The pathologic process is also characterized by cerebral edema and petechial hemorrhages, especially in the parieto-occipital and occipital lobes. The spectrum of cerebral lesions in eclampsia seen with MRI varies from initially reversible areas of vasogenic edema to those that may progress to cytotoxic edema and infarction in up to a fourth of women. Eclamptic seizures might be considered as one of the symtoms of PRES in severely preeclamptic patients (20, 21). In the present severe preeclamptic case, sensory and motor deficits rather than seizure developed as the manifestations of PRES, which is an atypical presentation.

The widespread use of MRI technology has made PRES familiar to many clinicians. The recently described PRES classically consists of reversible vasogenic edema in the posterior circulation territories. However, when the diagnosis and treatment was delayed, conversion to irreversible cytotoxic edema leading to chronic sequela has been described. Early recognition of PRES with immediate and effective treatment of the inciting conditions - which were the patient's hypertension and seizures - allow complete resolution of the clinical picture (22). In this case, diagnosis was made without delay and treatment initiated immediately. On control examination one month after delivery, no sequela remained except for intermittent amnesia. Normalization of high blood pressure, especially if accompanied with fever, is very important and deserves particular attention. In our case, fever together with blood pressure rise during labor might have triggered the development of PRES.

In conclusion, this paper reports a severe preeclampsia case complicated with PRES. In the postpartum period of a preeclamptic woman, appropriate control of blood pressure and quick management of sudden blood pressure increases are important, as those sudden increases might trigger PRES. The physician should be aware of PRES in the postpartum period of a preeclamptic woman with neurological signs and symptoms, as prompt treatment will avoid permanent brain injury with complete resolution of clinical and imaging findings.

Conflict of interest

No conflict of interest is declared by authors.

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Laparoscopic management of primary abdominal pregnancy: a case report

Primer abdominal ektopik gebeliğin laparoskopik tedavisi: olgu sunumu

Mehmet Metin Altay, Betül Dündar, Ahmet Okyar Erol, Volkan Kurtaran, Orhan Gelişen

Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Turkey

Abstract

This is a case report of a primary abdominal pregnancy managed by laparoscopic intervention. A 22 year old, gravida 1, woman was admitted to our emergency room with vaginal bleeding and pain in lower abdomen. She was 4 weeks pregnant according to her last menstrual period. She had undergone right salpingoophorectomy previously. Pelvic examination revealed cervical motion tenderness, bilateral adnexal tenderness and rebound tenderness. Her vital signs were normal. Beta hCG was 15826 IU/ml and hemoglobin was 10.0 g/dl. Transvaginal sonography showed an endometrium of 3 mm thickness and free fluid in the pelvis. Upon admission to the Early Pregnancy Clinic, abdominal pain became worse and hemoglobin decreased to 8.0 g/dL. Therefore, we performed a laparoscopy which showed that the uterus, left tube and ovary were completely normal with absence of the right ovary and tube. Approximately 500 cc blood was aspirated from the pelvis. Between the right sacrouterine ligament and rectum, there was a bleeding area 2 cm in width which was removed with forceps and sent for frozen pathological examination,which revealed 'placental tissue fragments'. Endometrial sampling was reported to be 'secretory endometrium'. A rapid decrease in the beta HCG post operative titer confirmed the resolution of the pregnancy. Primary abdominal pregnancy is extremely rare. The diagnosis is confirmed according to Studdiford's criteria. In the literature, there only a few cases of abdominal pregnancy in which laparoscopic procedure has been used effectively as treatment. However, laparoscopic procedure is usually successful in treatment of abdominal pregnancy if the gestational age is early enough.

(J Turkish-German Gynecol Assoc 2010; 11: 220-2)

Key words: Primary abdominal pregnancy, ectopic pregnancy, laparoscopic surgery

Received: 23 August, 2010 **Accepted:** 20 October, 2010

Özet

Kliniğimizde laparoskopik olarak tedavi edilen bir primer abdominal gebelik olgusunu sunduk. 22 yaşında, gravida 1 olan hasta acil servise vajinal kanama ve alt abdominal ağrı yakınmasıyla başvurdu. Son adet tarihine göre yaklaşık 4 haftalık gebe olduğu ve daha önce tuboovaryan torsiyon tanısıyla sağ salpingoooferektomi yapıldığı öğrenildi. Pelvik muayenede serviks hareketleri ağrılıydı, bilateral adneksal hassasiyet ve rebound mevcuttu. Vital bulguları stabildi. Beta-hCG: 15826 IU/mL, Hb: 10.0 g/dL idi. Transvajinal ultrasonografide pelviste yaygın sıvı vardı, endometrium kalınlığı 3 mm, intrauterin ve/veya ektopik gebelik izlenmiyordu. Erken Gebelik Kliniği'ne kabulünde hastanın karın ağrısı arttı, Hb: 8.0 g/dL ye düştü. Hastaya intraabdominal kanama tanısıyla laparoskopik cerrahi uygulandı. Laparoskopide sağ over ve sağ tubanın cerrahi yokluk halinde olduğu izlendi. Uterus, sol over ve sol tuba normal görünümdeydi. Douglas boşluğundan yaklaşık 500 cc kan aspire edildi. Sağ sakrouterin ligament ile rektum arasında 2 cm genişliğinde kanamalı alan izlendi ve çıkarıldı. Doku örneği frozen incelemeye gönderildi, sonuç plasental doku parçaları olarak bildirildi. Aynı anda yapılan endometrial örnekleme sonucu sekretuar endometrium olarak rapor edildi. Post operatif dönemde beta-hCG değerlerinde hızlı bir düşüş izlendi. Primer abdominal gebelik son derece nadirdir. Tanı, Studdiford kriterleri ile konur. Literatürde laparoskopik cerrahinin abdominal gebelik tedavisinde etkin bir şekilde kullanıldığı olgu sayısı oldukça azdır, ancak, gebelik haftasının erken olduğu uygun vaka grubunda başarı oldukça yüksektir.

(J Turkish-German Gynecol Assoc 2010; 11: 220-2)

Anahtar kelimeler: Primer abdominal gebelik, ektopik gebelik, laparoskopik cerrahi

Geliş Tarihi: 23 Ağustos 2010 **Kabul Tarihi:** 20 Ekim 2010

Introduction

An ectopic pregnancy is one in which the blastocyst implants anywhere other than the endometrial lining of the uterine cavity. Ectopic pregnancy accounts for 1.3 to 2 percent of reported pregnancies (1). Ectopic pregnancy remains the leading cause of early pregnancy related death. It is the 4th common cause of maternal mortality (2, 3). Serial serum beta human chorionic gonadotropin (beta HCG) titers with subnormally decreasing or increasing pattern and transvaginal sonography are the most valuable diagnostic tools for confirming a clinical suspicion of ectopic pregnancy.

Clinical presentation varies from mild vaginal bleeding to hemoperitoneum and shock in the case of rupture. Nearly 95 percent of ectopic pregnancies implant in the fallopian tube and the remaining 3.2 percent are ovarian and 1.3 percent abdominal (4). Transvaginal sonography helps us to localize the ectopic pregnancy.

Abdominal pregnancy is an extremely rare and serious form of ectopic pregnancy with an incidence of 1 in 2200 to 10200

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Mehmet Metin Altay, Department of Obstetrics and Gynecology, Etlik Zübeyde Hanim Women's Health Training and Research Hospital, Ankara, Turkey Mobile: +90 532 367 22 38 Fax: 0 312 323 81 91 e.mail: altay_metin@yahoo.com*

doi:10.5152/jtgga.2010.42

of all pregnancies (5). We would like to report a case of primary abdominal pregnancy which is managed successfully by laparoscopic intervention.

Case Report

A 22 year old, gravida 1, para 0 woman admitted to our emergency room with mild vaginal bleeding and pain in lower abdomen. It was learned that she had 4 weeks of pregnancy according to the first day of her last menstrual period. She had undergone right salpingooferectomy previously because of tuba ovarian torsion. Upon admission, pelvic examination revealed cervical motion tenderness, adnexal tenderness bilaterally and rebound tenderness. Beta HCG assay was reported as 15826 IU/ml and hemoglobin concentration was 10.0 g/dl, hematocrit was 29.8 percent,blood pressure and pulse rate were normal. Transvaginal sonography demonstrated an empty uterus with an endometrium of 3 mm thickness and free fluid in the right adnexal region, in the left paraovarian localization and in front of the uterus. The right ovary could not be visualized since it was surgically removed and the left ovary was normal and intrauterine or extrauterine pregnancy could not be demonstrated in sonographic scanning. During her clinical follow up, from admission of the patient at the Emergency Room to evaluation of her at the Early Pregnancy Clinic of our hospital, vital signs remain stable but the patient's complaints got worse and hemoglobin concentration decrease from 10.0 to 8.0 and hematocrit from 29.8 to 25.9 percent.

With those findings, we suspected intraabdominal bleeding due to tubal abortion or abdominal pregnancy. Therefore we did a laparoscopy by using dual puncture technique. Standard surgical techniques were used with a camera and monitor set up. The uterus, the left tuba and the ovary were completely normal, no bleeding was observed from the left fimbria and there weren't any signs of tubal rupture. The right ovary and tuba had been amputated surgically 3 years previously, and there weren't also any signs of bleeding from the stump. From the pouch of Douglas and abdomen approximately 500 cc blood was aspirated. In the area between the right sacrouterin ligament and rectum, there was a bleeding area 2 cm in width containing trophoblastic tissue (Figure 1). The trophoblastic tissue was removed with forceps and sent for frozen pathological examination. Moderate active bleeding occured from the implantation site during the procedure and bleeding was controlled by electrocautery using bipolar forceps. Pelvis was irrigated with saline at the end of procedure and dilatation and curettage (D/C) was performed. A rapid decrease in the beta HCG titer post operatively confirmed the resolution of the pregnancy. Since the post operative hemoglobin concentration is 6.2 g/dl, 2 units of red blood cell were transfused and the patient was discharged 48 hours post operatively.

The frozen examination of the tissue removed intraoperatively revealed placental tissue fragments confirming the diagnosis of an abdominal pregnancy and histological examination of D/C material revealed secretory endometrium fragments, which was also confirming a primary abdominal pregnancy and excluding a uteroplasental fistula.

Discussion

Abdominal pregnancy is classified as primary or secondary. The diagnosis of primary abdominal pregnancy was confirmed according to Studdiford's criteria (6). According to those criteria the diagnosis of primary abdominal pregnancy is based on the following conditions:

1. Presence of normal tubes and ovaries,
2. Absence of a uteroplasental fistula,
3. Attachement exclusively to a peritoneal surface early enough in gestation to eliminate the likelihood of reimplantation after tubal abortion (7).

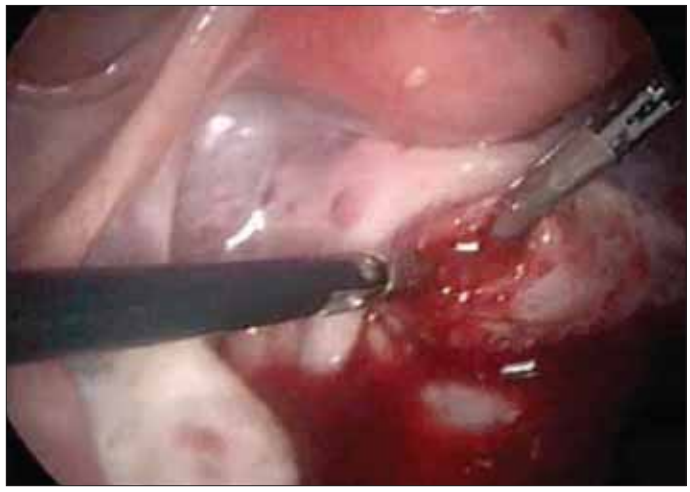

Figure 1. Primary abdominal pregnancy located next to the right sacrouterine ligament in the pouch of Douglas

Usual sites for implantation of an abdominal pregnancy are intraabdominal organs especially the bowel or mesentery or the peritoneum. Transvaginal sonography and MRI are the diagnostic imaging methods which may be used in case of abdominal pregnancy. Transvaginal sonography is the first choice for diagnosis. MRI may be helpful when the transvaginal sonography is inadequate and anatomic relationships are important for determination of surgical approach.

Most of the abdominal pregnancies are secondary, resulting from the reimplantation of a tubal abortion (8). Our case was an example of primary abdominal pregnancy which was managed by laparoscopic intervention. According to Studdiford's criteria tubes and ovaries should be normal. In our case there weren't any evidences of tubal abortion or tubal rupture or uteroplasental fistula, and the gestational age was as early as 4 weeks which also meets the Studdiford's criteria.

Laparoscopic procedure in diagnosis and treatment of ectopic pregnancy is gradually replacing laparotomy (9). Although in most cases of abdominal pegnancies, surgical management is via laparotomy because of risk of massive sometimes uncontrollable intraoperative hemorrhage from the implantation site (10). In the literature, there only a few cases of abdominal pregnancy in which laparoscopic procedure are used effectively in diagnosis and treatment (11-13). Laparoscopic procedure is usually successfull in treatment of abdominal pregnancy if the gestational age is early enough.

The vascular supply of implantation site of abdominal pregnancy is also important for determination of surgical approach. Sometimes the implantation site involves a vascular area such as the surface of colon as it was reported by Dover and Powell (11). In that case, the majority of gestational product had been removed laparoscopically from the surface of ascending

colon, leaving a small remnant of organized clot at the site because of the risk of colonic perforation and active bleeding.
If the diagnosis of abdominal pregnancy is made early enough, the laparoscopic management will be successfull, as in our case we presented here. We recommend laparoscopic approach for similar cases because laparoscopy is less invasive than laparotomy and it has shorter hospital stay.

Conflict of interest

No conflict of interest is declared by authors.

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Labial flap vaginoplasty with sacrospinous fixation

Sakrospinöz fiksasyonlu labial flap vajinoplasti

Chandrashekar Murthy[1], Kiran Ashok[2], Susheel Kumar Kalal[3]
[1]*Department of Gynaecology, Global Hospital, Bangalore, India*
[2]*Department of Gynecology, Pes Medical College, Kuppam, India*
[3]*Tara Hospital, Koppal, India*

Abstract

We present a case of congenital absence of Vagina which was treated by reconstruction of the vagina using vascular labial flaps. Furthermore, we anchored the neo-vagina to the Sacro-spinous ligament on either side. The aim of the attachment to the sacro-spinous ligament is to provide a durable apical support and to give an immediate, good vaginal length. Various techniques have been described for the construction of Neo-vagina. Except for sigmoid vaginoplasty, most other procedures are associated with a significant risk of post-operative re-stenosis, for which prolonged dilatation is necessary. Attaching to the sacro-spinous ligament gives the vagina good depth and, to some extent, decreases the risk of re-stenosis. This technique is simpler, does not require sophisticated instruments or prolonged post operative dilatation and is particularly suitable for under-developed countries.

(J Turkish-German Gynecol Assoc 2010; 11: 223-4)

Key words: Vaginoplasty, sacrospinous ligament

Received: 24 November, 2009 **Accepted:** 14 March, 2010

Özet

Vasküler labial flap kullanılarak yapılan vajina rekonstrüksiyonu ile tedavi edilmiş bir konjenital vajina yokluğu olgusunu sunuyoruz. Ayrıca, neovajinayı her iki tarafta sakrospinöz ligamente sabitledik. Sakrospinöz ligamente tutturulmasının nedeni kalıcı bir apikal destek sağlamak ve anında iyi bir vajinal uzunluk oluşturmaktır. Neovajinanın konstrüksiyonu için çeşitli teknikler tanımlanmıştır. Sigmoid vajinoplasti hariç diğer işlemlerin çoğu, uzun süreli dilatasyonun gerekli olduğu, ameliyat sonrası yeniden kapanma açından belirgin risk ile ilişkilidir. Sakrospinöz ligamente tutturmak vajinaya iyi bir derinlik sağlar ve yeniden kapanma riskini bir ölçüde azaltır. Bu teknik daha basittir, karmaşık donanım gerektirmez, ameliyat sonrası uzun süreli dilatasyon gerektirmez ve az gelişmiş ülkeler için özellikle uygundur.

(J Turkish-German Gynecol Assoc 2010; 11: 223-4)

Anahtar kelimeler: Vajinoplasti, sakrospinöz ligament

Geliş Tarihi: 24 Kasım 2010 **Kabul Tarihi:** 14 Mart 2010

Case Report

A 23 years old lady presented with primary amenorrhea. She was aware of her condition and requested construction of a neo-vagina. On examination, it was found that she had a normal feminine body habitus, normal pubic and axillary hair, normal labia majora and minora, good breast development, but absent vagina. Ultrasound showed absence of the uterus and presence of ovaries. Ultrasound and intravenous pyelogram revealed that her renal system was normal. She had no skeletal anomalies. Her karyotype was 46 XX. A diagnosis of Mullerian agenesis was made.

We planned to construct a neo-vagina using labial skin flaps. The patient was told about the cosmetic changes of appearance of her genitalia and she had no problem with this. An informed consent was obtained. A neo-vagina was created using bilateral labial flaps and this was anchored to the sacro-spinous ligament on either side. Her post-operative course was uneventful and at 6 weeks she had a functional neo-vagina. The follow-up up to 8 months revealed no complications.

Surgical Procedure

Under spinal anesthesia, with the patient in the lithotomy position, the area was painted and draped. Vertical incisions were made just inside the labia minora on both sides of midline. Through these incisions, a space was developed on each side and extended into the corresponding para-rectal space. By excising the tissue remaining in the midline, the two spaces were united. The sacro-spinous ligament was identified on each side and stitches were inserted on each side using vicryl 2-0.

Next, full thickness skin flaps were taken from each labia majora (Figure 1) with the intact end at the lower part, and these were passed through a rent made in the labia minora into the space created. A sacro-spinous stitch was passed through the apex of each flap and held long. The sides of each flap were attached to each other by vicryl stitches. When the sacro-spinous stitch was tied, a 10 cm long tube of neo-vagina was obtained. Finally, the raw area on each labia majora was closed with interrupted stitches. A 10cm mould was kept in the neovagina, to be removed 10 days later. On the 10th post operative day the mould was removed, the cavity was irrigated with warm saline and a fresh mould was kept. Mould changing and irrigation continued weekly for 4 weeks, at the end of which the wound had healed and a functional vagina of 10cm was obtained (Figure 2).

Intra-operative bleeding was about 400ml. There was no bladder or bowel injury in our case.

Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Kiran Ashok, Pes Medical College, Kuppam, Chittor Dist Kuppam, India*
Phone: +91 9964015207 e.mail: drkirana@gmail.com
doi:10.5152/jtgga.2010.43

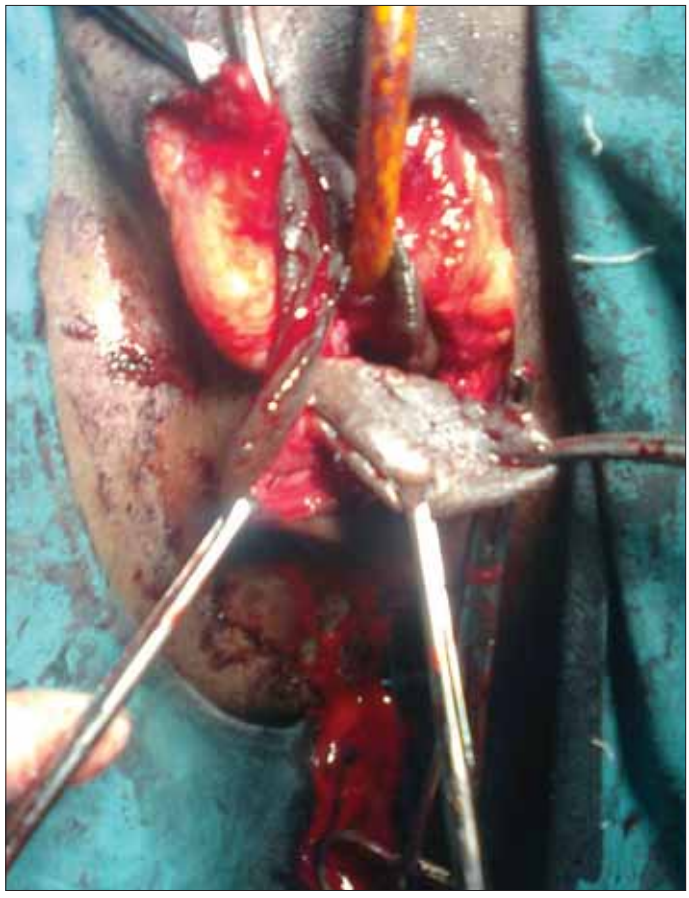

Figure 1. Formation of labial flaps

Figure 2. End result of the procedure- note the vaginal depth

Discussion

The reported incidence of congenital absence of the vagina varies from 1 in 4,000 to 1 in 80,000. Nonsurgical creation by successive dilatation of the vagina (Frank method) is the appropriate first line of approach in the majority of patients because of its low morbidity. However, this method necessitates highly motivated young women. Surgical methods include the Abbe-McIndoe procedure, using a peritoneal flap, buccal mucosa, and pudendal thigh flap (1-3). The most common operation performed to date is the McIndoe operation but it has the disadvantage of shrinking of the neovagina in the upper third, with complete and partial vaginal obliteration (4). Intestinal flaps have also been used in the correction of vaginal agenesis, particularly by pediatric surgeons in children because intestines have a luminal structure where lubrication is sustained by secretion of intestinal segments and their long-term dilatation is unnecessary (5). However, this requires laparotomy and intestinal resection and anastomosis, which is a technically challenging procedure with its own complications. Recently, various vaginoplastic techniques using laparoscopic assistance have been described (6, 7). In many underdeveloped countries, laparoscopic facilities may not be available. Our procedure of using labial flaps is a new technique which is technically simple and does not require sophisticated instruments. The intact lower end of the flap brings blood supply from the internal pudendal vessels. Using labial flaps gives a vascularized pedicle which decreases the chance of flap ischemia and necrosis. Fixation of the flaps to the sacro-spinous ligament provides an immediate, good vaginal length, prevents the stenosis that can occur at the apex and also provides a durable vault support. Although a short period of moulding is necessary, long term dilatation may not be required. In our case, the only complication was intra-operative hemorrhage of about 400 ml. Expected complications include injury to the bladder and rectum, and infection beneath the flaps. Our method of creation of a neovagina can be used for reconstruction after oncological procedures such as vaginectomy, exenteration surgery etc.

We conclude that labial flap vaginoplasty with sacro-spinous fixation is a simple and effective procedure for construction of a neo-vagina. This technique is simpler, does not require sophisticated instruments, does not require prolonged post operative dilatation and is particularly suitable for underdeveloped countries.

Conflict of interest:
No conflict of interest is declared by authors.

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Prenatal diagnosis and postmortem findings of Neu-laxova syndrome

Neu-laxova sendromunun prenatal tanısı ve postmortem bulguları

Ebru Tarim[1], Filiz Bolat[2]

[1] *Department of Obstetrics and Gynecology, Baskent University, Adana, Turkey*

[2] *Department of Pathology, Baskent University, Adana, Turkey*

Abstract

Neu-laxova syndrome is a lethal, autosomal recessive condition associated with ectodermal abnormalities and other characteristic features, including microcephaly, marked intrauterine growth restriction, limb deformities, central nervous system malformations and abnormal facial features, consisting of severe proptosis with ectropion, hypertelorism, micrognathia, flattened nose, malformed ears, and gaping mouth. Here we present a fetus having a dysmorphic face with proptotic eyes, retracted eye lids, depressed nasal bridge and micrognathia at 25 weeks of gestation. The extremities were contracted and no fetal movements were observed during the ultrasonographic examination. The fetus also had microcephaly and the amniotic fluid was increased. The pregnancy was terminated and the abnormalities demonstrated on prenatal ultrasound were confirmed at autopsy.

(J Turkish-German Gynecol Assoc 2010; 11: 225-7)

Key words: Neu- laxova syndrome

Received: 8 January, 2010 **Accepted:** 23 February, 2010

Özet

Neu-laxova sendromu yaşamla bağdaşmayan, otozomal resesif bir hastalıktır ve ektodermal anormalliklerle birliktelik gösterir. Diğer karakteristik özellikleri; mikrosefali ile birlikte belirgin gelişme geriliği, ekstremite deformiteleri, santral sinir sistemi anormallikleri ve anormal yüz görüntüsü, ektropiyon ile birlikte ciddi proptozis, hipertelörizm, mikrognati, düzleşmiş burun sırti, malforme kulaklar ve açık ağızdır. Bu vaka sunumunda 25. gebelik haftasında propitotik gözle birlikte dismorfik yüz, retrakte göz kapakları, düzleşmiş burun sırtı ve mikrognatinin eşlik ettiği fetal anomaliyi sunduk. Ultrasonografik incelemede ekstremitelerin kontrakte olup, fetal hareket hiç izlenmedi. Fetusun ayrıca mikrosefalisi olup, polihidramniosu mevcuttu. Gebelik termine edildi ve prenatal dönemde ultrasonografi ile tespit edilen bulgular otopsi ile konfirme edildi.

(J Turkish-German Gynecol Assoc 2010; 11: 225-7)

Anahtar kelimeler: Neu- laxova sendromu

Geliş Tarihi: 08 Ocak 2010 **Kabul Tarihi:** 23 Şubat 2010

Introduction

Neu-laxova syndrome (NLS) is a rare, autosomal recessively inherited syndrome characterized by intrauterine growth restriction (IUGR), central nervous system (CNS), and skin and limb abnormalities (1, 2). Here we present a fetus with this syndrome with a description of its prenatal and postmortem findings.

Case report

A twenty seven year old G2 P2 pregnant woman was referred with a presumed diagnosis of fetal anomaly. She did not report for the routine antenatal follow-up. Her previous history was unremarkable except for first degree consanguinity with her partner. She did not report any drug use or radiation exposure. The last menstrual period was uncertain.

At the ultrasound examination; the fetus had a biparietal diameter and head circumference concordant with 22 weeks, and an abdominal circumference and femur length with 25 weeks (estimated gestational age was 23,5 weeks according to the ultrasound measurement). Microcephaly was prominent. The forehead was sloping, the eyes markedly proptotic, intraorbital distance was15 mm, extraorbital distance measured 46mm The mouth was gaping and micrognathia was present (Figure 1). Cardiac examination was normal,but the stomach was not visible. The penis was 7, 9 mm, (<10 p), giving the impression of ambiguous genitalia (Figure 2) (3). The hands were clenched, the elbows and the hips were flexed, the

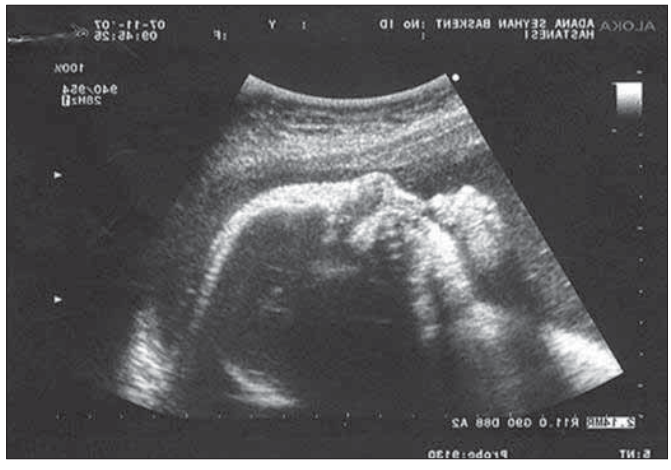

Figure 1. Abnormal facial profile on ultrasound

Address for Correspondence / Yazışma Adresi: *Doç. Dr. Ebru Tarim, Baskent Üniversitesi Adana Uygulama ve Arastırma Merkezi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Baraj Yolu 1. Durak 01110, Adana, Turkey Phone: +90 322 458 68 68-2203 e.mail: eatarim@hotmail.com*

doi:10.5152/jtgga.2010.44

knees hyperextended. The feet seemed dysmorphic. The fetus did not move during the 30 minute examination. The amniotic fluid was increased and 82 mm by single pocket measurement. To exclude a chromosomal abnormality, a cordocentesis was performed which revealed a normal male karyotype. At this time, the diagnosis ofNLS was strongly suspected. The poor prognosis was discussed with the couple and they opted for termination. At the post mortem examination the skin was thick. The baby seemed to be covered by a thick membrane. Microcephaly and micrognathia were present. The eyes were proptotic with almost no eyelids. The nasal ridge was broad, ears were low set (Fig. 3) with multiple bilateral contractures present at the extremities. The arms were flexed at the elbows, the hands were clenched. The legs were flexed at the hips and hyperextended at the knees (Fig. 4). The external genitalia had a male appearence;however, the thick skin covering the genitalia gave the impression of ambiguous genitalia (Fig. 5).

At autopsy, the confirmed the sonographic findings of microcephaly, proptotic with mild ocular hypertelorism, microphthalmia, an open mouth, micrognathia, a flattened nose, low set ears, very short neck and abnormal joint positioning, as predicted by ultrasound. The penis and scrotum were hypoplastic. The skin was thick, shiny and peeling in places, and this was specially marked on the trunk and inguinal regions. Histological section of the skin demonstrated a thick, compact hyperkeratosis with a normal granular layer, and dermal edema, and increased subcutaneous fat (Fig. 6). Hair follicles and subcutaneous glands were present. Additionally, the lungs were hypoplastic. No cardiac or renal abnormalities were found.

Neuropathololologic examination revealed a brain weight of 22.5 g, with post-fixation weight 11.2 g (concordant with $<20^{th}$ weeks). On gross examination, the surface of the brain was smooth and the gyral pattern was poorly developed, with a limited number of well-formed gyri. The cerebellum was normal. The ventricular system was dilated, especially the occipital horns of the lateral ventricles. Cortical parenchyma was thinned in the occipital lobe adjacent to the ventricules. Histological examination of the brain revealed findings of focal neuronal migration disorder.

Based on the clinical and histopathological findings, a diagnosis of NLS was made.

Discussion

Neu-laxova syndrome is an autosomal recessively inherited, lethal syndrome characterized by intrauterine growth restriction, CNS abnormities and skin disease (1, 2). Microcephalies, sloping forehead, ocular hypertelorism, exophthalmus, flat nasal bridge, lowset ears, micrognathia, a gaping mouth with everted lips and flexion contractures are the main features of the syndrome. It is invariably fatal. The CNS defects, pulmonary hypoplasia and infection are thought to be responsible for the short survival of these infants. IUGR, swollen limbs, poor bone mineralization and short survival can also be caused by the loss of protein through skin fissures (1, 4).

CNS anomalies, skin disease and limb contractures are the main features in NLS. Among the reported CNS abnormalities are lissencephaly, dilated ventricles, absent corpus callosum, absent or small anterior fontanel, calcifications, cerebellar defects (4).

The characteristic limb posture is flexed elbows, wrists, clenched hands, flexed hips and hyperextended legs. Syndactyly, brachidactyly, overlapping digits, webbing, vertebral anomalies, flexion deformities and poor bone mineralization are common

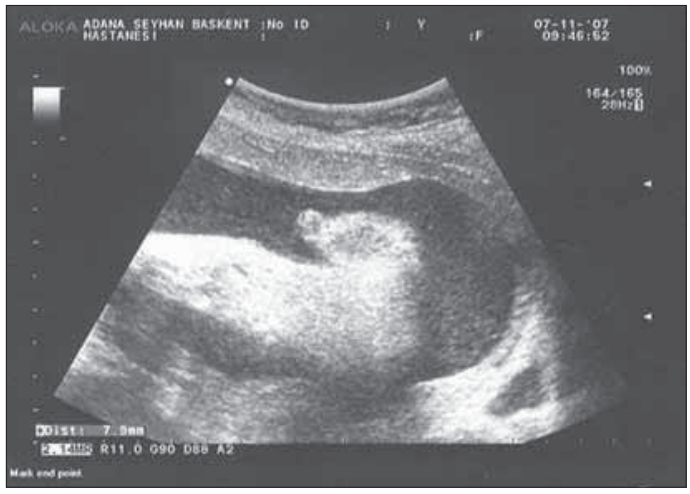

Figure 2. Ultrasonographic appearance of external genitalia

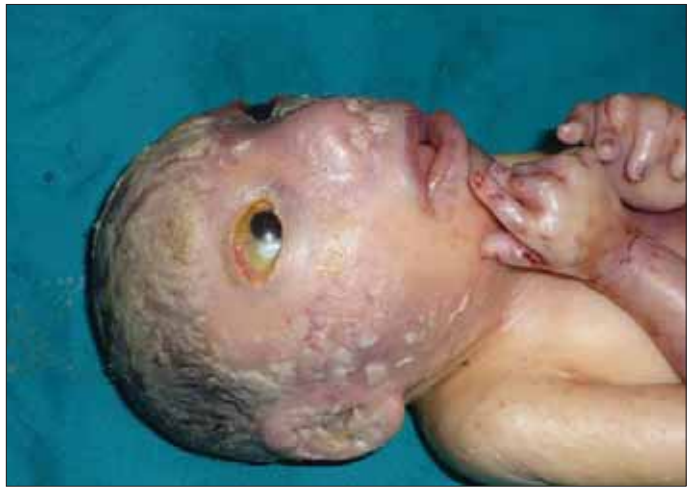

Figure 3. Proptotic eyes with almost no eyelids and broad nasal ridge at postmortem examination

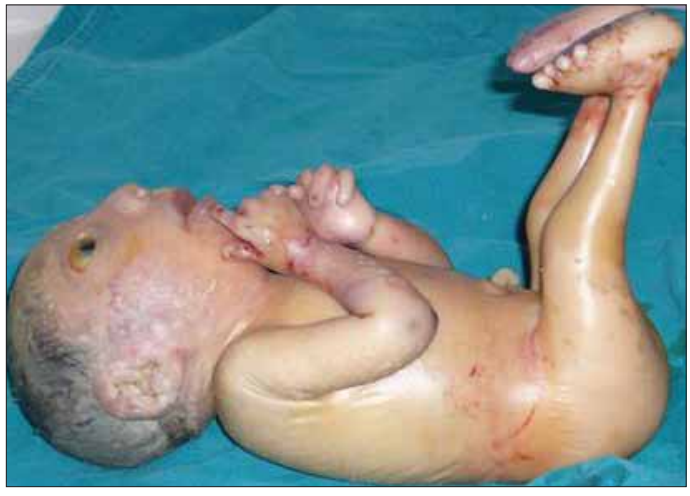

Figure 4. The legs were flexed at the hips and hyperextended at the knees

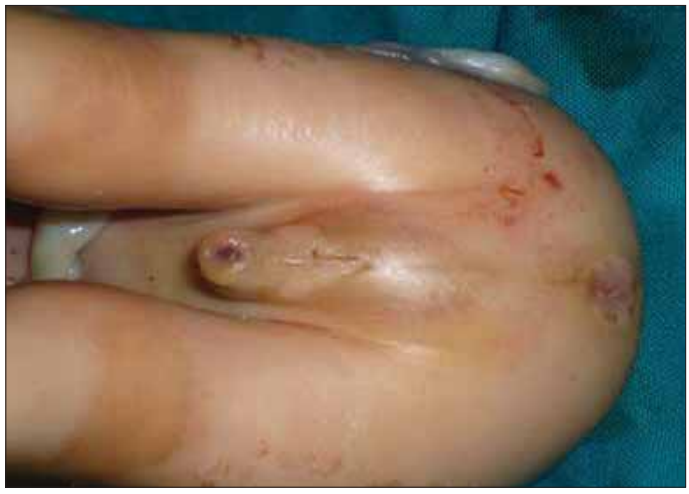

Figure 5. External genitalia at post mortem examination

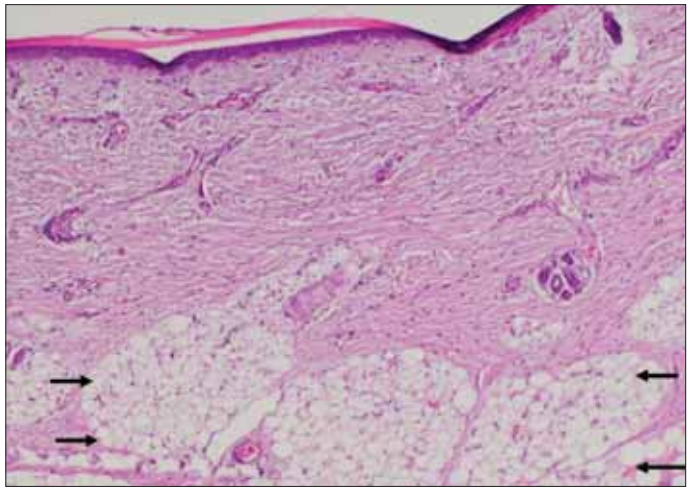

Figure 6. Skin biopsy specimen revealed a thick, compact hyperkeratosis with a normal granular layer. Deposition of fat in the dermis (arrows). [Hematoxylin and eosin (H&E)x100]

features of these fetuses (5).

NLS is characterized by a yellow, scaling ichthyosis or a taut, shiny, incomplete, collodion like membrane involving the upper body. In approximately 40% of the cases, the skin disease manifests itself as ichthyosis. The skin looks taut and shiny, reminiscent of restrictive dermopathy (6).

The differential diagnosis includes severe arthrogryposis syndromes such as cerebro-ocular-facial-skeletal (COFS) syndrome, the lethal multiple pterygium syndrome, restrictive dermopathy, fetal akinesia/ hypokinesia sequence, cerebro-arthro-digital syndrome, Harlequin fetus, Smith- Lemli- Opitz syndrome and Miller – Dieker syndrome (4, 7, 8).

Microcephaly with brain hypoplasia, flexion contractures, and micrognathia are also seen in COFS syndrome, but the typical, deep set eyes with blepharophimosis and prominent root of the nose are very different from the protruding eyes and flattened nose seen in NLS. The lethal multiple pterygium syndrome shares many abnormalities with Neu-laxova, such as flexion contractures, and prenatal onset growth deficiency, but the pterygia bridging of virtually all joints seen in this syndrome was not present in our case. Intrauterine growth restriction, hypertelorism, micrognathia, and joint contractures are also seen in restrictive dermopathy, but the rigid and tense skin, small “pinched” nose, and small mouth also associated with this disorder were not seen in our case (6).

Fetal akinesia/ hypokinesia sequence (Pena-Shoiker) demonstrates pulmonary hypoplasia, limb deformities, and a facies similar to NLS, but lacks CNS and skin manifestations (8).

Harlequin fetus is a lethal condition with ichthyosis, eclabion, ectropion, and limb contractures similar to NLS. Absence of severe microcephaly and CNS abnormality in Harlequin fetus may help in differentiating the NLS (7).

Smith- Lemli- Opitz syndrome is characterized by prenatal and postnatal growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the second and third toes and severe mental retardation. Miller-Dieker syndrome is characterized by microcephaly, lissencephaly, pachygyria, narrow forehead, hypoplastic male external genitalia, growth retardation, seizures and profound mental retardation. Microcephaly and IUGR are features of both Smith- Lemli- Opitz and Miller-Dieker syndromes (9). However, specific findings such as severe microcephaly, ichthiyosis, and peculiar face and cerebral anomalies are sufficient elements to differentiate NLS from other syndromes, as in our case.

In conclusion, NLS is a rare and uniformly lethal disorder characterized by multiple abnormalities. Since the prognosis is extremely poor, prenatal diagnosis is important. Counseling is mandatory for the affected consanguineous couples, as autosomal recessive inheritance with a 25% recurrence risk is obvious (10).

Conflict of interest

No conflict of interest is declared by authors.

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Prenatally diagnosed partial trisomy 3q case with an omphalocele and less severe phenotype

Prenatal tanısı konulmuş, omfalosel ve hafif fenotipik anormalliklere sahip kısmi trizomi 3q olgusu

Deniz Cemgil Arıkan[1], Ayhan Coşkun[1], İlker Arıkan[2], Gürkan Kıran[1], Gülay Ceylaner[3]

[1] *Department of Obstetrics and Gynecology, Kahramanmaraş Sütçü Imam University, Kahramanmaraş, Turkey*

[2] *Department of Obstetrics and Gynecology, Zonguldak Karaelmas University, Zonguldak, Turkey*

[3] *Intergen Genetics Center, Ankara, Turkey*

Abstract

Trisomy 3q is a very rarely reported chromosomal disorder. Duplication of part of the long arm of human chromosome 3 causes a distinct and severe syndrome that leads to multiple congenital abnormalities. A 27 year-old pregnant woman was admitted to our clinic at 17 weeks of gestation. Prenatal sonography identified a fetus with an omphalocele that contained the liver and bowel , mild ventriculomegaly and polyhydramnios. Amniocentesis revealed the karyotype of 46, XY, der (3) (3qter→3q21: : 3pter→3qter). The pregnancy was subsequently terminated. Postnatally, the proband showed midfacial hypoplasia, micrognathia, hypoplastic 12th ribs, omphalocele and prominent heels. We reported this partial trisomy 3q case because he had less marked malformations compared to other reported cases and also different features such as an omphalocele and hypoplastic 12th rib which have not been described previously in an isolated Trisomy 3q case with this karyotype.

(J Turkish-German Gynecol Assoc 2010; 11: 228-32)

Key words: Partial Trisomy 3q, omphalocele, amniocentesis

Received: 16 December, 2009 **Accepted:** 11 February, 2010

Özet

Trizomi 3q nadir görülen bir kromozom anomalisidir. İnsan 3. kromozomunun uzun kolunun bir kısmının duplikasyonu multipl kongenital anormalliklerle birlikte olan farklı ve ciddi bir sendroma yol açar. Yirmi-yedi yaşındaki gebe kadın mevcut gebeliğinin 17. haftasında polikliniğimize başvurdu. Fetusta yapılan prenatal ultrasonografide, karaciğer ve barsak içeren omfalosel, hafif ventrikülomegali ve polihidramnios tespit edildi. Yapılan amniyosentez sonucunda karyotip 46, XY, der (3) (3qter→3q21: :3pter→3qter) geldi. Ardından tıbbi terminasyon uygulandı. Terminasyon sonrası fetusta; midfasiyal hipoplazi, mikrognati, hipoplastik 12. kosta, omfalosel ve çıkıntılı topuklar tespit edildi. Biz bu olguyu, daha önce yayınlanmış izole Trizomi 3q olgularına göre daha hafif malformasyonlar içermesi ve ayrıca omfalosel ve hipoplastik 12. kosta gibi onlarda bulunmayan ek anomalilere sahip olması nedeniyle yayınladık.

(J Turkish-German Gynecol Assoc 2010; 11: 228-32)

Anahtar kelimeler: Kısmi Trizomi 3q, omfalosel, amniyosentez

Geliş Tarihi: 16 Aralık 2009 **Kabul Tarihi:** 11 Şubat 2010

Introduction

Trisomy 3q is a very rarely reported chromosomal disorder. The majority of cases have involved duplication of the segment 3q21-qter and, in most cases, these duplications are the result of unbalanced segregations of balanced parental translocation involving chromosome 3 (1).

Duplication of part of the long arm of human chromosome 3 causes a distinct and severe syndrome that leads to multiple congenital abnormalities. Some of the malformations include congenital heart defects (septal defects), renal malformations (polycystic kidneys or dysplasia), ocular malformations (strabismus, nystagmus, cataract, corneal opacities, colobomas of the iris, and anophthalmia), facial malformations (hypertrichosis, hypertelorism, anteverted nostrils, long philtrum, maxillary prognathism, downturned corners of the mouth, cleft palate, micrognathia) and limb anomalies (hypoplasia of the phalanges, camptodactyly and clinodactyly), malformed auricles, short/webbed neck, seizures and brain malformations (2).

Here we report a prenatally diagnosed partial Trisomy 3q (46, XY, der(3) (3qter→3q21::3pter→3qter) karyotype) case with an omphalocele (containing liver and bowel) and a less severe phenotype than the previously reported cases with such a large duplicated segment.

Case Report

A 27 year-old G3P1A1C0 pregnant woman was admitted to the Kahramanmaras Sutcu Imam University Obstetrics Outpatient Clinic for pregnancy follow-up. She had a first trimester pregnancy loss and pregnancy termination history due to diaphragmatic hernia, short extremities and Dandy-Walker malformation. The parents were relatives (first degree cousins). There was no positive family history. Prenatal sonography at 17 weeks revealed a 31x21 mm sized ompha-

Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Deniz Cemgil Arıkan, Kahramanmaraş Sütçü İmam Üniversitesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Yörük Selim Mah. Gazi Mustafa Kuşçu Cad., Kahramanmaraş, Turkey Mobile: +90 505 802 28 47 e.mail: drdenizarikan@hotmail.com*

doi:10.5152/jtgga.2010.45

locele protruding out of the abdominal wall on the right side of the umbilical cord that contained the liver and bowel (Figure 1), mild ventriculomegaly and polyhydramnios. The couple was counseled and amniocentesis was performed after their written informed consent form had been obtained. Amniocytes were cultured in three independent culture flasks and then harvested. Chromosome analysis was performed at 550 band level and 46,XY,der(3)(3qter→3q21::3pter→3qter), partial trisomy 3q was detected. This trisomy includes the segment between q21 band to q terminal. The couple decided to terminate the pregnancy which was carried out at 21 weeks gestation. Postmortem examination revealed midfacial hypoplasia, micrognathia, hypoplastic 12th ribs, omphalocele and prominent heels (Figure 2). As the couple did not permit autopsy, prenatal ultrasound findings were confirmed with magnetic resonance imaging. Parental chromosome analysis was performed and maternal pericentric inversion of chromosome 3 (46, XX, inv (3) (p26q21)) was detected, while the father had normal (46, XY) karyotype.

Research ethics approval was obtained from the Ethics Committee of Kahramanmaras Sutcu Imam University and signed informed consent was obtained from the patient.

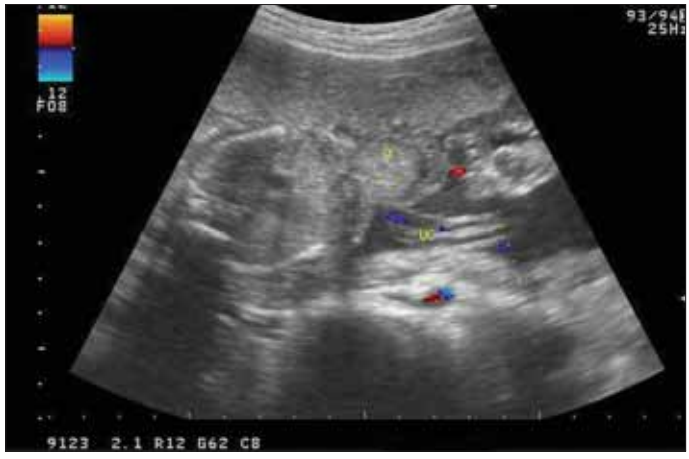

Figure 1. **Ultrasonographic view of omphalocele (o: omphalocele, uc: umbilical cord)**

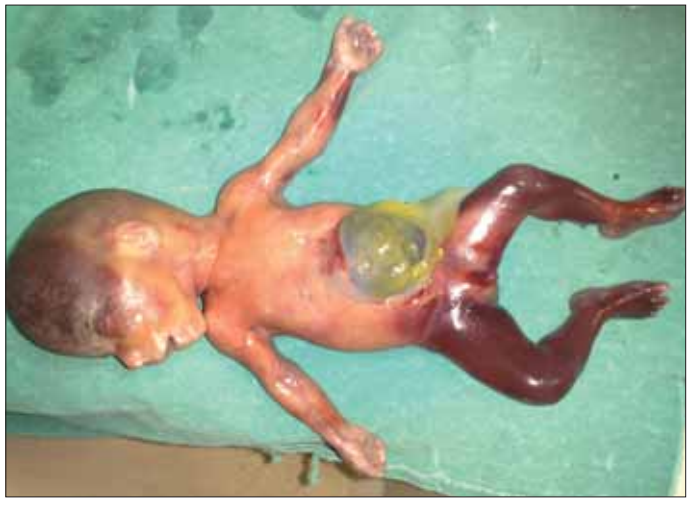

Figure 2. **Anterior view of baby**

Discussion

In the literature, to our knowledge, 94 patients with duplication of 3q have been reported. However, pure duplications are rare because most of the reported patients appear to carry unbalanced translocations. Also, recently mostly cases with more distal duplications-either single abnormalities or associated with a deletion of another chromosomal segment-have been described. Our case had 46, XY, der (3) (3qter→3q21::3pter→3qter) karyotype and we could only find 8 familial and 6 de novo cases with the same duplicated segment in the literature. The dysmorphic findings reported in these cases, and in partial Trisomy 3q cases with duplication of different segments, show significant differences from each other, as given in Table 1 (3-23). Compared to these cases, our patient manifested a less severe clinical picture, with some unusual characteristic features such as midfacial hypoplasia, hypoplastic 12th rib and prominent heels (Table 1). The case we present is a new example of familial cases.

Steinbach et al. described the most common abnormal features in these cases, such as statomotoric retardation, shortened life span, and multiple congenital anomalies (MCA) including abnormal head configuration, hypertrichosis, hypertelorism, ocular anomalies, anteverted nostrils, long philtrum, maxillary prognathia, down-turned corners of the mouth, highly arched or cleft plate, micrognathia, malformed auricles, short, webbed neck, clinodactyly, simian crease, talipes, and congenital heart disease (4). As shown in Table 1, micrognathia, short neck and eye anomalies were the most common findings among reported cases. Thoracic abnormality (absent ribs) was reported only by Steinbach et al (4) while our case had a hypoplastic 12th rib.

An omphalocele is a herniation of bowel, liver and other abdominal viscera into a membranous sac with the umbilical cord at its apex. The prevalence of omphalocele varies considerably, ranging from 0.8 to 3.9 per 10,000 births (23). Abnormal karyotypes have been reported in 10 to 40% (combined mean rate of 12%) of neonates with omphaloceles. Trisomy 18 and 13 are the most common associating chromosomal anomalies, followed in frequency by trisomy 21, 45, X (Turner syndrome) and triploidy (24). Usually, abnormal karyotype incidence increases when the liver is intracorporeal (25). Chen et al. (3) reported a case with duplication of 3q21→qter and deletion of 11q23→qter resulting from an unbalanced segregation of a maternal t (3;11) reciprocal translocation. At prenatal sonographic examination they demonstrated an omphalocele containing the liver (3). Yatsenko et al. (23) reported a case with karyotype of 46,XY,der (4)t(3;4)(q27.3;q32.3)mat, resulting in trisomy for 3q27.3→qter and monosomy for 4q32.3→qter. Their case had an omphalocele that contained part of the left hepatic lobe, stomach, and transverse colon. They also searched the literature to identify previously reported cases of partial trisomy 3q associated with omphalocele, and found that 26 of 93 cases presented with an omphalocele (23). In all of them, the area of duplication includes the region 3q27.3→qter. Yatsenko et al also attempted to specify which chromosomal region is responsible for omphalocele and searched previously reported 40 patients with monosomy of 4q. They found that none of them had omphalocele. As a result, they suggested that a dosage-sensitive locus on

Table 1. Comparison of clinical phenotype of our case with cases in the literature

	Literature	Our case
Head and neck	• Cleft lip, plate (Blumberg, 1980; Pires, 2005) • Broad and flat nasal bridge (Blumberg, 1980; Zafra de la Rosa, 2005; Gamerdinger, 2006; Gimelli, 2007) • Anteverted nostrils (Chiyo,1976; Fear,1979; Blumberg, 1980; Ismail, 1991; Gimelli, 2007) • Malformed ears (Blumberg, 1980; Ismail, 1991; de Azevedo Moreira, 2005; Carreira, 2009) • Downturned corners of the mouth and thin lips (Ismail, 1991; Zafra de la Rosa, 2005; Gamerdinger, 2006; Grossmann, 2009) • Micrognathia (Chiyo,1976; Fear,1979; Kondo,1979; Ismail,1991; Pires, 2005; Zafra de la Rosa, 2005) • Short neck (Chiyo,1976; Fear,1979; Kondo,1979; Ismail,1991; de Azevedo Moreira, 2005; Zafra de la Rosa, 2005; Gimelli, 2007) • Cystic hygroma (Pires, 2005) • Wide nasal bridge (Zafra de la Rosa, 2005; Grossmann, 2009) • Prominent philtrum (Zafra de la Rosa, 2005; Gamerdinger, 2006; Grossmann, 2009) • Prominent forehead (Gamerdinger, 2006)	Midfacial hypoplasia Micrognathia
Eye	• Coloboma of iris (Fryns, 1984) • Cataract (Mulcahy, 1979; Gustashaw, 1985) • Microphthalmia (Fear, 1979; Steinbach, 1981; Qureshi, 1994; de Azevedo Moreira, 2005) • Corneal opacities and other eye malformations (Blumberg, 1980; Qureshi, 1994; de Azevedo Moreira, 2005) • Congenital glaucoma (Kondo,1979; Blumberg, 1980) • Coloboma of optic nerve (Ayral, 1984) • Hypertelorism (Ismail, 1991; Zafra de la Rosa, 2005; Gamerdinger, 2006; Grossmann, 2009) • Epicanthic folds (Zafra de la Rosa, 2005; Grossmann, 2009)	Could't evaluated
Thorax	• Absent ribs (Steinbach, 1981)	Hypoplastic 12th rib
Skeletal system	• Thoracic hemivertebrae (Steinbach, 1981) • Narrow pelvis (Steinbach, 1981) • Dislocated elbow (Steinbach, 1981; Zafra de la Rosa, 2005) • Dislocated wrist (Steinbach, 1981) • Dislocated phalanx (Steinbach, 1981)	Normal X-rays
Extremities	• Clenched hands (Steinbach, 1981) • Abnormal dermatoglyphics (Steinbach, 1981) • Bifid thumb (Mulcahy, 1979; Steinbach, 1981) • Polydactyly (Fryns, 1979) • Syndactyly (Kondo, 1979; Zafra de la Rosa, 2005) • Fifth-finger clinodactyly (Chiyo, 1976; Fear,1979; Blumberg, 1980; Zafra de la Rosa, 2005; Gimelli, 2007) • Short limbs (Blumberg, 1980; Gimelli, 2007)	Prominent heels

	• Abnormal foot position (de Azevedo Moreira, 2005; Zafra de la Rosa, 2005; Carreira, 2009) • Brachydactyly (Grossmann, 2009) • Congenital hip dysplasia (Gamerdinger, 2006)	
Internal organ anomalies	• Cardiac anomalies (Chiyo, 1976; Fear, 1979; Steinbach, 1981; Pires, 2005; Zafra de la Rosa, 2005) • Polycystic kidney (de Azevedo Moreira, 2005) • Renal anomalies (Blumberg, 1980) • Renal cystic dysplasia (Blumberg, 1980) • Renal cortical cysts (Chiyo, 1976; Fear, 1979) • Unilateral renal agenesis (Blumberg, 1980) • Renal calcification (Ismail, 1991) • Adrenal neuroblastoma (Qureshi, 1994) • Malrotation (Blumberg, 1980) • Lung hypoplasia (Blumberg, 1980; Qureshi, 1994) • Omphalocele (Mulcahy, 1979; Chen, 1996; Yatsenko, 2003; Park, 2008)	Omphalocele (containing liver and bowel)
Central nervous system	• Dandy- Walker malformation (Chiyo, 1976; de Azevedo Moreira, 2005) • Cerebellar hypoplasia (Steinbach, 1979) • Arhinencephaly (Steinbach, 1979) • Hypoplasia of corpus callosum (Steinbach, 1979) • Microcephally (Blumberg, 1980) • Spina bifida (de Azevedo Moreira, 2005; Gimelli, 2007)	Ventriculomegaly
Genital system	• Hypospadias (Fryns, 1984) • Bicornuate uterus (Chiyo, 1979; Blumberg, 1980) • Streak ovaries (Blumberg, 1980) • Duplication of the vagina and cervix (Blumberg, 1980) • Ambiguous genitalia (Gimelli, 2007)	
Anal anomalies	• Anteriorly placed anus (Fryns, 1979) • Anal stenosis (Gustashaw, 1985)	

the distal 3q could be responsible from an omphalocele (23). Our case also has an omphalocele and no other chromosomal component other than a duplicated 3q segment.

In partial Trisomy 3q cases the abnormal genotypes are usually the result of parental abnormalities of chromosome 3. Reciprocal translocation is the most frequent parental chromosome anomaly. In our case, parental chromosome analysis demonstrated a maternal pericentric inversion of chromosome 3 (46, XX, inv (3) (p26q21)). Fear et al (8) demonstrated 5 (83%) maternal and 1 (17%) paternal structural anomalies in parents of 6 Trisomy 3q cases. Yatsenko et al. (23) demonstrated malsegregation of a parental balanced chromosomal rearrangement in 41 (64%) of 64 families, and the remaining (36%) were de novo. In cases with omphalocele, inheritance was maternal in 6 (%75) and paternal in 2 (25%) of 8 families. Pericentric inversions, unlike other balanced chromosomal variations, may cause deletion and duplication in conceptuses due to unbalanced cross-over in meiosis. These deletions or duplications may be either of a size detectable under the microscope as in our case, or be very small and may escape observation. Thus, if unbalanced chromosomal alterations have not been detected by conventional cytogenetic analyses in such cases, the recently developed array-CGH method should be recommended for scanning submicroscopic deletions and duplications.

In conclusion, we reported this partial trisomy 3q case because he had less marked malformations compared to other reported cases and also different features such as an omphalocele and hypoplastic 12th rib, which have not been described previously in an isolated Trisomy 3q case with 46, XY, der (3) (3qter→3q21::3pter→3qter) karyotype. For detection of etiology and determination of the risk in subsequent pregnancies, parental chromosomal analysis is mandatory in cases with this kind of structural chromosomal alt.

Conflict of interest

No conflict of interest is declared by authors.

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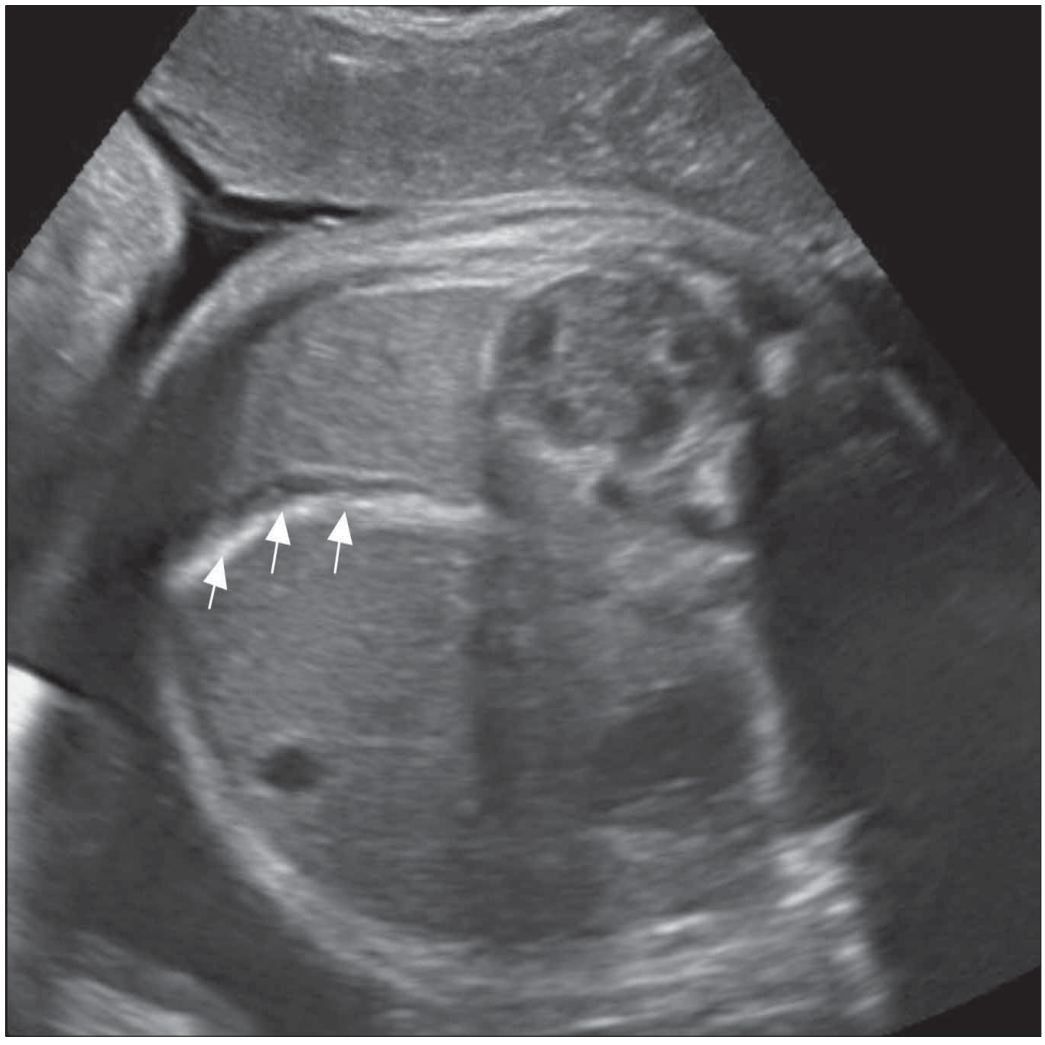
What is Your Diagnosis?



Address for Correspondence / Yazışma Adresi: *Doç. Dr. Özlem Pata, Ataköy Konakları, C4- B9 33070 Ataköy, Bakırköy, İstanbul, Türkiye*
Phone: +90 212 414 41 37 e.mail: ozpata@yahoo.com
doi:10.5152/jtgga.2010.46

Answer

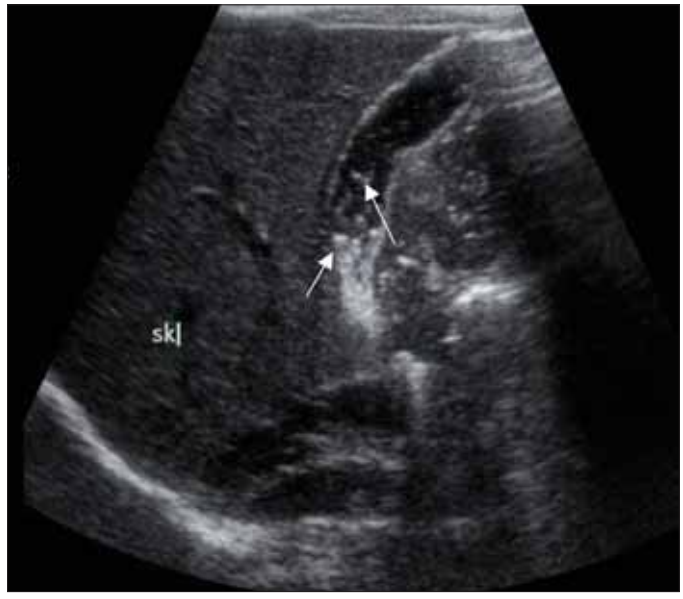
Fetal cholelithiasis is a rare finding with controversial clinical significance. Although recent advances in fetal ultrasonography have allowed these cases to be diagnosed prenatally, little is known about the natural history and clinical significance of fetal gallstones (1-3).

Fetal gallstones are rare conditions and the prevalence of fetal gallstones is unknown. Although, echogenic foci or formation of fetal calculi in the gall bladder are uncommon in pediatric patients, the lesions associated with these conditions are well established and the incidence is reported as 1.5% in the first year of life (4). The incidence and predisposing factors known for postnatal life seems not to be applicable to prenatal diagnosis. Fetal gallstones are a rare condition, and only a few cases have been described in the literature.

Kiserud et al. reported a list of predisposing factor associated with echogenic fetal gallbladder including chromosomal aberrations, cardiac malformations, gastroshisis and intrauterine growth restriction, influence of prostaglandin and possibly prenatal leukomoid reaction (2). However, in our case, and in those described by others, no common etiological factor was found (2, 3, 5). The only common factor, in a case in the literature was reported as echogenic foci in the gall bladder as a third trimester phenomenon (3, 5, 6). It was emphasized that,the production, composition and mode of transportation of bile in the biliary tract permits the formation of any echogenic condensation after 28 weeks of pregnancy.

A 28-year-old women, gravida 1, para 0, was followed in our clinic for routine obstetric examinations. There was no history of maternal administration of drugs or family disease. Detailed ultrasonography at 20-22 weeks had demonstrated a live singleton fetus with no apparent structural abnormalities and normal morphological development. However, at 36 weeks of gestation, ultrasound examination showed that the gallbladder was filled with multiple small echogenic foci (Figure 1, arrows). No other abnormality or evidence of fetal ascites or hydrops was detected. At 39 week of gestation, a 3900 gram female fetus was delivered by cesarean section. During the first days of delivery, the newborn was examined and an abdominal scan was performed. Abdominal scan confirmed multiple gallstones with no other abnormalities (Figure 2). At 2 days of age, transverse sections through the abdomen showed multiple echogenic foci in the gallbladder (Figure 2). Neonatal abdominal ultrasound scan was repeated during the first month after birth and complete spontaneous resolution was observed.

The effect of fetal gender on the formation of gallstones is not clear. Although we reported a female fetus with no predisposing factor, greater numbers of cases reported in the literature were male (1-3). However, no clear explanation could be suggested regarding this association (2). We suggested that due to the scarcity of cases found and the fact that underlying etiologicl reasons could not be found, the fetal gender may not be associated with gallstones.



In conclusion, fetal gallstones may be seen during the third trimester with no predisposing factors. It may be a benign phenomenon and can resolve spontaneously.

Özlem Pata[1], Melih Gündüz[2], Cihat Ünlü[2]
[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Acıbadem University, Istanbul, Turkey
[2] Acıbadem Health Group, Acıbadem Bakırköy Hospital Istanbul, Turkey

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On behalf of the office staff and the editorial board of the *Journal of the Turkish-German Gynecological Association* (JTGGA), we would like to extend our thanks to all of our reviewers during the past year for your outstanding contributions.

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We would like also to acknowledge the professionals contributing at the technical development process of the journal:

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CONGRESS CALENDAR

4-11 February 2011	**3. Ankara Urojinekoloji Kongresi** *Swissotel, Ankara* www.urojin2011.org
10-13 February 2011	**SLS AsianAmerican Multispecialty Summit Laparoscopy and Minimally Invasive Surgery Hilton Hawaiian Village® Beach Resort & Spa, Honolulu,** *Hawaii, USA* http://www.laparoscopy.blogs.com/asianamerican_summit
24-26 March 2011	**World Symposium on Endometriosis InterContinental Hotel** *Atlanta, GA, USA* http://www.endometriosisatlanta.com
2-6 March 2011	**10. Uludağ Jinekoloji ve Obstetri Kış Kongresi** *Uludağ, Bursa, Turkey* http://www.uludagkadindogum.org
6-10 April 2011	**5th International Congress On Minimally Invasive Gynecology (AAGL & JED) Swıssotel The Bosphorus,** *Istanbul* www.tsge2011.org
7-9 April 2011	**Excellence in Female Surgery (NESA Days)** *Florence, Italy* http://www.nesaflorence2011.org
13-16 April 2011	**13. Ulusal Perinatoloji Kongresi&43rd International Meeting of Gestosis Organisation,** *İstanbul, Turkey* http://www.perinatoloji2011.org/
23-25 April 2011	**7. Ulusal Üreme Sağlığı ve Aile Planlaması Kongresi** *Ankara, Turkey* www.uremesagligi2011.org
4-8 May 2011	**9. TAJEV Kongresi** *Antalya, Turkey* http://www.tajev2011.org
17-22 May 2011	**TJOD (9th) Kongresi** *Kervansaray Hotel, Antalya* http://www.tjod.org
25-29 May 2011	**19th International Pelvic Pain Society Annual Scientific Meeting** *Istanbul, Turkey* http://www.ipps2011.org
3-6 July 2011	**27th Annual Meeting of ESHRE Stockholm,** *Sweden* http://www.eshre.eu/home
1-4 July 2012	**28th Annual Meeting of ESHRE** *Istanbul, Turkey* http://www.eshre.eu/home

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Keynote Speaker

Alan H. DeCherney, MD
National Institute of Child Health and Human Development

WSE 2011 Faculty

Mauricio S. Abrao - Brazil
Arnold Advincula - United States
Robert Albee - United States
Wayne L. Ambroze - United States
Vincent Anaf - Belgium
Aydin Arici - Turkey
Mary Lou Ballweg - United States
Vicki Barnett - United States
Sarah L. Berga - United States
Ivo A. Brosens - Belgium
Michel Canis - France
Charles Chapron - France
Thomas M. D'Hooghe - Belgium
Tommaso Falcone - United States
Asgi T. Fazleabas - United States
Emilio Fernandez - Chile
Linda C. Giudice - United States
Mordechai Goldenberg - Israel
Victor Gomel - Canada
Lone Hummelshoj - United Kingdom
Keith B. Isaacson - United States
Grace Janik - United States
Joerg Keckstein - Austria
Charles H. Koh - United States
Philippe R. Koninckx - Belgium
Anthony A. Luciano - United States
Daniel C. Martin - United States
Charles E. Miller - United States
Camran Nezhat - United States
Ceana Nezhat - United States
Farr R. Nezhat - United States
Michelle Nisolle - Belgium
David L. Olive - United States
George Pistofidis - Greece
David B. Redwine - United States
Harry Reich - United States
John A. Rock - United States
Tamer Seckin - United States
Antonio Setubal - Portugal
Michael Stark - Germany
John Steege - United States
Pam Stratton - United States
Mark W. Surrey - United States
Christopher J. G. Sutton - United Kingdom
Radha Syed - United States
Robert N. Taylor - United States
Bulent Tiras - Turkey
Togas Tulandi - Canada
Cihat Unlu - Turkey
Bulent Urman - Turkey
Arnaud Wattiez - France
Paul Wetter - United States
Errico Zupi - Italy

**Faculty Invited As Of 12/14/10*

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WSE AGENDA: Thursday, March 24th

The Enigma of Endometriosis

- Update on the Pathobiology of Endometriosis - Linda C. Giudice
- How Far Have We Come in the Practical Treatment of the Patient? - Camran Nezhat
- Keynote Address - The Enigma of Endometriosis: Is There a Cure? - Alan H. DeCherney

Appearance and Diagnosis

- Appearance of Endometriosis - Daniel C. Martin
- History and Physical: A Neglected Art in the Diagnosis of Endometriosis - John A. Rock
- Diagnosis, Treatment & Pain Management of Endometriosis - Pam Stratton

Medical Management of Endometriosis

- Antiproliferative Effects of Cannabinoid Agonists on Deep Infiltrating Endometriosis - Charles Chapron
- Can Non-Human Primates Help Us Understand Endometriosis Better? - Asgi T. Fazleabas
- Experimental Immune Therapies: What Is in the Pipeline? - Thomas M. D'Hooghe
- Hormone Therapy in Post-Menopausal Management of Endometriosis - Sarah L. Berga
- Debate: Does Medical Management Work? - Moderator: Mark W. Surrey; Protagonist: David L. Olive; Antagonist: Joerg Keckstein

Endometriosis and Pain

- Pain Recurrence After Surgery - Tommaso Falcone
- The Management of Endometriosis-Related Pain Must Include Prevention of Recurrence - Anthony A. Luciano
- Debate: Presacral Neurectomy and LUNA for the Management of Pain - Moderator: John A. Rock; Protagonist: Errico Zupi; Antagonist: John Steege

Other Pathologies

- Cancer and Endometriosis: Should We be Concerned? - Farr R. Nezhat
- Endometriosis and the Pathophysiology of Adhesion Formation and New Strategies for Prevention - Surgical and Medical - Togas Tulandi
- Endometriosis in Patients with Fibroids - Charles E. Miller

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WSE AGENDA: Friday, March 25th

Live Surgery Transmission

Arnaud Wattiez; David B. Redwine

Endometriomas

- Excision of Endometrioma: How to Minimize Ovarian Damage and Maximize Ovarian Reserve - Michel Canis
- Endometriomas and ART - Aydin Arici
- Debate: Origin of Endometriomas and Management - Cystectomy or
- Vaporization - Moderator: Farr R. Nezhat; Cystectomy: Arnaud Wattiez; Vaporization: Victor Gomel

Infertility

- ART and Endometriosis - Mark W. Surrey
- What is the Benefit of Laparoscopy for Endometriosis-Related Infertility? - Grace Janik
- A New Approach to Endometriomas: Laparoscopic Combined Technique Cihat Unlu

Live Surgery Transmission

Arnold Advincula; Charles H. Koh

Endometriosis and Adenomyosis

- Imaging Methods and Therapeutic Strategies for Endometriosis and Adenomyosis - Mauricio S. Abrao
- Uterine Adenomyosis: A New Classification System Based on Clinical Symptoms, Ultrasound Findings, Laparoscopy and Histology Results - George Pistofidis
- Endometriosis and Adenomyosis: How Hysteroscopy Can Help - Keith B. Isaacson

Live Surgery Transmission

Cihat Unlu; Joerg Keckstein

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Endometriosis affects approximately 10% of women worldwide and costs are estimated at over $22-billion annually in the US alone.* How can you help your patients?

WSE AGENDA: Saturday, March 26th

Social and Political Issues and Alternative Therapies

- Is Endometriosis a Political Disease? The Social Impact of Endometriosis on Family, Productivity and Finances - Lone Hummelshoj
- Alternative Therapies - Radha Syed
- Prevention of Endometriosis: It's Possible! - Mary Lou Ballweg

New Modalities in the Treatment of Endometriosis

- Surgical Treatment of Endometriosis: Hand Tools or Power Tools - What's the Evidence? - John Steege
- Robotic Surgery for Endometriosis - Michelle Nisolle
- Is There a Need for a New System of Classification? - Charles H. Koh

Surgical Training

- All About Outcomes: What is the Role of Societies? - Paul Wetter
- TELELAP - Haptic Sensation in Endometriosis Surgery: Toward Renaissance of Abdominal Surgery - Michael Stark

Hysterectomy and Endometriosis

- Total Laparoscopic Hysterectomy for Endometriosis: Why and How - Harry Reich
- Laparoscopic Subtotal Hysterectomy for Endometriosis: How to Do It and Make It Work - Robert Albee
- Debate: Excision vs. Vaporization of Endometriosis - Why Not Both? - Moderator: Camran Nezhat; Excision: David B. Redwine; Vaporization: Philippe R. Koninckx

Interactive Video Session: Tips and Tricks from the World's Leaders

- Bowel - Mauricio S. Abrao; Charles Chapron; Charles H. Koh; Michelle Nisolle; David B. Redwine; Arnaud Wattiez
- Diaphragm, Lung and Liver and More! - Camran Nezhat
- Urinary Tract - Grace Janik; Joerg Keckstein; Philippe R. Koninckx

Agenda Updated As Of 12/14/10

*Simsa P, Mihalyi A, Kyama C, Mwenda J, Fulop V, D'Hooghe T. Future of Endometriosis Research. Future Medicine 2007; 3(5): 647-654.

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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, anginа pektoris), ▪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 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 vaginal kanama, ▪Bilinen gebelik veya şüphesi ▪Etkin ya da yardımcı maddelerden 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 tedaviye başlamadan önce kullanacak olan kadınla birlikte tartışılmalıdır. Dolaşım 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 kullanımı sırasında ortaya çıkabilir. Tümörler: Servikal kanser için en önemli risk faktörü süregelen human papilloma virüs (HPV) enfeksiyonudur. Bazı epidemiyolojik çalışmalarda uzun süre kombine oral kontraseptif kullanımının servikal kanser riskinde artışa neden olabileceği bildirilmiştir ancak bu bulguların kombine oral kontraseptif kullanımının hangi etkilerine bağlı olabileceği (servikal inceleme, hormonal olmayan kontraseptif kullanımı dahil olmak üzere seksüel davranış) halen tartışılmaktadır. 54 epidemiyolojik çalışmayı kapsayan bir meta-analiz sonuçlarına göre halen kombine oral kontraseptif kullanan kadınlarda meme kanseri teşhis edilmesi bağıl riskinde (bağıl risk = 1.24) hafif bir artış olduğu rapor edilmiştir. Bu risk artışı kombine oral kontraseptif kullanımının kesilmesiyle birlikte 10 yıl içinde göreceli olarak ortadan kalkar. Diğer uyarılar: Böbrek yetmezliği olan hastalarda potasyum atılım kapasitesi sınırlı olabilir. Hipertrigliseridemisi olan ya da bu şekilde bir aile öyküsüne sahip bulunan kadınlarda, 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 kontraseptifleri 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 kaşıntı, safra taşı oluşumu, porfiri, sistemik lupus eritematozus, hemolitik üremik sendrom, Sydenham koresi, herpes gestationis, otoskleroza bağlı işitme kaybı gibi durumların gebelik ve kombine oral kontraseptif kullanımı sırasında ortaya çıktığı ya da kötüleştiği bildirilmişse de, bunların kombine oral kontraseptiflerle olan ilişkisi kesinlik kazanmamıştır. Ailesel anjiyoödemi olan kadınlarda egzojen estrogenler anjiyoödem 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 gravidarum 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 etkileşmeleri) azalabilir. Azalmış siklus kontrolü: Tüm kombine oral kontraseptiflerde, özellikle kullanımın ilk aylarında düzensiz kanamalar (lekelenme 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: Mikrozomal enzimleri etkileyen ilaçlarla (örn. fenitoin, barbitüratlar, primidon, karbamazepin, rifampisin ve muhtemelen okskarbazepin, topiramat, felbamat, griseofulvin ve "St. John's wort (Sarı kantaron)" içeren ürünler) olan etkileşimler, seks hormonlarının klerensinin artması ile sonuclanabilir. 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 kullanım 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: Kontakt lense toleranssızlık **Gastrointestinal sistem:** Yaygın: Bulantı, batında ağrı, Yaygın olmayan: Kusma, diyare **İmmün sistem bozuklukları:** Seyrek: Hipersensitivite **İncelemeler:** Yaygın: Kiloda artış, Seyrek: Kiloda azalma **Metabolizma ve beslenme:** Yaygın olmayan: Sıvı tutulumu **Sinir sistemi:** Yaygın: Baş ağrısı, Yaygın olmayan: Migren **Psikiyatrik düzensizlikler:** Yaygın: Depresif duygu durumu, duygu durum değişiklikleri Yaygın olmayan: Libido azalması, Seyrek: Libido artışı **Üreme sistemi ve meme:** Yaygın: Meme ağrısı, meme hassasiyeti, Yaygın olmayan: Memede hipertrofi, Seyrek: Vaginal akıntı, memede akıntı **Cilt ve cilt altı:** Yaygın olmayan: Döküntü, ürtiker, Seyrek: Eritema nodozum, eritema multiforme. Ailesel anjiyoödemi olan kadınlarda egzojen estrogenler anjiyoödem 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. Şti., Çakmak 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 Fiyatı: KDV dahil perakende satış fiyatı: 21.53 TL Ayrıntılı bilgi için Firmamıza başvurunuz.

R-VH-04-09-0121-TR

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