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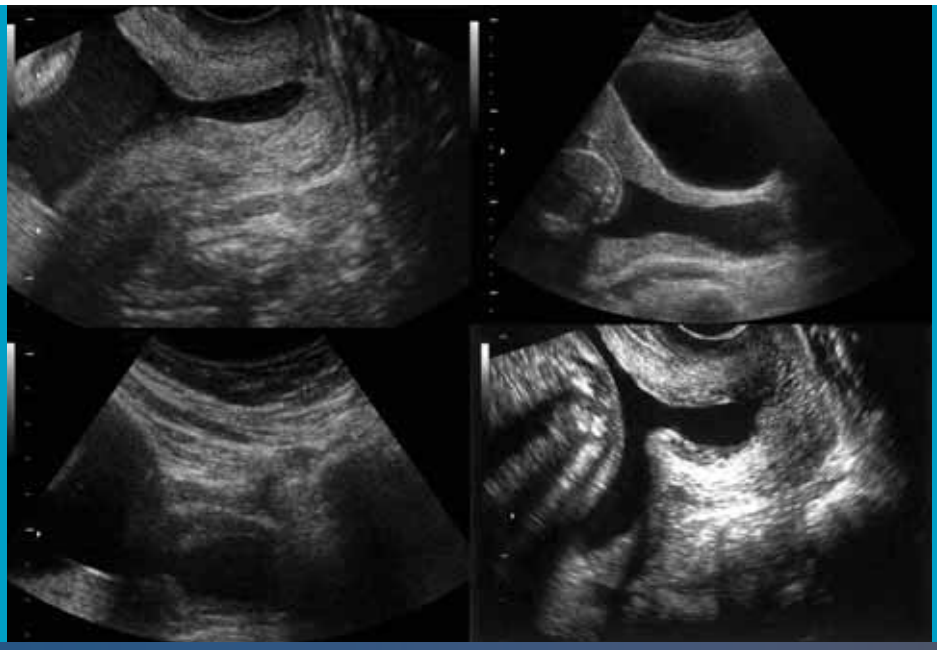

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Original Investigations

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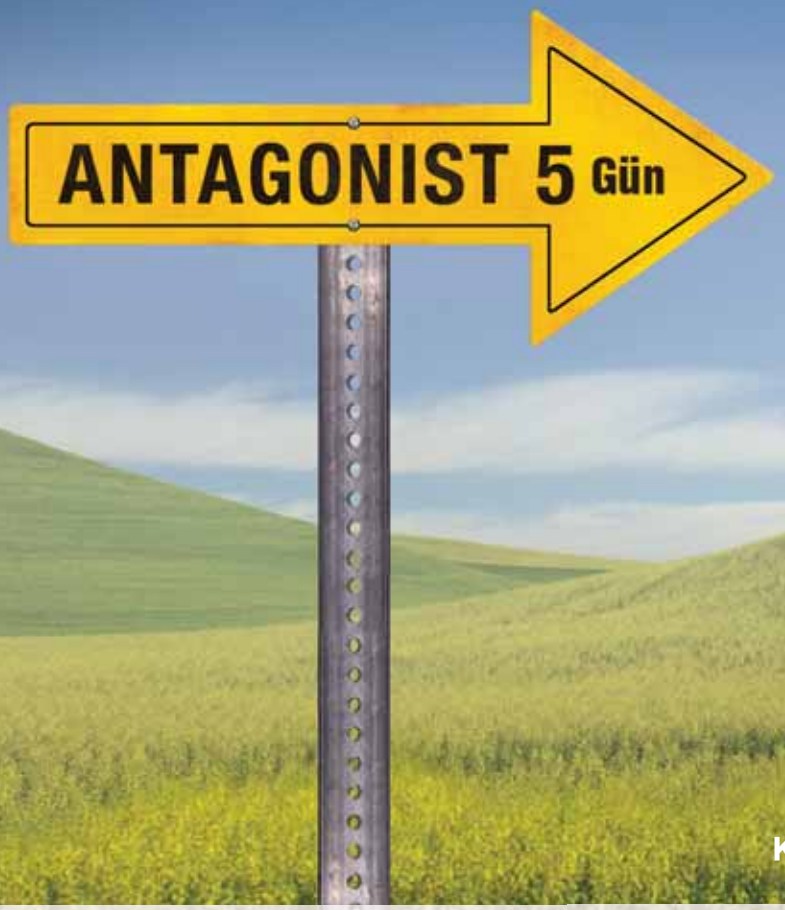
Sadece 5 tedavi günü yüksek gebelik oranı sağlar[1-6]



Başarılı, kolay, kısa süreli tedavi,[1-6]

- Kanıtlanmış sonuçlar %38 devam eden gebelik oranı[1]
- Anlamlı derecede daha az sayıda enjeksiyon[4]
- Kullanıma hazır şırınga olarak sunulan tek GnRH antagonisti[7]
- Daha düşük OHSS riski[2,3]
- LH pikini önler[4,8,9]

Orgalutran®
ganirelix

Kanıtlanmış sonuçlar, Güvenilir deneyim.[6]

Referanslar: 1. Doody K, Witjes H, Mannaerts B, Gordon K. Success rates of a fixed rFSH/GnRH antagonist protocol are not affected by endogenous LH levels. Abstract presented at: the 25th Annual Meeting of the European Society of Human Reproduction and Embryology; June 28-July 1, 2009; Amsterdam, The Netherlands. **2.** Kolibianakis EM, Collins J, Tarlatzis BC, et al. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Hum Reprod Update. 2006;12:651–71. **3.** Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception (Review). Cochrane Database Syst Rev. 2006;3;CD001750. **4.** Fluker M, Grifo J, Leader A, et al. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. Fertil Steril. 2001;75:38–45. **5.** Devroey P, Aboulghar M, Garcia-Velasco J, et al. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Human Reprod. 2009;24(4):764-774. **6.** The European Orgalutran® Study Group; and Borm G, Mannaerts B. Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. Hum Reprod. 2000;15(7):1490-1498. **7.** Orgalutran SMPC. **8.** Lambalk CB, Leader A, Olivennes F, et al. Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial. Hum Reprod. 2006;21(3):632-639. **9.** European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation.

Hum Reprod. 2001;26:644-651.Orgalutran® 0.25 mg / 0.5 ml Enjeksiyonluk Çözelti.

Formülü: Önceden dolum yapılmış bir şırınga 0.5 ml solüsyonda etkin madde olarak 0.25 mg ganirelix yardımcı maddeler olarak da 23.5 mg mannitol, 0.1 mg asetik asit, pH ayarı için sodyum hidroksit ve/veya asetik asit ve yeteri miktarda enjeksiyonluk su içerir. Orgalutran® , hipotalamik-hipofizer-gonadal ekseni hipofiz bezindeki GnRH reseptörlerine kompetitif olarak bağlanmak suretiyle etkileyen bir GnRH antagonistidir. Orgalutran®'ın subkütan uygulamayı takiben biyoyararlanımı yaklaşık %91'dir.0.25 mg/gün dozunda mükerrer uygulamayı takiben 0.6 ng/ml'lik durağan durum düzeyine 2-3 gün içerisinde ulaşılmaktadır. Endikasyonları: Kontrollü over hiperstimülasyonu (COH) uygulanan kadınlarda prematür LH salgılanmasının önlenmesi. Kontrendikasyonları: Etken maddeye veya yardımcı maddelerden herhangi birine karşı aşırı duyarlılık,GnRH veya diller GnRH analoglarına karşı aşırı duyarlılık, Gebelik ve laktasyon. Uyarılar ve önlemler: Alerjisi olmakla birlikte o anda semptom sergilemeyen hastalara Orgalutran® güvenli bir şekilde uygulanabilir. Mevcut ciddi alerji semptomları olan hastalara Orgalutran® uygulanması tavsiye edilmemektedir. Alerjik reaksiyon oluşması halinde hastaların doktorla temasa geçmeleri önerilmektedir. Gebelik ve laktasyonda kullanım: Orgalutran® gebelik veya laktasyon sırasında kulanılmamalıdır. Araç ve makina kullanmaya etkisi: Araç ve makina kullanma üzerinde herhangi bir etki gözlenmemiştir. Yan etkiler / Advers etkiler: Orgalutran® enjeksiyon yerinde cilt reaksiyonuna yol açabilmekte fakat normal koşullarda bu reaksiyon uygulamadan 4 saat sonra kaybolmaktadır. Nadiren baş ağrısı (<%4) ve bulantı (<%2) rapor edilmiştir. Rapor edilen diller advers olaylar, Orgalutran®'dan ziyade destekli üreme tekniklerine (ART) yönelik kontrollü over hiperstimülasyonu ile bağlantılıdır (örneğin kanın aşırısı, over hiperstimülasyon sendromu (OHSS), ektopik gebelik ve düşük). BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. Kullanım şekli ve dozu: FSH ile kontrollü over hiperstimülasyonuna adet döneminin 2 veya 3'üncü gününde başlanılabilmektedir. Orgalutran® (0.25 mg), tercihen FSH uygulamasının 6. gününden itibaren başlanılarak günde tek sefer subkütan yoldan enjekte edilmelidir. Orgalutran® FSH ile karıştırılmamalı, fakat her iki preparat yaklaşık olarak aynı saatlerde uygulanmalıdır. Günlük Orgalutran® uygulamasına, yeterli büyüklükte ve yeterli sayıda follikül oluşana kadar devam edilmelidir. İlk Orgalutran® enjeksiyonu ile son Orgalutran® enjeksiyonu ile hCG enjeksiyonu arasındaki süre, 30 saati geçmemelidir. Orgalutran® subkütan yoldan uygulanmalıdır. Lipoatrofi oluşmaması için enjeksiyon yeri değiştirilmelidir. Hasta veya partneri, yeterli eğitim almaları ve bilgi için uzmanlara ulaşabilmeleri koşuluyla Orgalutran® enjeksiyonunu kendileri yapabilir. Uygulama şekli: Orgalutran® enjektör ile yavaşça, ciltaltına enjekte edilir (örneğin üst bacak). Uygulama şekli için prospektüsü inceleyiniz. Enjeksiyonun unutulması: Orgalutran®'ı enjekte etmeyi unuttuğunuzu fark ettiğiniz anda enjeksiyonu yapınız, doktorunuza danışınız. Çift enjeksiyon yapmayınız. Saklama koşulları: 25ºC' nin altındaki oda sıcaklığında saklayınız. Işıktan koruyunuz. Dondurmayınız. Ticari takdim şekli: Orgalütran® 0.25 mg/0.5ml, 5 adet önceden doldurulmuş, tek kullanımlık şırınga içinde 0.5 ml solüsyon, karton kutuda veya 1 adet önceden doldurulmuş tek kullanımlık şırınga içinde 0.5 ml solüsyon karton kutuda. Genel uyarılar: Çocukların ulaşamayacakları yerlerde ve ambalajında saklayınız. Hekime danışmadan kullanılmamalıdır. Başvurularda ambalaj seri numarasını belirtiniz. Ruhsat Sahibi: Organon İlaçları A .Ş., PK. 120, 34673 Üsküdar-İstanbul Ruhsat tarihi: 23.09.2003 Ruhsat no. 114/76 Fiyat: 5'lik Paket: PSF (KDV Dahil) 362,42 YTL;(Eylül 2009) 1'lik Paket: PSF (KDV Dahil) 83,96 TL (Ağustos 2009)

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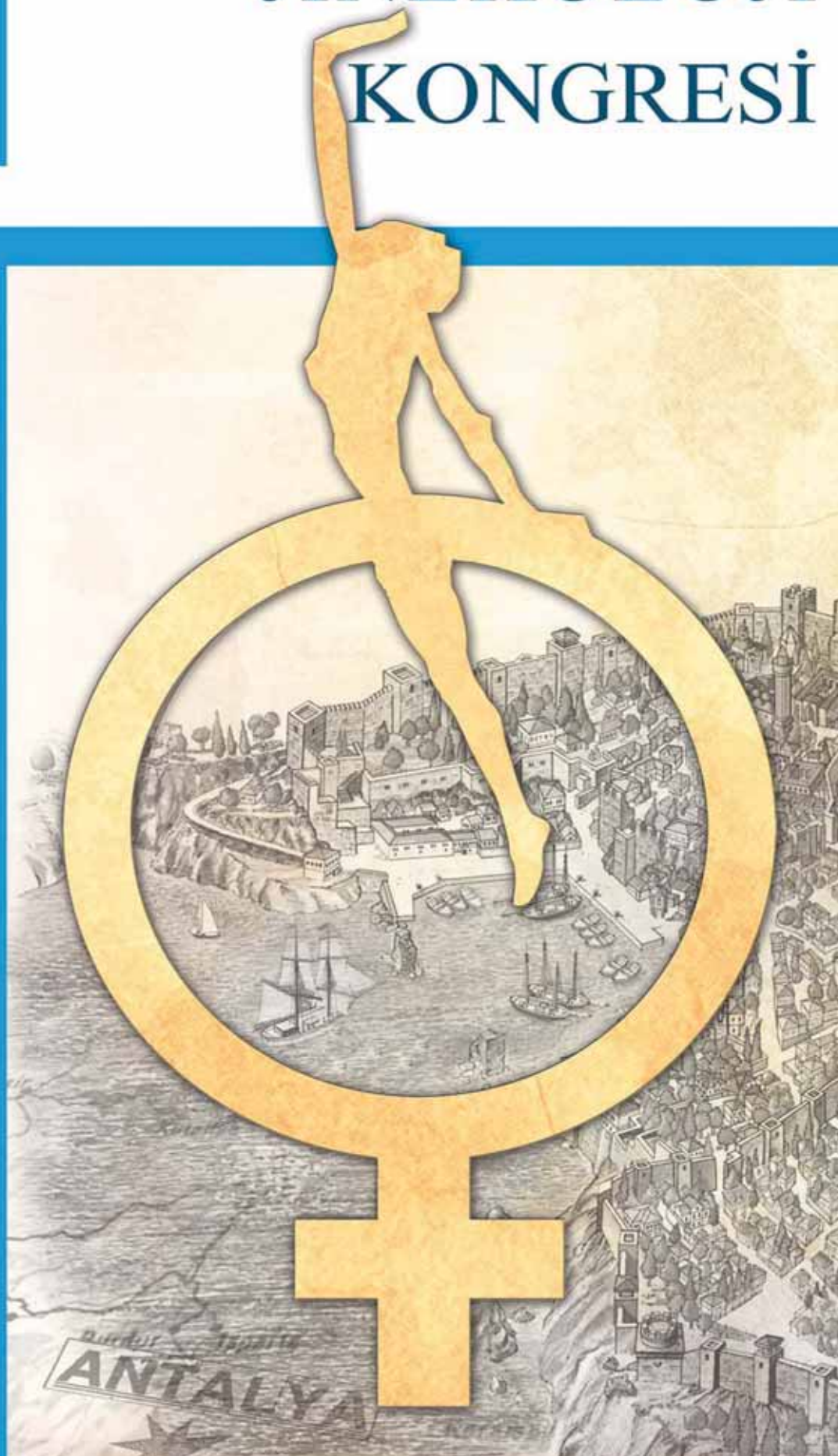

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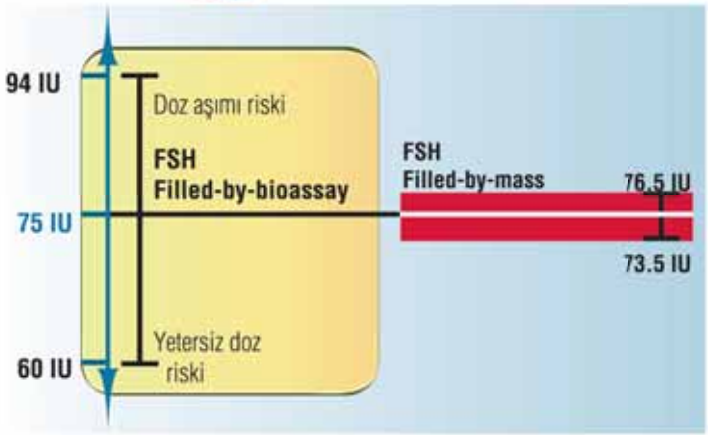

Bioassay yöntemi ile ölçülen FSH aktiviteleri ± %20 varyasyon gösterirken, Filled by Mass yönteminde bu varyasyon sadece ± %2'dir.[2]

Kontrollü ovaryen stimülasyonlarda doğru dozu vermek, tedavi başarısını olumlu etkilemektedir.[1]

Filled by Bioassay ve Filled by Mass yöntemleriyle etiketlenen FHS'ların karşılaştırıldığı 6 çalışmanın meta-analizi[3]

Parametre	Tahmini AOF*	p değeri
Ortalama doz (IU)	-230.29	(p<0,001)
Tedavi günü	-0.48	(p<0,001)
Alınan oosit sayısı	0.84	(p=0,013)
Elde edilen embriyo sayısı	0.88	(p<0,001)

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2. Basset et al. 'Continued improvements in the quality and consistency of follitropin alfa, recombinant human FSH' RBM Online, Vol. 10, No. 2, p. 169-177, 2005
3. Saz Parkinson et. al. Biodrugs 2009;23:37-42'den uyarlanmıştır.

GONAL-f® 300 IU (22 mcg) / 0.5 ml (450 IU (33 mcg) / 0.75 ml, 900 IU (66 mcg) / 1.75 ml) Enjeksiyonluk çözelti içeren kullanıma hazır dolu enjeksiyon kalemi Formülü: 1 kartuş, etkin madde olarak 300 (450 veya 900) IU'ya eş değer 22 (33 veya 66) mikrogram follitropin alfa (rekombinant folikül stimülan hormon (FSH) içerir. **Endikasyonları:** Klomifen sitrat ile tedaviye cevap vermemiş kadınlarda anovulasyon durumunda (polikistik yumurtalık hastalığı dahil), in vitro fertilizasyon (IVF), gamet intra fallopian transfer (GIFT) ve zigot intra fallopian transfer (ZIFT) gibi yardımcı üreme teknolojileri (ART) için süperovulasyon yapılan hastalarda multifoliküler gelişimin uyarılmasında, GONAL-f® ve lüteinizan hormon (LH) preparatı birlikte oldü LH ve FSH eksikliği olan kadınlarda folikül gelişmenin uyarılması için tavsiye edili. GONAL-f®, doğuştan veya edinsel hipogonadotropik hipogonadizm gösteren erkeklerde, spermatogenez stimülasyonu için, insan Koryonik Gonadotropin'i (hCG) tedaviyle birlikte endikedir. **Kontrendikasyonları:** Follitropin alfa'ya, FSH'ye veya ekspiyanlardan herhangi birine karşı önceden aşırı duyarlılık, hipotalamus ve hipofiz tümörleri kadınlarda; polikistik over hastalığından kaynaklanmayan yumurtalık büyümesi veya kisti, etiyolojisi bilinmeyen jinekolojik kanamalar, yumurtalık, rahim veya göğüs kanseri. GONAL-f®, aşağıdaki durumlarda etkili bir cevap alınmadığı takdirde kontrendikedir: Kadınlarda: Primer over yetmezliği, cinsel organların gebeliğe uyumsuzluk yaratan malformasyonları, rahmin gebeliğe uyumsuzluk yaratan fibroid tümörleri, Erkeklerde: Primer testis yetersizliği **Kullanım şekli ve dozu:** GONAL-f® ile tedavi, fertilite problemlerinin tedavisinde uzmanı bir hekimin gözetimi altında başlatılmalıdır. GONAL-f® subkutan uygulama için hazırlanmıştır. GONAL-f®'nin klinik değerlendirmesi, günlük dozlarının, verilme şekillerinin ve tedavi süresinin bilinen klasik yöntemlerden farklı değildir. GONAL-f®'nin monodoz preparatları ve multidoz preparatlarının eşdeğer dozlarının beosştiği de gösterilmiştir. Anovulatuvar kadınlarda (PKOS dahil); adet gören hastalarda, tedaviye menstrüasyon devresinin ilk 7 günü içerisinde başlanmalıdır. Tedavi, ultrason ile folikül boyutunun ve / veya östrojen salgılanmasının ölçümü ile değerlendirilerek, hastanın tedaviye bireysel olarak verdiği cevaba göre uyarlanmalıdır. Genel olarak günlük 75-150 IU FSH ile başlanır ve yeterli, ancak aşırı olmayan bir cevap alınsa için, gerektiğinde 7 veya tercihen 14 günlük aralıklar ile tercihen 37.5 veya 75 IU oranında artırılır. Günlük maksimum doz genellikle 225 IU FSH'den daha yüksek değildir. Eğer hasta 4 haftalık tedavinin sonra yeterli cevabı vermezse, o siklus bırak.malı ve hastaya bir sonraki siklustakinden daha yüksek bir başlama dozuyla tedaviye yeniden başlanmalıdır. Optimal cevap alındığında, son GONAL-f® enjeksiyonunun sonraki 24-48 saat içerisinde 5000 IU ila 10 000 IU'ya kadar tek bir hCG enjeksiyonu yapılmalıdır. Hastaya, hCG uygulamasının yapıldığı gün ve bir sonraki gün cinsel birleşmede bulunması tavsiye edilir. Alternatif olarak, intrauterin inseminasyon (IUI) yapılabilir. Tedaviye aşırı cevap alındığı takdirde, tedavi durdurulmalı ve hCG uygulanmamalıdır. Tedaviye, bir sonraki siklusta, bir önceki siklusun dozajından daha düşük bir dozajla tekrar başlanmalıdır. In vitro fertilizasyon ve diğer yardımcı üreme teknolojileri öncesi çoğul folikül gelişme için over stimülasyonu yapılan kadınlarda, siklusun 2. veya 3. gününde başlanan günlük 150-225 IU GONAL-f® ile başlanır. Yeterli folikül gelişimi elde edilene kadar genellikle günlük 450 IU'nun üzerine çıkmayacak şekilde, hastanın tedaviye verdiği cevaba göre ayarlanan dozaj ile tedaviye devam edilir. Gerekiye tedavinin ortalama olarak 10. gününde (5-20 günde) yeterli folikül gelişimine ulaşılır. Kesin foliküler olgunlaşmayı başlatmak için, son GONAL-f® enjeksiyonundan sonraki 24-48 saat içerisinde 250 mikro gram r-hCG ya da 5000 IU ila 10 000 IU'ya kadar tek bir hCG enjeksiyonda yapılır. Ciddi LH ve FSH eksikliğine bağlı anovulasyonu kadınlarda (Lutropin alfa ile birlikte GONAL-f® tedavisinin amacı, hCG uygulandıktan sonra, yumurtlamanın gerçekleşeceği tek bir olgun Graff folikülü geliştirmektir. GONAL-f®, Lutropin alfa ile birlikte aynı anda günlük enjeksiyonlar halinde verilmelidir. Bu hastalar amenorenik olduklarından, ve düşük endojen östrojen salgısına sahip olduklarından, tedaviye her zaman başlanabilir. Genel olarak önerilen bir tedavi rejiminde tedaviye günlük 75 IU lutropin alfa 75-150 IU FSH ile başlanır. FSH dozunda artış gerekliği düşünülürse, dozlar tercihen 7-14 günlük aralıklar ile ve tercihen 37.5-75 IU'luk basamaklarla artırılır. Stimülasyon süresi herhangi bir siklusta 5 haftaya kadar uzatılabilir. Tedaviye aşırı cevap alındığı takdirde, tedavi durdurulmalı ve hCG uygulanmamalıdır. Tedaviye, bir sonraki siklusta, bir önceki siklusun dozajından daha düşük bir dozajlarakar başlanmalıdır. Hipogonadotropik hipogonadizm'li erkeklerde; GONAL-f® en az 4 ay boyunca haftada üç defa 150 IU dozda ve hCG ile bir arada verilmelidir. Eğer bu dönemden sonra, hasta cevap vermemişse, kombine tedaviye devam edilebilir; mevcut klinik deneyimler spermatogeneze ulaşmak için en az 18 aylık tedavinin gerekli olabileceğini göstermektedir. **Uyarılar/önlemler:** Kadınlarda GONAL-f®'nin etkisi ve emniyeti kullanımı, düzenli olarak ultrason ile over cevabının izlenmesini, tercihen beraberinde serum estradiol düzeylerinin ölçümünü gerektirir. Kadınlarda ve erkeklerde tedavi amacına uygun, etkili en düşük doz kullanılmalıdır. Hastanın GONAL-f®'yi kendi kendine uygulaması, ancak yeterince eğitilmiş hastalarda ve uzman tavsiyesine uyulması ile gerçekleşebilir. Hastanın kendine uygulamasının eğitimi esnasında kullanıma hazır kalemin kullanımı için verilen talimatlara özenle dikkat gösterilmelidir. GONAL-f®'nin ilk enjeksiyonu mediksi gözetim altında yapılmalıdır. Ka d inlarda tedavi. Tedaviye başlamadan önce, hastalar özellikle hipotiroidizm, adrenokortikal bozukluklar, hiperprolaktinemi ve hipofiz veya hipotalamik tümörler açısından değerlendirilmeli ve uygun tedavi verilmelidir. Anovulatuvar infertilite ya da ART prosedürleri tedavisi olarak, folikuler gelişme için stimülasyon tedavisi uygulanan hastalar; bir stimülasyon gelişimi veya yumurtalık büyümesine narsız kalabilirler. Ovaryen hiperstimülasyon sendromu (OHSS) riski hastalar yakından takip edilmelidir. Tedaviye başlamadan önce hastalar potansiyel çoğul gebelik riski konusunda uyarılmalıdır. Ovulasyon indüksiyonu veya ART için folikuler gelişimin stimüle edildiği hastalarda düşük gelişmesi sonucu gebelik kaybının oranı, normal gebelik kayıplarından daha fazladır. Tubal hastalık hikayesi olan kadınlarda, dış gebelik riski vardır. Üreme sistemi neoplazilerin bazal riskini artırıp artırmadığı henüz tespit edilmemiştir. ART'tan sonra konjenital malformasyonlarını sıklığı, spontan gebelliğe göre biraz daha yüksek olabilir. Bunun parental özelliklerin farklılığına (anne yaşı, sperm özellikleri vs.) ve çoğul gebeliklere bağlı olduğu düşünülmektedir. Tromboembolik olaylar için kişisel veya aile öyküsü gibi genellikle bilinen risk faktörleri olan kadınlarda, gonadotropin tedavisi bu riski artırabilir. Erkeklerde tedavi: Tedavinin başlangıcından 4-6 ay sonra, cevabı değerlendirmek için sperm analizi yapılması tavsiye edilir. Gebelik esnasında kullanım endikasyonu yoktur. Gonadotropinlerle klinik kullanımda, kontrollü ovaryen hiperstimülasyonu takiben hiç teratojenik risk rapor edilmemiştir. Gebelikte bu ilaca maruz kalındığında, bu güne kadar malformasyona yol açtığını gösterir bir etki rapor edilmemiştir. Laktasyonda kullanım GONAL-f®, süt verme döneminde kullanılmaz. Araç ve makina kullanmaya etkisi üzerine çalışma yapılmamıştır. Kullanıma hazır kalem içindeki çözelti pamuklu içeriyorsa ya da benzak değilse uygulanmamalıdır. **Yan etkiler/advers etkiler:** Enjeksiyon yerinde lokal reaksiyonlar (ağrı, kızarıklık, morarma, enjeksiyon yerinde şişlik ve / veya irritasyon), baş ağrısı, ve abdominal ağrı, bulantı, kusma ve ishal, abdominal krampları ve genellikle gibi gastrointestinal semptomlar bildirilmiştir. Kadınlarda tedavi GONAL-f® ile tedavi esnasında, yumurtalığı hiperstimülasyon, çoğul gebelik insidansında artış, tromboembolik olay gelişme olasılığı göz önünde bulundurulmalıdır. Erkeklerde tedavi GONAL-f® hCG tedavisi sırasında jinekomasti, akne ve kilo alma görülebilir . BEKLENMEYEN BİR ETKİ GÖRÜLDÜĞÜNDE DOKTORUNUZA BAŞVURUNUZ. **İlaç etkileşmeleri ve diğer etkileşmeler:** GONAL-f® ovaryonu stimüle eden diğer ilaçlarla (Or. hCG, Klomifen sitrat) birlikte kullanıldığında foliküler cevapta artış gözlenebilir, bunun yanında, hipofizer desensitizasyonu indüklemek için GnRH agonisi ya da antagonisti ile birlikte kullanılması, yeterli derecede over cevabı almak için ihtiyaç duyulan GONAL-f® dozajını artırabilir. GONAL-f® tedavisi esnasında klinik olarak belirgin başka ilaç etkileşimi rapor edilmemiştir. **Doz aşımı:** GONAL-f®'nin aşırı doz etkileri bilinmemektedir, yine de ovaryen hiperstimülasyon sendromunun oluşması beklenebilir. **Saklama koşulları:** Kullanılmaya başlayıncaya kadar 2°C - 8°C'de buzdolabında saklayınız. Dondurmayınız. Ilk kullanımdan sonra 25°C ya da altında 28 güne kadar saklanabilir. 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Journal of the
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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.

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FORMÜLÜ: Triptorelin asetat **ENDİKASYONLARI:** İVF Endometriozis, uterus miyomu **KONTRENDİKASYONLARI:** Klinik olarak belirgin osteoporoz ya da osteoporoz 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. **UYARILAR/ 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 kullanımına hiçbir etkisi yoktur. **YAN ETKİLER/ ADVERS ETKİLER:** Hormon üretiminin baskılanması sonucu en çok sıcak basması olmak üzere %75-100 hastada yan etkiler görülebilir. Kanama veya dende lekelanma, tedema, 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), anaflaksi, 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 epifizyolziz 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.I mg uygulanır. İVF'te dozaj uygulanan protokole göre değişir. Genellikle, siklus/ilk foliküler faz ilk gününden itibaren hCG uygulamasına kadar günde 0.1mg (kısa protokol); siklus/ilk foliküler faz 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, ambalaj içinde ve ışıktan korunarak saklanmalıdır. **TİCARİ TAKDİM ŞEKLİ ve AMBALAJ MUHTEVASI:** Decapeptyl® 0,I mg: 1 ml solüsyon içeren, kullanıma hazır 7 şırıngalık kutularda **RUHSAT SAHİBİ:** FERRING İlaç San. Tic. Ltd. Sti, 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:** 127,27 TL (Nisan 2009 itibariyle), **ÜRETİM YERİ:** Ferring GmbH Kiel, Almanya REÇETE İLE SATILIR. Ayrıntılı bilgi için lütfen firmamıza başvurunuz.

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5. YIL

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FORMÜLÜ: Liyofilize toz içeren bir flakonda: 75 I.U. FSH (follikül stimüle eden hormon) ve 75 I.U. LH'a (luteinizan hormon) tekabül eden yüksek derecede saflaştırılmış (HP) menotropin (insan menopozal gonadotropini, HMG) vardır. 1 ml çözücü içeren bir ampulde: 1 ml izotonik sodyum klorür solüsyonu bulunur. **ENDİKASYONLARI:** Hipo veya normogonadotropik over yetersizlikleri olan kadınlarda kısırlık tedavisinde (follikül büyümesinin uyarılması), hipo veya normogonadotropik hipogonadizm olan erkeklerde kısırlık tedavisinde (HCG ile birlikte, 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. Erkeklerde; prostat kanseri, testislerde tümör. **UYARILAR/ÖNLEMLER:** Menopur®, gebe hastalara verilmemelidir. Anormal genital kanaması olan hastalarda, meme, uterus, prostat, yumurtalık veya testislerin hormon duyarlı tümörler, over kistler, polikistik over sendromunun neden olmadığı over kistler veya bunların büyümesinde kullanılmamalıdır. Menopur® ile tedaviye başlamadan önce, infertilite nedenleri olarak hipofiz veya hipotalamik lezyonlar, adrenal veya tiroid bozuklukları ve hiperprolaktineminin ortadan kaldırılması için uygun şekilde tedavi edilmelidir. Over büyümesi yaşayan hastalar, rupture 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. Erkeklerde: 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 çukur ve rupture 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 pıhtılaşla kan damarlarının tıkanması (tromboembolik olay) olabilir. Aşırı uyarılmanın ilk belirtileri ortaya çıktığında 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 erkeklerde HMG, HCG ile bir arada enjekte edilebilir. **KULLANIM ŞEKLİ VE DOZU:** Ambalajın içindeki çözücü ile çözüldükten sonra I.M. ya da S.C. olarak uygulanır. Hekim tarafından başka türlü tavsiye edilmedikçe, aşağıdaki dozlarda uygulanır: Kadınlarda Kısırlık: Normo veya hipogonadotropik kadınlarda follikülerin 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 follikküllerde 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. **FİYATI:** KDV dahil perakende satış fiyatı, 229,12 TL (Nisan 2009 itibariyle). Reçete ile satılır. Ayrıntılı bilgi için lütfen firmamıza başvurunuz.

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Journal of the
Turkish-German
Gynecological Association

Contents

Original Investigations

Review

Case Reports

Quiz

Journal of the
Turkish-German
Gynecological Association

Editorial

Dear Colleagues,

I'm glad to introduce you the first issue of the year 2010 with interesting and valuable studies. Since our journal have made a tremendous impression in Turkey and worldwide, and raised the bar gradually, we have included "Index Copernicus" to our index network. Hereby, I would like to express my gratitude to our valuable readers, for the authors who sent their articles to our journal and to the referees due for their efforts during the review of the articles. We would like to share with you that our journal was suggested to ISI (Institute for Scientific Information) citation index by TUBITAK and now the evaluation process still continues. We are in the expectancy of including ISI to our index network.

The activities of Turkish-German Gynecological Education Foundation are not limited to journal and congress organizations. We have started to the preparations of the 2nd Social Responsibility Project which we wish to make it traditional and an example to all associations and foundations in Turkey. Currently, we are preparing the background work of the project which is planned to be in Urfa at the last week of May, we are assessing and determining the needs by consulting with the Ministry of Health, local directors, health care professionals and academicians in the region, and getting their supports. This social project called **"Just For Me"** is being intended to be performed to two target groups. Sessions directed to the health care professionals are performed in order to provide continuity in medical education, give information on the developments in gynecological diseases and obstetrics, and share and find a solution to their problems in the region. On the other hand, **sessions directed to raise the awareness of public** are performed in order to provide a healthy pregnancy and birth process to the pregnant women and mothers-to-be, to decrease the mortality rate of mothers and newborns, to decrease the rate of cervical cancer and thus to prevent mortality. We are honored to serve our country.

Besides, we have already started preparations for the 9th Turkish-German Gynecology Congress which has been traditional and accepted as an ecole in its field. In order to meet the expectations and to introduce "novelties" to our country in our congresses, novelties, we make improvements by evaluating the feedbacks of the previous congresses and we try to raise the bar. We are more assertively preparing for the 9th Turkish-German Gynecology Congress with a broad scientific committee and thus we formed scientific sub committees from specialists in different branches. We have already received the confirmation of attendance from foreign speakers, who are well known worldwide in scientific area, to our congress that is going to be conducted in May 2011 in Antalya.

I wish you health and happiness in these beautiful spring days.

With our best regards,

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

Termination of pregnancy and reasons for delayed decisions

Gebelik sonlandırması ve karar almada gecikme nedenleri

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Abstract

Objective: To assess the indications and distribution of cases chosen for termination of pregnancy and reasons delaying until third trimester termination.

Methods: Retrospective study of cases between 2002 and 2006 in the hospital council. Cases were divided in two groups , as early termination (<23 weeks of gestation) and late termination (≥23 weeks of gestation). All pregnant women who underwent termination were classified according to related systemic pathology and chorionicity. Reasons for delaying until third trimester termination were evaluated in four groups.

Results: During this five year period 1.449 complicated pregnancies were counseled and in 713 cases termination was offered. Of 677 cases (94.95%) with termination, 412 cases (60.09%) had early and 265 cases (39.91%) late termination. The most frequent indications were central nervous system abnormalities (51.7%), chromosomal abnormalities (11.7%), and urogenital abnormalities (8.4%). The main reason for delaying termination was failure of screening by ultrasound (65.6%).

Conclusion: Systematic screening for fetal anomalies is the main step for prevention of affected pregnancies. Information given to parents for TOP is important, but the decision for TOP is influenced by many factors. (J Turkish-German Gynecol Assoc 2010; 11: 1-7)

Key words: Prenatal diagnosis, fetal anomaly, pregnancy termination

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Özet

Amaç: Gebelik sonlandırması kararı alınan olguların endikasyonu ve dağılımı ile bu işlemin üçüncü trimestere kadar gecikme nedenleri.

Yöntem: 2002 -2006 yılları arasında hastane konseyinde görüşülen olguların retrospektif çalışması. Olgular, (erken sonlandırma (<23.gebelik haftası) ve geç sonlandırma (≥23.gebelik haftası) olmak üzere iki grupta değerlendirildi. Gebelik sonlandırması uygulanan gebelerin tümü, etkilenmiş sistemin patolojisi ve koryonisiteye göre sınıflandırılmıştır. Üçüncü trimesterde sonlandırmaya neden olan gecikmeler dört grupta incelenmiştir.

Bulgular: Bu beş yıllık dönemde 1.449 komplike gebelik değerlendirildi ve 713 olguya sonlandırma seçeneği sunuldu. 677 olgunun (%94.95) 412' sine (%60.09) ve 265' ine (%39.91) sırasıyla, erken ve geç sonlandırma uygulanmıştır. En sık görülen endikasyonlar santral sinir sistemi anomalileri (%57.7), kromozom anomalileri (%11.7) ve ürogenital anomalilerdi (%8.4). Gebelik sonlandırmasında gecikmelere yol açan en sık neden, ultrasonografi taramasındaki yetersizlik (%65.6) olarak değerlendirilmiştir.

Sonuç: Etkilenmiş gebeliklerden korunmanın en önemli adımı, fetal anomaliler açısından sistematik taramadır. Gebelik sonlandırması açısından ailelere verilen bilgi önemli olup, sonlandırma kararında pek çok etken rol almaktadır. (J Turkish-German Gynecol Assoc 2010; 11: 1-7)

Anahtar kelimeler: Prenatal tanı, fetal anomali, gebelik sonlandırması

Geliş Tarihi: 29 Kasım 2009 **Kabul Tarihi:** 30 Ocak 2010

Introduction

Prenatal screening for congenital anomalies has increased (Eurocat study; 1-3), and consequently, the number of terminations of pregnancy (TOPs) has increased. The identification of serious untreatable abnormalities is sometimes a reason for a woman to request a TOP. The rate of infant deaths due to lethal congenital anomalies has remained stable and the percentage of infant deaths attributable to lethal congenital anomalies has increased over time (4). Wen et al. (5) reported that the infant mortality rate in Canada due to fatal congenital anomalies decreased from 3.11 per 1000 live births in 1981 to 1.89 per 1000 live births in 1995. This statistic suggests that patterns of lethal congenital anomalies may have changed in recent years, primarily because of advances in prenatal diagnosis. A 13.2% perinatal mortality rate due to congenital malformations is the third most common cause of infant mortality after stillbirths and prematurity, according to Erdem (6). It is likely that many of these fetuses would have died perinatally if the pregnancy had continued.

Turkish law (law no. 2827, paragraph 5; 27 May 1983)authorizes legal TOP for two distinct conditions: (a) voluntary TOP up to 10 weeks in unwanted pregnancies and (b) elective TOP for medical reasons (7). Elective TOP is possible at every stage of gestation with no stated upper gestation limit if there are

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serious maternal (ongoing pregnancy is life-threatening) or fetal (a high risk of severe disabilities or an untreatable fatal disease) circumstances. The legal process requires the agreement of one obstetrician and one associated physician who declare a maternal or fetal cause justifying elective TOP.

The aim of the current study was to evaluate the indications of TOP in our institution as determined by the hospital's perinatology-neonatology council and counseled and/or agreed to by parents, and to discuss the reasons leading to third trimester TOPs.

Material and Methods

This was a retrospective study conducted between January 2002 and December 2006 at the Istanbul Bakirkoy Maternity and Children Diseases Hospital. Our hospital is a tertiary referral center in Istanbul, with 92,239 births during the study period. It is routine practice to propose ultrasound examinations for all gravidas, especially at 11-14, 20-22, and 28-32 weeks gestation. Four specialists in maternal and fetal medicine performed the ultrasonographic examinations (Voluson 730 Expert TM; GE Healthcare, Milwaukee; Wİ, USA) and invasive procedures. Pregnancies detected with congenital abnormalities and those that underwent TOP in our hospital constituted the study population.

Fetal anomalies were classified according to the International Classification of Disease 10 (1994) and Eurocat (2) with respect to pathology and chorionicity. Pathologic classification included central nervous system (CNS), facial abnormalities (eye, ear, cleft lip, and palate malformations), congenital heart disease (CHD), digestive system abnormalities, urogenital system abnormalities (UGS), limb abnormalities, musculoskeletal and connective tissue pathologies, and chromosomal abnormalities. In addition to the 2003 EUROCAT classification (3), we added thoracic pathologies, hydrops fetalis, placenta and associated pathologies, multiple pregnancies and related complications, and specific maternal and social conditions. After completion of the fetal anomaly work-up, a multidisciplinary medical panel, including members of the Perinatology Division and related subdivisions of the Pediatrics and Pediatric Surgery Departments, counseled the couple. Our hospital's Ethical Committee and the Perinatal-Neonatal Council offered patients an opportunity to discuss the prenatal findings, neonatal prognosis, and pregnancy management and options, including TOP. The decisions and attitudes of families towards TOP or continuing pregnancy based on fetal anomalies, divided into two groups with early and late diagnoses, were also evaluated. In our hospital, misoprostol induction is the main procedure for TOP beyond 14 weeks of gestation. From 26 weeks gestation onwards, fetocide is performed prenatally. Afterwards, the vaginal misoprostol dose for TOP is usually 200 μg every 6 h. In third trimester pregnancies with a scarred uterus, TOP is performed using 50 μg (one-fourth of a 200 μg tablet) vaginal misoprostol every 6 h. An oxytocin infusion is another method used in multigravidas with favorable cervices, or combined techniques of misoprostol plus oxytocin and / or Foley catheter dilatation were used to accelerate induction.

The reasons why some third trimester TOPs were not performed earlier were categorized retrospectively as follows: 1) third trimester prenatal diagnosis of conditions potentially identifiable earlier (false negative earlier screening); 2) fetal diagnosis and related conditions could not be evaluated and predicted accurately until the third trimester, although second trimester diagnosis is possible; 3) diagnosis and prognostic assessment performed during second trimester, although a poor fetal prognosis had been recognized, but the decision to terminate was made later in gestation; and 4) second trimester diagnosis not achievable due to a later onset of clinical conditions.

Statistical analysis

The GraphPad Prisma V.3 package program (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Descriptive statistical methods (mean and standard deviation), chi-square (χ^2), Fisher's exact test, and odds ratios (ORs) were used for qualitative data determination. The results were evaluated with a confidence level (CI) of 95%, and a significance level of $p < 0.05$.

Results

A total of 1449 cases were evaluated by the hospital council, 713 TOP decisions (49.2%), and 677 pregnancy TOPs (46.7%) were registered during the study period. Most of the gravidas (87.8%) were <35 years of age, with a mean age of 27.1±5.71 years and a mean gestational age of 21.82±5.31 weeks (minimum 10, weeks; and maximum, 37 weeks) at the time of diagnosis (Table1).

The total TOP rate was 7.30%, with an increasing frequency and highest level in 2006 (12.03‰). The late TOP rate was 2.87‰, and also had an increasing frequency and highest level in 2006 (5.52‰). Six hundred seventy-seven pregnancies (94.95% of 713 cases) opted for TOP at our hospital. The proportion of identified reasons for TOP and related percentages is listed in Table 2. Of 285 late TOP decisions, 265 cases (92.98%) were terminated.

The most common pathologies related to TOP were CNS (51.7%), chromosomal (11.7%), and UGS abnormalities (8.4%). The order in early and late terminations was similar with

Table 1. Demographic characteristics (n = 713)

	Mean±Std. Deviation	Minimum	Maximum
Age <35 (n=626, 87.8%) ≥35 (n=87, 12.2%)	27.1±5.71	14	45
Gravidity	2.38±1.68	1	15
Parity	0.99±1.26	0	10
Gestational week at diagnosis	21.82±5.31	10	38
Gestational week of termination	22.17±5.35	11	38

Table 2. Pregnancy termination rate and late pregnancy termination rate (n: 677 cases for total TOP; n: 265 cases in late TOP)

Year	Total births	Total Terminations (n)	‰	Late Terminations (n)	‰
2002	19.074	128	6.71	52	2.73
2003	20.743	130	6.27	38	1.83
2004	21.244	130	6.12	49	2.31
2005	16.130	108	6.70	43	2.67
2006	15.048	181	12.03	83	5.52
Total	92.239	677	7.30	265	2.87

different percentages for CNS abnormalities, chromosomal, and UGS abnormalities (51.5%, 12.4%, and 8.7% in early TOPs; and 52.1%, 10.6%, and 7.9% in late TOPs, respectively).

Three triplet pregnancies, and 12 dichorionic and 15 monochorionic twin pregnancies with abnormalities were diagnosed. All triplets were trichorionic pregnancies with CNS pathologies and feticide was performed for the affected because of anencephaly in the 22nd gestational week, spina bifida in the 27th gestational week, and anencephaly in the 21st gestational week. Eight dichorionic pregnancies had CNS abnormalities, two pregnancies had non-immune hydrops fetalis, and one pregnancy had a cardiac abnormality, and these affected fetuses were terminated. In one case diagnosed as a molar pregnancy, the entire pregnancy was terminated at 14 gestational weeks. Our database for monochorionic twins constituted four cases with co-twins diagnosed as acardiac twins, two cases with thoracopaghus, one case with twins both diagnosed with trisomy 21, four cases in which one of the twins had CNS abnormalities, two cases in which one of the twins were diagnosed with non-immune hydrops, one case with a cardiac abnormality in co-twin, and one case with non-immune hydrops because of twin-to-twin transfusion syndrome. We performed bipolar cord coagulation in 10 cases and alcohol injection into the umbilical arteries in 5 cases.

The process for delaying third trimester TOPs was analyzed in more detail (Table 3). In 174 terminations (65.6%) we determined that the prenatal diagnosis of fetal pathology could have been made earlier. The reasons for these cases were a failure in screening by ultrasound in the second trimester and throughout pregnancy. The main pathologies in this group were central nervous system abnormalities (n=121; neural tube defects, hydrocephaly, and holoprosencephaly), urogenital abnormalities (n=14; bilateral renal agenesis), and aneuploidies (n=17; trisomies 18 and 21) (Table 4).

In 15 cases (5.7%), the prognosis of the anomaly could not have been recognized definitely until the third trimester, although prenatal diagnosis of the anomaly was possible earlier. The majority of these cases consisted of cerebral ventriculomegaly (n=4), in which a poor prognosis could only be established when associated cerebral anomalies became visible or rapid enlargement of ventriculomegaly occurred.

The third group consisted of 23 cases (8.7%) with a poor prognosis of fetuses established in the second trimester screening, but TOP was postponed because the couple required a longer time to make a decision about the TOP.

In 53 cases (20.0%) the diagnosis of anomalies or pregnancy conditions were not possible earlier than the third trimester, with a regular ultrasound examination which was routinely performed. This group consisted of 16 cases with severe pre-eclampsia, HELLP syndrome, and intrauterine growth restriction. We also had 13 cases with skeletal dysplasia with late onset/recognition of short limbs and associated abnormalities. Another group had neurologic defects (n=6), including microcephaly and hydrocephaly and urogenital defects (n=6) with congenital hydronephrosis and non-functional kidneys associated with late onset of anhydramnios and renal failure.

From 26 weeks onwards, fetocide was performed in 183 cases, with only 1 failed case. The diagnosis in this case was non-immune hydrops fetalis and fetocide was performed twice without success because of the fetal position and a posteriorly-located placenta. After consulting the parents, the decision to proceed with delivery was made and fetal death occurred during labor.

In 588 women (86.9%), labor induction was achieved by vaginal misoprostol. In multigravidas with favorable cervices, oxytocin induction was another method for labor induction (3.4%). In cases with failed inductions, additional oxytocin induction and/or Foley catheter application with vaginal misoprostol were performed (9.0%). There was statistical significance in the additional need of oxytocin and / or a Foley catheter in the late termination group (p=0.017). We had 5 cases with 2 uterine ruptures in each group, both with an obstetric history of a previous cesarean section. Another three cases were terminated due to hysterotomies, 1 week after induction with the aforementioned methods (Table 5).

Discussion

The goal of maternal-fetal medicine is to support the treatment of neonates affected by disorders diagnosed during pregnancy. However, the prognosis of several pathologies is so poor that TOP may be considered in countries where it legally exists. We are aware that TOP raises many ethical problems, particularly in the third trimester (8-10). Fears have been expressed that improving prenatal diagnosis leads to a lower tolerance of disability, with a subsequent increase in the prevalence of elective TOP (11). Most terminations are carried out on gravidas at low risk for fetal abnormalities (12).

Table 3. Distribution of fetal abnormalities, cases with early and late termination

	Total Anomaly (n) (%)	Early termination (<23GW) (n) (%)	Late Termination (≥23GW) (n) (%)
1. Central Nervous System (CNS) Neural tube defects (Anencephaly and similar, encephalocele, 2pina Bifida), hydrocephaly, microcephaly, holoprosencephaly, other	350 (total) 51.7	212 51.5	138 52.1
2.Face and Neck Cystic hygroma, face abnormalities (eye abnormalities, ear abnormalities, cleft lip with or without palate)	16 (total) 2.4	15 3.6	1 0.4
3.Congenital Heart Disease (CHD) Anomalies of cardiac chambers and connections (common arterial truncus, transposition of great arteries, single ventricle), malformation of cardiac septa (VSD, ASD, AVSD, tetralogy of Fallot and double outlet right ventricle), malformations of valves (tricuspid atresia and stenosis, Ebstein' s anomaly, aortic valve atresia/ stenosis, hypoplastic left heart), malformation of great arteries and veins (coarctation of aorta, pulmonary artery anomaly), complex cardiac anomaly, cardiomyopathy	27 (total) 4.0	12 2.9	15 5.7
4.Digestive-Gastrointestinal system Esophageal atresia and stenosis with or without fistula, small intestine anomaly (duodenal anomalies, other specified parts of small intestines), ano-rectal atresia and stenosis	No cases	No cases	No cases
5.Urogenital system anomalies (UGS) Renal anomalies (bilateral renal agenesis, bilateral polycystic kidney disease, congenital hydronephrosis, bladder extrophy), genital anomalies (hypospadias, indeterminate sex), adrenal anomalies (congenital adrenal hyperplasia)	57 (total) 8.4	36 8.7	21 7.9
6.Limb anomalies Upper limb anomalies (complete absence of upper limb, absence of upper arm and forearm with hand present, absence of both forearm and hand, absence of hand and fingers), lower limb anomalies (complete absence of lower limb, absence of thigh and lower leg with foot present, absence of both lower leg and foot, absence of foot and toe, abnormalities and deformities of foot)	6 (total) 0.9	2 0.5	4 1.5
7.Musculoskeletal – connective tissue and metabolic defects Skeletal dysplasia / Dwarfism, Pierre Robin Syndrome, omphaloceles, gastroschisis,fetal metabolic defect, fetal tumor, other	50 (total) 7.4	32 7.8	18 6.8
8.Chromosomal anomalies Down syndrome, Patau syndrome, Edward syndrome, other trisomies and partial trisomies of autosomes, monosomies and deletions from autosomes, Turner syndrome, Klinefelter's syndrome, other	79 (total) 11.7	51 12.4	28 10.6
9.Thoracic anomalies Diaphragmatic hernia, congenital cystic adenoid malformation, pulmonary sequestration, bronchogenic cyst, congenital airway obstruction, pleural effusion, thoracic hypoplasia	6 (total) 0.9	3 0.7	3 1.1
10.Hydrops Immune hydrops, non-immune hydrops (anemia-thalassemia, other reasons)	26 (total) 3.8	19 4.6	7 2.6

11.Placenta and chord anomalies Amniotic band, placental insufficiency and intrauterine growth retardation, premature rupture of membrane (PROM)	8 (total) 1.2	3 0.7	5 1.9
12.Multiple pregnancy and associated complications Twin to twin transfusion syndrome (TTTS), major fetal anomaly in co-twin, other	30 (total) 4.4	21 5.1	9 3.4
13.Maternal, infection and social complications Medical complication associated with pregnancy (pregnancy induced hypertension, preeclampsia, superimposed preeclampsia, gestational diabetes mellitus), maternal – fetal infection (rubella, toxoplasmosis, cytomegalovirus), teratogenic exposure, rape	22 (total) 3.2	6 1.5	16 6.0
Total of cases	677 100.0	412 100.0	265 100.0

The main reason for TOP is CNS abnormalities, which is in agreement with other single institute publications and public studies (12-18). Evaluation of the fetal CNS anomalies revealed that the CNS was responsible for more than one-half of the cases. Neural tube defects, especially anencephaly, constituted a substantial cause in the early termination group, while the diagnosis and rate of hydrocephalus increased in the late group. This finding is explained by the fact that anencephaly can be easily diagnosed in the first trimester in a competent sonographic screening program, while hydrocephaly usually develops late in the second trimester or early in the third trimester (12). There will always be cases, such as microcephaly and progressive ventriculomegaly, in which severe fetal conditions are difficult to diagnose before 23 weeks of gestation, but in our cohort, a large number of TOPs was due to lack or failure of ultrasound screening in the second trimester.

Our perinatology database consisted of 155 cases with CHDs and 27 cases with TOPs. Our hospital's neonatology database consisted of 350 cases with cardiac abnormalities diagnosed in the postnatal period during 2002-2006. Ventricular and atrial septal defects (n=185) constituted the main two groups in postnatal cardiac abnormalities (52.9 %). Cardiac abnormalities have a changing intrauterine nature. Therefore, prenatal diagnosis is not always accurate. Even the postnatal nature of these pathologies is different; specifically, muscular ventricular septal defects have the potential for spontaneous closure. However, the severity of cardiac pathologies is varying and life-threatening abnormalities are rare. We have found a similar mean rate (4.0%) of cardiovascular malformations to other investigators. This finding increased (5.7%) in the late TOP group with a definite diagnosis. The rate of cardiovascular malformations is 4%-8% in earlier reports (12, 17) and up to 16%-26% in recent reports (13, 16).

We found chromosomal abnormalities to be the second most common indication for TOPs, among early and late TOPs. The most common chromosomal abnormality was trisomy 21, constituting 57.0% of chromosomal abnormalities as found by us and other investigators (12, 13, 16). First and second trimester screening programs are related with early terminations, but late terminations are correlated with second trimester ultrasound screening. This study confirmed that ultrasonography is an important tool for the prenatal detection of chromosomal abnormalities. The association between chromosomal abnormalities and structural defects is well-known and the association with minor ultrasound anomalies has been well-studied (18, 19). The global ultrasound detection rate for chromosomal abnormalities in unselected populations varies from 21.5%-55.6% (20-23).

Clinicians usually deal with two major problems in twins discordant for a major fetal anomaly (development of polyhydroamnios associated with the risk of preterm delivery and intrauterine death of one fetus that poses a risk of death in monochorionic placentation to the co-twin) (24-26). We found that severe polyhydroamnios developed at 26-30 weeks of gestation; delivery was 2 weeks earlier (27). Active management is another way in these complicated multiple pregnancies and feticides in dichorionic pregnancies and alcohol ablation or cord occlusion in monochorionic pregnancies are proposed management techniques (28-30).

UGS pathologies constituted the third common group of TOPs (9.1%). The overall sensitivity rate for renal malformations is approximately 55% in different countries (21, 22). Bilateral involvement, associated malformations, and anhydramnios are unfavorable determinants of the prognosis in individual cases (31-33).

Late TOPs (39.1% of 677 cases) has a high percentage with a large number of TOPs (65.6%) in the third trimester due to failure of ultrasound screening in the second trimester. Improving the effectiveness of ultrasound screening in the second trimester performed by maternal-fetal medicine specialists and / or sonographers may reduce the number of terminations in late pregnancy. The late onset of clinical pathology (20.0%), and poor prognosis and delayed diagnosis (5.7%) are two other acceptable conditions of third trimester TOPs.

Conflict of interest

None declared

Table 4. Diagnostic procedure leading to late termination (n=265)

A - Third trimester prenatal diagnosis of conditions potentially identifiable earlier	**n=174 (65.6%)**
1- Central nervous system abnormalities	121
2- Face and neck	1
3- Congenital heart disease	7
4- Urogenital system anomalies	14
5- Limb anomalies	4
6- Musculoskeletal – connective tissue and metabolic defects	4
7- Chromosomal anomalies	17
8- Thoracic anomalies	-
9- Hydrops	-
10- Placenta and chord anomalies	1
11- Multiple pregnancy and associate anomalies	4
12- Maternal, infection and social complications	1
B - Fetal diagnosis could not be evaluated until third trimester, although second trimester diagnosis achievable	**n=15** (5.7%)
1- Central nervous system abnormalities	4
2- Face and neck	-
3- Congenital heart disease	1
4- Urogenital system anomalies	4
5- Limb anomalies	-
6- Musculoskeletal – connective tissue and metabolic defects	-
7- Chromosomal anomalies	4
8- Thoracic anomalies	1
9- Hydrops	-
10- Placenta and chord anomalies	-
11- Multiple pregnancy and associate anomalies	1
12- Maternal, infection and social complications	-
C - Diagnosis and prognostic assessment made during second trimester, but choice to TOP taken later in gestation	**n = 23** (8.7%)
1- Central nervous system abnormalities	8
2- Face and neck	-
3- Congenital heart disease	2
4- Urogenital system anomalies	1
5- Limb anomalies	-
6- Musculoskeletal – connective tissue and metabolic defects	4
7- Chromosomal anomalies	1
8- Thoracic anomalies	1
9- Hydrops	2
10- Placenta and chord anomalies	1
11- Multiple pregnancy and associate anomalies	3
12- Maternal, infection and social complications	-
D - Second trimester diagnosis probably not achievable due to late onset of the condition	**n = 53 (20.0%)**
1- Central nervous system abnormalities	6
2- Face and neck	-
3- Congenital heart disease	-
4- Urogenital system anomalies	6
5- Limb anomalies	-
6- Musculoskeletal – connective tissue and metabolic defects	13
7- Chromosomal anomalies	3
8- Thoracic anomalies	-
9- Hydrops	4
10- Placenta and chord anomalies	3
11- Multiple pregnancy and associate anomalies	2
12- Maternal, infection and social complications	16

Table 5. Method of TOP in early and late terminations

	Early termination (<23 GW) (n) (%)	Late Termination (≥23 GW) (n) (%)	n (%)	P
Misoprostol	371 (%90.0)	217 (%81.9)	588 (%86.9)	0,003
Hysterotomy / Hysterectomy*	2 * (%0.5)	3 * (%1.1)	5 (%0.7)	0,617
Oxytocin	11 (%2.7)	12 (%4.5)	23 (%3.4)	0,277
Misoprostol + Oxytocin or Foley catheter	28 (%6.8)	33 (%12.5)	61 (%9.0)	0,017
Total	412 (%100.0)	265 (%100.0)	677 (%100.0)	

($p < 0.05$)

*in each group with one case due to uterine rupture

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Atrioventricular and ventricular septal defects; topographical analysis and impact of associated cardiac and extracardiac findings and postpartum outcome

Atrioventriküler ve ventriküler septal defektler; topografik değerlendirme ve ek kalp ve kalp dışı bulguların etkisi ile doğum sonrası sonuçları

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Abstract

Objective: The aim of this study was to evaluate prognosis of types of ventricular septal defects and coexistence of associated cardiac and extracardiac defects.

Methods: 120 prenatal diagnosed pregnancies associated with ventricular septal pathology were retrospectively evaluated and divided into four groups, as atrioventricular septal defects, perimembranous septal defects, muscular septal defects and univentricular formation. Each group was divided further into four groups, as isolated defect, co-existing extracardiac defect, septal defect with extracardiac defect and septal defect with co-existing cardiac and extracardiac defect. Postnatal follow-up was continued at least until 8 months of life.

Results: Median gestational age at diagnosis was 26.3 weeks, 47 cases were diagnosed before 24 weeks. After dispersion of septal defects there was a statistical significance of p=0.0089 between groups. Of 31 cases with atrioventricular septal defects, only one case survived (3.2%) and there was a high association with extracardiac defects and abnormal karyotype (p=0.002). 69 cases with perimembranous ventricular septal defects were diagnosed, and 24 cases (34.8%) survived with significance for abnormal karyotype (p=0.039). Of 18 cases born with muscular septal defects 12 cases (66.7%) stay alive. We had two cases with univentricular structure; both cases decided for termination of pregnancy.

Conclusion: The more complicated and severe the pathology, the worse the prognosis. Individualized counseling is the most important point in decision making together with families.

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Key words: Atrioventricular septal defects, perimembranous ventricular septal defects, muscular ventricular septal defects, associated abnormalities, prognosis

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Özet

Amaç: Bu çalışmamızın amacı venriküler septumdaki defektleri ve eşlik eden ek kardiyak ve kalp dışı defektlerin prognoz üzerine etkisini değerlendirmektir.

Yöntemler: Prenatal dönemde tanı almış 120 ventriküler septal patoloji olgusu, retrospektif olarak, atriovenriküler septal defekt, perimembranöz septal, müsküler septal defekt ve tek ventrikül oluşumu olarak 4 ayrı grup içinde değerlendirilmiştir. Her bir grup daha sonra tekrar izole defektler, eşlik eden kalp dışı defektler, eşlik eden kalp defektleri ve eşlik eden kalp ve kalp dışı defektleri olmak tekrar 4 grup içinde değerlendirildi. Olgular doğum sonrası süreçte en az 8 aylık oluncaya kadar izlendi.

Bulgular: Prenatal tanı sırasında ortalama gebelik haftası 26.3 olup, 47 olgu 24. gebelik haftasından önce tanı almıştır. Septal defektlerin dağılımından sonra gruplar arasında istatistiksel olarak anlamlılık saptanmıştır (p=0.0089). 31 atrioventriküler septal defekt olgusunun sadece 1 tanesi (%3.2) hayatta kalmış olup, bu grupta kalp dışı defektler ve anormal karyotip ilişkisi yüksek olarak saptanmıştır (p=0.002). 69 perimembranöz ventriküler septal defekt olgusunun 24 tanesi (%34.8) hayatta kalmış ve anlamlı anormal karyotip ilişkisi saptanmıştır (p=0.039). 18 müsküler septal defekt olgusunun 12 tanesi (%66.7) hayatta kalmıştır. Olgularımızn içinde iki univentriküler ventrikül oluşumu olgusu, gebeliğin sonlandırılmasını istemiştir.

Sonuç: Olgulardaki komplike ve patolojik ciddiyet arttıkça, prognoz kötüleşmiştir. Aileler ile yapılan danışmanlıkta, olguların kişiselleştirilerek verilmesi ve buna uygun karar verilmesi uygundur.

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Anahtar kelimeler: Atrioventriküler septal defekt, perimembranöz ventriküler septal defekt, müsküler ventriküler septal defekt, eşlik eden anomaliler, prognoz

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Introduction

Congenital heart disease (CHD) is the most frequent congenital disorder and has significant pre- and post-natal morbidity and mortality (1). CHDs are believed to be multifactorial disorders arising from the combined effect of genetic predisposition and environmental factors (2). Ventricular septal defects (VSDs) are the most frequent congenital cardiac anomalies (3-5). The incidence of VSDs ranges from 3-56/1000 live births (3), depending on the screening method. Anatomically, VSDs are divided into defects of the membranous or muscular part of the interventricular cardiac septum. The etiology of VSDs is still uncertain. It is expected that in 4% of cases, a chromosomal or genetic defect exists (3, 6-8).

Atrioventricular septal defects (AVSDs) are a group of anomalies that share a defect of the atrioventricular septum and abnormalities of the atrioventricular valves. AVSDs are divided into partial and complete forms. In partial AVSDs, a primum atrial septal defect (ASD) is always present and there are two distinct mitral and tricuspid valve annuli. The complete form of AVSDs also includes a primum ASD, but it is contiguous with an inlet ventricular septal defect (VSD), and the common atrioventricular valve has a single annulus (9). The estimated incidence of AVSDs ranges from 24-31/100,000 (10) live births. There is a strong association between AVSDs and Down's syndrome; one-half of patients with AVSDs having Down's syndrome (11).

The objective of this study was to portray the characteristics and outcome of prenatally detected peri-membranous VSDs, muscular VSDs, and AVSDs, depending on the associated cardiac and extracardiac abnormalities and their effect on aneuploidy and the outcome of fetuses, after a 1-year follow-up.

Material and Methods

Between January 2002 and December 2007, 8953 pregnancies were screened using fetal echocardiography and genetic sonogram, and 155 cases with CHD were detected in our Perinatology Unit. When a heart defect is diagnosed or suspected, one of our four physicians at the center performs a detailed anatomic assessment, in most cases in the presence of a pediatric cardiologist. For optimal fetal heart screening, the five short-axis views (12) are used for the examination, including the sagittal view of the aortic and ductal arches, if needed. This was a retrospective study with 120 cases of fetuses with peri-membranous and muscular VSDs and AVSDs as a component of other CHDs, associated with other extracardiac congenital abnormalities or as isolated findings. CHDs without a septal defect were excluded from the study. Partial and complete forms of AVSDs were counted together. All cases were diagnosed prenatally and counseled about clinical outcomes and follow-up.

Every group of VSDs was subdivided into the four subgroups as (a) isolated cardiac findings, (b) septal defects with co-existing cardiac findings, (c) septal defects with extra-cardiac defects, and (d) septal defects with co-existing cardiac and extracardiac findings.

The study was closed to new follow-up data on 1 January 2008, but the follow-up period for survivors was calculated to the last follow-up available, rather than the closing date of the study.

The following information was retrieved for all cases from our computerized database: gestational age at diagnosis, presence of other cardiac defects, presence of extracardiac defects and chromosomal anomalies, location of the defect, Doppler demonstration of a flow defect, pregnancy outcome, and neonatal follow-up. The location of the defect was categorized as an ASD, peri-membranous septal defect, muscular septal defect, or univentricular formation.

Fetal karyotypes were available in 108 cases (90.0%), except for 6 cases with isolated muscular VSDs. When genetic abnormalities were suspected in the neonatal period, postnatal karyotyping was also offered to the parents.

After completion of the fetal anomaly work-up, including cardiac and extracardiac abnormalities, a multidisciplinary medical panel consisting of perinatologists, pediatricians, and pediatric surgeons counseled the couple. Our hospital's Ethical Committee and Perinatal - Neonatal Council offered patients an opportunity to discuss prenatal findings, neonatal prognosis, and pregnancy management and options, including termination of pregnancy (TOP). Our hospital's Ethical Committee, Perinatal-Neonatal Council, and Institutional Review Board approved the follow-up and clinical management.

All neonates who survived the 2nd day of life and all fetuses that died after birth due to associated cardiac, extracardiac, or chromosomal anomalies were examined by our pediatric cardiologist. All surviving neonates were followed directly until 12 months of age. In the case of cardiac surgery, they were referred to three other cardiac surgery centers in Istanbul, but follow-up after surgery was continued in our center. Necropsies of all fetuses undergoing TOP were performed by our pathologists.

The GraphPad Prisma V.3 package program was used for statistical analyses in this study. In the data evaluation, descriptive statistical methods (mean and standard deviation) were used. Chi-square (χ^2) and Fisher's exact tests were used for qualitative data determination. The results were evaluated with a confidence level of 95%, and a significance level of $P < 0.05$.

Results

A final prenatal diagnosis of septal defects was made in 120 of 8953 cases referred to our Prenatal Diagnosis Unit. Thirty-one (25.8%) fetuses had AVSDs, 69 (57.5%) cases had peri-membranous VSDs, 18 (15.0%) fetuses had muscular VSDs, and 2 cases (1.7%) had univentricular heart formations. Of these 120 cases with septal defects, 6 cases with a prenatal diagnosis and normal karyotype findings were lost to follow-up after birth in the neonatal period and were excluded.

The mean gestational age at diagnosis was 24.3 weeks (range, 14-39 weeks). The mean maternal age at diagnosis was 27.0 years (range, 17-42 years). The indications for fetal echocardiography were as follows: suspected extracardiac malformations in 31 cases (25.8%), suspected CHD in 29 cases (24.1%), maternal diabetes in 3 cases (2.5%), growth restriction in 8

cases (6.7%), routine scan in 28 cases (23.3%), sibling history of CHD in 5 cases (4.2%), sibling history of extracardiac defects in 8 cases (6.7%), and other indications in 8 cases (6.7%).
Fetal karyotyping was performed in 108 cases, of which 22 (20.4%) had aneuploidies, as follows: 1 case (0.9%) of trisomy 13, 8 cases (7.4%) trisomy 18, and 12 cases (11.1%) of trisomy 21.

The dispersion of septal defects and associated cardiac and extracardiac findings in the described subdivided groups, aneuploidy findings, clinical outcomes of each group, and live cases after a 1-year follow-up are shown in Table 1. Thirty-seven cases (32.5% of 114 cases with a 1-year follow-up) survived with statistical significance between all 3 groups (AVSD, peri-

Table 1. Dispersion and outcome of cases (n=120)

Type of defect (n)	Outcome	Isolated	Coexisting cardiac	Extra-cardiac	Coexisting Cardiac + extra-cardiac
Alive at follow-up (%)					
AVSD (n=31)		1	10	6	14
	Alive birth	1	6	0	4
	TOP: a- aneuploidy	-	-	6 (5xT21, 1xT18)	5 (4xT21, 1xT18)
	b- other	-	3	-	5
	IUDF	-	1	-	-
	Postpartum death	1	5	-	4
Survivor: 1 (3.2%)	Alive (%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
	Aneuploidy (%)	-	-	100%	35.7%
Perimembranous VSD (n=69)		12	26 (29, but 3 cases lost in follow-up)	13	13 (15, but 2 cases lost in follow-up)
(five cases lost in follow-up)	Alive birth	10	19	4	7
	TOP: a- aneuploidy	1 (1xT21)	2 (1xT21, 1xT18)	5 (1xT21, 3xT18, 1xT13)	3 (1xT21, 2xT18)
	b- other	-	4	3	2
	IUDF	1	1	1	1
	Postpartum death	-	11	3	4
Survivor: 24 (34.8%)	Alive (%)	10 (83.3%)	8 (27.6%)	1 (7.7%)	3 (20.0%)
	Aneuploidy (%)	8.3%	6.9%	38.5%	20.0%
Muscular VSD (n=18)		6	3 (4, but 1 case lost in follow-up)	6	2
(one case lost in follow-up)	Alive	6	3	4	-
	TOP: a- aneuploidy	-	-	-	-
	b- other	-	-	2	1
	IUDF	-	-	-	1
	Postpartum death	-	-	1	-
Survivor: 12 (66.7%)	Alive (%)	6 (100%)	3 (100%)	3 (50%)	0 (0%)
	Aneuploidy (%)	-	-	-	-
Univentricular (n=2)			1		1
	Alive Birth		-		-
	TOP: a- aneuploidy		-		-
	b- other		1		1
	IUDF		-		-
Survivor: - (%0.0)	Alive (%)		0 (0%)		0 (0%)
	Aneuploidy (%)		-		-

AVSD: Atrioventricular septal defect; IUDF: intrauterine demise / death of fetus; T13: trisomy 13; T18: trisomy 18; T21: trisomy 21; TOP: termination of pregnancy; VSD: ventricular septal defect

membranous VSD, and muscular VSD) related to an abnormality (Table 2; $\chi^2 = 17.09$; P = 0.0089).

AVSD outcome

There was only one isolated case (3.2%) of AVSD, 10 cases (32.3%) with other co-existing cardiac defects, 6 cases (19.3%) with additional extracardiac defects, and 14 cases (45.2%) with cardiac- and extracardiac-associated defects. The survival rate was very poor with only 1 survivor (3.2%) in this group with AVSD associated with tricuspid atresia, hypoplastic right ventricle, and dilated left heart after surgery and a regular 1-year follow up.

Cases with additional extracardiac defects were more often related to aneuploidies, which were seen in this group of AVSD cases with additional extracardiac defects with 100% involvement and AVSD cases related with cardiac and extracardiac defects with 35.7% involvement. No relationship was found in the other subgroups with isolated and additional cardiac findings.

Postpartum deaths were more related with complex cardiac defects, probably depending on severe postpartum neonatal circumstances and complications in pediatric cardiac surgery.

Peri-membranous VSD outcome

The database included 69 cases with peri-membranous VSDs, of whom 12 (18.8%) were isolated, 26 (40.6%) had co-existing cardiac defects, 13 (20.3%) had extracardiac pathologies, and 13 (20.3%) were diagnosed with cardiac and extracardiac defects. Five cases were diagnosed during pregnancy, but lost during postnatal follow-up.

The survival rate was 34.8%, although 20 cases (29.0%) had a TOP and 4 cases (5.8%) involved an intrauterine death of the fetus (IUDF). The survival rate was highest in the isolated group (83.3%), although 1 case had trisomy 21 and 1 case had an IUDF. Postpartum death was especially noticeable in complex, co-existing cardiac defects with 15 cases (21.7%).

Aneuploidies occurred in all groups, but were especially manifest in extracardiac defects (8.3%, 6.9%, 27.6%, and 20.0% for all subgroups, respectively).

Muscular VSD outcome

Cases with muscular VSD constituted 15.0% of our database (18 cases). None of these pregnancies had chromosomal pathologies; the survival rate was highest in the group, with 66.7%.

All six cases with isolated muscular VSD survived after a 1-year follow-up with spontaneous closure of muscular VSDs in 4 cases. The prognosis of muscular VSDs with cardiac defects was good, with 3 live cases after birth and regular follow-up and 1 case lost after birth during the follow-up period.

The main reason of loss in this group was the decision for TOP in 3 cases, 1 case with IUDF, and 1 postpartum death.

We diagnosed 2 cases with univentricular cardiac formation with decisions for TOP in both cases.

Among extracardiac anomalies, central nervous system anomalies were the most common group, followed by the musculoskeletal system, gastrointestinal system, and genitourinary system anomalies (Table 3).

There was a significant statistical correlation between the site of the defect, findings of extracardiac defects, and fetal karyotype in AVSDs and peri-membranous VSDs (Table 4). The relative risk for aneuploidy in association with extracardiac defects was remarkable, with 2.2 AVSDs and 2.14 peri-membranous VSDs. The relative risk for aneuploidy with respect to extracardiac defects was similar in both groups.

Prenatal ultrasound findings with associated cardiac and extracardiac findings of aneuploid fetuses are given in Table 5.

A major influence on overall outcome was the proportion of parents opting for TOP (n = 39, 32.5% of all cases). Termination was offered only in aneuploidy cases and severe cardiac abnormalities such as severe hypoplastic left or right heart, interruption of arcus aorta, mitral or tricuspid atresias causing chamber disproportion and / or defects and aortic and pulmonic hypoplasias causing severe outflow defects. All cases with aneuploidy (n = 22), 12 cases related with severe cardiac pathology, and 5 cases associated with extracardiac abnormalities accepted TOP.

Twelve of 37 surviving cases were operated without postoperative complications. In 8 of 25 cases, spontaneous closure of septal defects was noted. Three cases had a pre- and post-natal diagnosis of isolated peri-membranous VSD and 4 cases had a diagnosis of isolated muscular VSD, in which one closure was seen in the intrauterine period. One case with a muscular VSD and omphalocele (operated because of anterior wall defect) also had spontaneous closure of the septum. Follow-up continues in 17 cases.

Table 2. Statistical findings of septal defects related to abnormality

	Diagnosed (n)	Alive (n, %)	Isolated (n, %)		Coexisting Cardiac (n, %)		Extracardiac (n, %)		Coexisting + Extracardiac (n, %)	
AVSD	31	1 (3.2%)	1	3.23%	10	32.26%	6	19.35%	14	45.16%
Perimembranous VSD	69	24 (34.8%)	12	17.39%	26	37.68%	13	18.84%	13	18.84%
Muscular VSD	18	12 (66.7%)	6	33.33%	3	16.67%	6	33.33%	2	11.11%

χ^2:17.09; p = 0.0089

AVSD: atrioventricular septal defect; VSD: ventricular septal defect

Table 3. System specific and individual anomalies with septal defects

Anomalies	AVSD (n=31)*	Perimembranous VSD (n=69)*	Muscular VSD (n=18)*
Cardiovascular system	37	77	8
- Outflow tract anomalies	13	36	3
- Chamber disproportion	5	14	2
- Arrhythmias	2	-	1
- Isomerism	5	1	-
- Single umbilical artery	4	3	-
Musculoskeletal system	5	11	1
- Short limbs	1	1	-
- Polydactyly	3	3	1
- Talipes equinovarus	-	2	-
- Rockerbottom foot	1	2	-
Central nervous system	14	20	3
- Posterior fossa anomaly	-	6	1
- Ventriculomegaly	2	8	-
- Spine pathology	1	4	-
- Major findings (holoprosencephaly, corpus callosum agenesis etc.)	3	-	2
- Minor findings (choroid plexus cysts, nuchal fold etc.)	6	2	-
Genitourinary system	7	6	3
- Multicystic dysplastic kidney	1	1	1
- Pelvicaliectasis/hydronephrosis	5	4	1
Gastrointestinal system	6	8	5
- Omphalocele/gastroschisis	-	2	2
- Obstruction/duplication	2	4	2
- Echogenic intestines	3	1	1
Face, eye and neck	4	5	2
- cystic hygroma	2	2	1
- cleft lip/palate	1	3	-
Respiratory system	2	-	-

*A case can have more than one anomaly and hence the number of anomalies will exceed the total number

Table 4. Statistical findings of septal defect to chromosomal pathology /aneuploidy

		Isolated and/or coexisting cardiac defect (without extracardiac finding)		Extracardiac Findings (with isolated and/or coexisting cardiac findings)		P	RR
AVSD	Normal karyotype (n / %)	11	100.00%	9	45.00%	0.002	2.2
	Abnormal karyotype (n / %)	0	0.00%	11	55.00%		(1.36-3.60)
Perimembranous VSD	Normal karyotype (n / %)	35	92.11%	18	69.23%	0.039	2.14
	Abnormal karyotype (n / %)	3	7.89%	8	30.77%		(1.27-3.60)

AVSD: atrioventricular septal defect; VSD: ventricular septal defect

Table 5. Associated cardiac and extracardiac findings in aneuploidy cases

Karyotype	Gestational age at diagnosis (weeks)	Cardiac Findings	Extracardiac Findings
Trisomy 18	22	AVSD Double outlet right ventricle	Strawberry shaped head Micrognathia
Trisomy 18	18	AVSD	Strawberry shaped head Congenital diaphragmatic hernia Clenched hands
Trisomy 21	21	AVSD Single AV valve	Choroid plexus cyst Enlarged nuchal fold Hydronephrosis
Trisomy 21	19	AVSD	Ventriculomegaly Corpus callosum agenesis Hydrops fetalis Echogenic bowel
Trisomy 21	17	AVSD Single AV valve Tetralogy of Fallot	Enlarged nuchal Fold Hydronephrosis Skeletal dysplasia
Trisomy 21	19	AVSD	Enlarged nuchal Fold Echogenic bowel Hydronephrosis
Trisomy 21	16	AVSD Single AV valve	Enlarged nuchal Fold
Trisomy 21	24	AVSD	Choroid plexus cyst Hydronephrosis
Trisomy 21	22	AVSD	Multicystic dysplastic kidney Ambiguous genitalia
Trisomy 21	22	AVSD Tricuspid regurgitation	Gastrointestinal obstruction Single umbilical artery Polyhydroamnios
Trisomy 21	22	AVSD	Hydronephrosis Ventriculomegaly
Trisomy 13	24	Perimembranous VSD	Hypoplastic Vermis Facial cleft Polydactyly
Trisomy 18	27	Perimembranous VSD	Strawberry shaped head Hypoplastic Vermis Gastrointestinal obstruction Hydronephrosis Ambiguous genitalia Polyhydroamnios
Trisomy 18	15	Perimembranous VSD	Cystic hygroma
Trisomy 18	26	Perimembranous VSD Double outlet right ventricle Tricuspid atresia Aort stenosis	Hypoplastic Vermis Intrauterine growth retardation
Trisomy 18	27	Perimembranous VSD Double outlet right ventricle Aort stenosis	Dandy Walker variant
Trisomy 18	18	Perimembranous VSD	Choroid plexus cyst Rockerbottom foot

Trisomy 18	26	Perimembranous VSD Tetralogy of Fallot Pulmonary stenosis	none
Trisomy 21	24	Perimembranous VSD Double outlet right ventricle Pulmonary stenosis	none
Trisomy 21	18	Perimembranous VSD	Hydronephrosis
Trisomy 21	22	Perimembranous VSD	none
Trisomy 21	14	Perimembranous VSD Hypoplastic left heart Hypoplastic arcus aorta	Ventriculomegaly Neural tube defect Intrauterine growth retardation

AV: atrio-ventricular; AVSD: atrioventricular septal defect; VSD: ventricular septal defect

Discussion

Atrioventricular, peri-membranous, and muscular septal defects are important congenital cardiac abnormalities which can be diagnosed prenatally with significant accuracy. Fetuses with septal defects constitute a heterogeneous group which differ in their prognoses in association with additional cardiac and extracardiac defects. Those cases diagnosed prenatally are likely to be biased in favor of features that more readily bring them to the awareness of the ultrasonographer (10). The diagnosis of AVSD in a fetus should initiate not only a detailed examination of the rest of the heart, but also of the entire fetus. Even when the fetal karyotype and detailed ultrasound anomaly scan are apparently normal, important anomalies and genetic syndromes may become apparent after birth, and parents must be counseled with this in mind (10).

The embryologic development of AVSD and VSD differ. The normal embryogenesis of the atrioventricular septum consists of two processes: development of the AV canal occurs via proliferation of the 4 endocardial cushions (superior, inferior, right lateral, and left lateral) and the dextrodorsal conus cushion. As the superior and inferior cushions grow toward each other, the common AV canal becomes two separate and distinct orifices (mitral and tricuspid). The superior and inferior endocardial cushions also extend along the perimeter of the ostium primum, resulting in its closure. Partitioning of the embryonic heart into atrial and ventricular chambers begins at approximately 28 days of gestation. Initially, the interventricular septum forms as a median muscular ridge in the floor of the ventricle near the apex. The early primitive physiologic septal defect that occurs as the septum closes is called the interventricular foramen. Subsequently, the interventricular septum grows and active myoblast proliferation occurs. The free edge of the primitive septum joins with the fused endocardial cushions at approximately 49 days of gestation. The interventricular foramen closes at about 56 days (13).

First trimester screening by nuchal translucency measurements has facilitated early diagnosis of major chromosome abnormality and has also been shown to be a successful means of screening for heart defects in the absence of chromosomal abnormality (13). The poor prognosis of CHD diagnosed antepartum is attributed to the fact that more complex examples are likely to be detected in the fetus. Improvements in screening for fetal heart disease have led to the detection of increasing numbers of cases, including less severe or less complex cases. Our data consisted of six cases in the first trimester, including one case with trisomy 21, diagnosed during screening at 11-14 weeks gestation. Two of the six cases had cystic hygromas, one was born alive with a persistent peri-membranous VSD, aortic regurgitation, and neurologic underdevelopment, and the other case had trisomy 21 and was terminated.

The distribution of the different types of VSDs in our study differs from that of pediatric and prenatal series in the literature. In the pediatric and some prenatal studies, muscular septal defects were more frequent than peri-membranous defects (14-16). In other studies, the incidence of peri-membranous defects was higher than muscular defects (6), which is comparable to our results. Different study populations (prenatal vs. postnatal) and criteria of diagnosis and methods of echocardiography might account for these variations. The detection of muscular defects is facilitated by the pressure gradient existing between the left and right ventricles in the neonate. This determines a high velocity shunt that is easily detected by color Doppler echocardiography. Due to the physiologic patency of the ductus arteriosus and the foramen ovale, this pressure gradient is not present antepartum, rendering the diagnosis of small muscular VSDs very difficult in the fetus. Successful prenatal diagnosis relies primarily on the direct two-dimensional demonstration of the defect, although in some instances flow across small muscular VSDs can be demonstrated by color or pulsed-wave Doppler (6). Our data constituted 69 cases with peri-membranous VSDs and only 18 cases with muscular VSDs, although routine color Doppler use is routine practice in our clinic.

In published reports (17, 18), necropsy studies of live births and stillbirths showed that up to 66% of the cases had more than 1 cardiac anomaly. Our study consisted of 63.3% (n=76) cases with multiple cardiovascular anomalies, which represents a high detection rate of additional cardiac defects.

In the present study, 57 cases (47.5%) with congenital cardiac defects also had extracardiac malformations. The most frequent extracardiac anomalies were found in the central nervous system, musculoskeletal system, gastrointestinal system

and genitourinary system anomalies. Prenatal investigations have shown that heart defects often accompany defects in other organ systems in a wide range of 27%-66% (18-20). These findings point to the need to investigate the heart in cases of extracardiac anomalies and to search for extracardiac anomalies when cardiovascular malformations have been diagnosed. This high proportion of extracardiac anomalies reflects the detailed ultrasonic investigations in fetuses with CHDs, which in many cases led to deliberate termination of pregnancy.

There are different studies showing a wide range of association with chromosomal abnormalities between 5% and 28% (7, 17, 20, 21). The incidence of CHDs and chromosome abnormalities in fetuses is higher than in liveborn infants or stillbirths, as the fetuses often do not survive until birth and are therefore not included in statistical data collected by pediatric cardiologists (21). The frequency of chromosome abnormalities found after the discovery of a CHD varies between 16% (22) and 50% (22). Our data is in agreement with the literature, with an incidence of 18.3% (n=22) of cases associated with cardiac abnormalities. Another interesting point of our study was the relationship between aneuploidy connected to extracardiac and cardiac pathologies. Our results concluded a higher statistical incidence, impact, and relative risk of aneuploidy in the presence of extracardiac abnormalities, then isolated findings of septal pathology or co-existence of other cardiac defects (Table 4).

The present study had some limitations. First, this is a single institute investigation with a low number of pathologies in every subgroup, which causes difficulties in statistical calculation. Second, complete, partial, and intermediate forms of AVSD and inlet, outlet, trabecular, and apical forms of muscular VSD were encountered together. Third, patients requiring surgery were referred to three different cardiac surgery centers in Istanbul. Despite these limitations and the loss of six cases in follow-up, we consider that these data are worth reporting because of the information and differences in prognosis related to AVSDs, and peri-membranous and muscular VSDs. There are many reports in the literature written separately according to AVSD and VSD (peri-membranous and muscular defects together) and related outcomes, but none of them compared these headings together.

The number of cases existing in our series requires to be expanded through larger studies to allow confirmation of the significance of the data from the smaller subclass categories. Despite the small numbers, our study has shown that the risk of aneuploidy is increasing especially in the presence of extracardiac pathologies.

Conflict of interest

None declared

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Awareness, knowledge and attitudes related to HPV infection and vaccine among non-obstetrician-gynecologist healthcare providers

Kadın hastalıkları ve doğum klinikleri dışında çalışan doktor ve yardımcı sağlık personelinin HPV enfeksiyonu ve aşısına yönelik farkındalık, bilgi düzeyi ve tutumları

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Abstract

Objective: This study was designed to evaluate the awareness, knowledge and attitudes of healthcare providers related to HPV infection and vaccine.

Material and Methods: A total of 311 healthcare providers working in specialties other than obstetrics and gynecology at the Dr. Lutfi Kırdar Kartal Education and Research Hospital as physicians (n=142) or non-physician healthcare providers (n=169) were included in the present study. A questionnaire developed by researchers based on literature and including items concerning socio-demographic features, awareness of HPV infection and vaccine, attitudes related to HPV vaccine and regular gynecological controls and knowledge about HPV infection was applied to participants via a face to face interview method. Each correct answer was scored as one to decide the level of knowledge and awareness.

Results: The frequency of parenthood was lower and the ratio of males was higher in the physician group compared to the non-physician group. Awareness of virus mediated cancer (p=0.01), human papilloma virus (p=0.0001), cervical cancer, HPV vaccine, and types of HPV vaccine was significantly higher in the physician group. While consent levels for vaccine administration for themselves were similar for physician and non-physician subjects, the frequency of subjects favoring vaccine administration for their offspring was significantly higher among physicians (p<0.001 for daughters, p<0.05 for sons). HPV-related level of knowledge in the physicians was significantly higher when compared to the non-physician staff (p<0.001).

Conclusion: Physicians were more competent regarding the relation of HPV infection to cervical cancer and more aware of the presence and types of HPV vaccines which may lead to a higher degree of willingness for vaccination when compared with non-physician healthcare providers. (J Turkish-German Gynecol Assoc 2010; 11: 16-21)

Key words: HPV; vaccine, awareness, knowledge level, attitude, healthcare providers

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Özet

Amaç: Bu çalışma sağlık çalışanlarının HPV enfeksiyonu ve aşısına yönelik farkındalık, bilgi düzeyi ve tutumlarının belirlenmesi amacıyla tasarlandı.

Gereç ve Yöntemler: Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi'nde obstetrik-jinekoloji dışındaki uzmanlık alanlarında görev yapmakta olan hekim (n=142) ve diğer sağlık personeli (n=169) olmak üzere toplam 311 sağlık çalışanı ile yürütülen bu çalışmada, araştırıcılar tarafından literatür ışığında geliştirilen bir anket formu kullanıldı. Sosyodemografik özellikler, HPV enfeksiyonu ve aşısına yönelik farkındalık ve bilgi düzeyi, HPV aşısı ve düzenli jinekolojik kontrollere yönelik tutumun incelendiği maddeler içeren bu anket formu yüzyüze görüşme yöntemi ile katılımcılara uygulandı. Her bir doğru yanıt 1 puan ile kodlanarak bilgi ve farkındalık düzeyi değerlendirildi.

Bulgular: Diğer sağlık personeli ile kıyaslandığında, hekimler arasında ebeveyn olanların sayısı daha az, erkeklerin sayısı ise daha yüksek bulundu. Virüs kaynaklı kanser (p=0.01), human papilloma virüsü (p=0.0001), servikal kanser, HPV aşısı ve tiplerine yönelik farkındalığın hekimler arasında diğer sağlık çalışanlarına göre belirgin şekilde daha yüksek olduğu belirlendi. Kendilerine aşı yaptırma konusundaki tutumları arasında hekimler ve diğer sağlık çalışanları arasında belirgin bir farklılığa rastlanmazken, çocuklarına aşı yaptırma konusunda olumlu düşünenlerin sayısı hekim grubunda diğer sağlık personeline göre anlamlı şekilde daha fazla bulundu (kız çocukları için p<0.001 ve erkek çocukları için p<0.05). Hekimlerin HPV ile ilgili bilgi düzeylerinin de diğer sağlık personeline göre belirgin şekilde daha yüksek olduğu belirlendi (p<0.001).

Sonuç: Hekimlerin HPV enfeksiyonu ile servikal kanser arasındaki bağlantı konusunda daha bilgili olmalarının yanısıra, HPV aşı ve tiplerinin varlığı konusunda da daha yüksek farkındalığa sahip olmalarının, aşılama konusunda diğer sağlık personeline göre daha gönüllü olmalarında rol oynayabileceği düşünülmektedir.

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Anahtar kelimeler: HPV, aşı, farkındalık, bilgi düzeyi, tutum, sağlık çalışanları

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Introduction

One of the most common sexually transmitted infections (STIs), human papilloma virus (HPV) infection has a prevalence rate of 30-50% among sexually experienced young women (1,2). Infection with oncogenic types of HPV has been held responsible for causing all cases of cervical cancer and precancerous intraepithelial lesions (3).

Being one of the most preventable cancers (4), cervical cancer is the ninth most common cancer among women in Turkey and ranks 13th among cancer-related deaths. According to the GLOBOCAN database, more than 50% of the 1364 patients diagnosed with cervical carcinoma each year die from the disease in Turkey (5). In line with a significant decline documented in the incidence of cervical malignancies in countries with widespread use of the Papanicolaou test (6), less developed national or local cervical screening programmes have been reported to be characterized by a higher disease burden in cervical cancer (7). In this context, the significant public health burden of HPV-related disease, lack of access to Papanicolau test in many localities as well as the inability to totally eliminate the risk of HPV transmission via use of condoms has led to an interest in the development of vaccines aiming to prevent the HPV infection (2, 8, 9).

Relevant to the administration of the HPV vaccine, physician knowledge about HPV was demonstrated to be a predictor of intention to vaccinate patients with a direct influence on the widespread implementation of the HPV vaccine (2, 8). Hence, since professional recommendation was considered to be crucial for willingness of a vaccination in the general population, it has been of interest to study HPV-related practice patterns, opinions, and knowledge among physicians who have been known to play a significant role in the widespread administration of the HPV vaccine (5, 10).

While health professionals are known to be convinced about the efficacy of vaccines recommended by public health authorities, published heterogeneity in the opinions regarding different vaccines and among different specialties of health providers was indicated to raise a concern about the success of immunization programs (11, 12).

Since the success of HPV vaccines, the primary prevention strategy in the prevention of cervical cancer (7), will depend largely upon whether providers believe and recommend immunization (12). To be familiar with the healthcare provider's intention to recommend and prescribe immunization (2) has been considered as the critical step to establish effective vaccine delivery programs. Therefore the present study was designed to evaluate this intention among healthcare providers of different specialties excluding obstetrics and gynecology in terms of awareness and attitudes towards HPV infection and vaccine.

Material and Methods

From a targeted population of 350 subjects, 311 healthcare providers (88.5%) working in different specialties other than obstetrics and gynecology at the Dr. Lutfi Kırdar Kartal Education and Research Hospital as physicians (n=142) or non-physician healthcare providers (n=169) were included in the present study. A questionnaire developed by researchers based on literature and including items concerning socio-demographic features (n=7), awareness of HPV infection and vaccine (n=8), attitudes related to HPV vaccine and regular gynecological controls (n=4) and knowledge about HPV infection (n=6) was applied to participants via a face to face interview method (2, 13, 14). Each correct answer was scored as 1 and the knowledge level was classified to be poor (0-2), moderate (3-4) and high (5-6) according to total score obtained by the subject.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki". The study was approved by the institutional ethics comittee.

Statistical analysis

Statistical analysis was made using software (version 13.0, SPSS Inc. Chicago, IL). The comparison between physician and non-physician groups in terms of demographic features, awareness and attitudes related to HPV infection and vaccine were made using Chi-square (χ^2) and Fisher's tests. Student's t test was used for the analysis of knowledge scores. Evaluation of primary differences between physicians and the major determinants of the knowledge scores was determined via regression analysis. Data were expressed as "mean±standard deviation (SD)" and percent (%) where appropriate. Probability value (p) <0.05 was considered statistically significant.

Results

Physician (n=142) and non-physician (n=169) groups were similar in terms of marital status and smoking habit. There were more males (p=0.0001) but fewer parents (p=0.0003) in the physician group (Table 1).

Awareness of virus mediated cancer (p=0.01), HPV (p=0.0001), cervical cancer (p=0.006), HPV vaccine (p=0.0001), and types of HPV vaccine (p=0.0001) was more significant in the physician group. While consent levels for vaccine administration for themselves were similar for physician and non-physician subjects, the percentage of subjects who consent to vaccine administration for their children (p=0.0001 for daughters and p=0.02 for sons) were significantly higher among physicians (Table 1).

Identification of medical publications as the main information source for awareness of HPV vaccine was more significant for physicians (68.3 vs. 28.4; p=0.000; Table 1).

While both physicians and non-physician providers were found to have scores indicating a moderate level of knowledge about HPV infection, the scores of physicians were significantly higher than non-physician persons (4.88±0.77 vs 4.07±0.73; p=0.0001). Correct answers concerning symptomatic nature of HPV, healing process of the disease and the value of smear

Table 1. Demographic features and awareness of HPV infection and vaccine among subjects in the physician and non-physician groups

	Occupational status						p value
	Physician (n=142)		Non-physician (n=169)		Total (n=311)		
Demographics	**n**	**%**	**n**	**%**	**n**	**%**	
Gender							
Female	53	37.3	156	92.3	209	67.2	<0.0001
Male	89	62.7	13	7.7	102	32.8	
Marital status							
Single	51	35.9	48	28.6	99	31.9	0.34
Married	83	58.5	107	63.7	190	61.3	
Other	8	5.6	13	7.7	21	6.8	
Having a child	61	19.6	106	34.0	167	53.7	0.0003
Active smoking	48	34.0	57	33.9	105	34.0	0.98
Awareness							
Sexually transmitted diseases	142	100.0	167	98.8	309	99.4	0.50
Virus mediated cancer	140	99.3	157	94.0	297	96.4	0.01
Human papilloma virus	138	97.2	136	81.0	274	88.4	0.0001
Cervical cancer	134	95.0	141	85.5	275	89.9	0.006
Early diagnosis of cervical cancer	141	100.0	162	98.8	303	99.3	0.50
Prevention of cervical cancer	140	99.3	156	97.5	296	98.3	0.37
HPV vaccine	126	90.0	107	64.8	233	76.4	0.0001
Types of HPV vaccine	113	86.3	64	43.2	177	63.4	0.0001
Favor HPV vaccine for							
Her/himself	69	52.7	90	57.0	159	55.0	0.46
Her/his daughter	113	84.3	101	66.0	214	74.6	0.0001
Her/his son	75	56.8	60	43.2	135	49.8	0.02
Information source for HPV vaccine							
Medical publications	97	68.3	48	28.4	145	46.6	
Physician	7	4.9	23	13.6	30	9.6	<0.001
Friends and family	9	6.3	11	6.5	20	6.4	
Internet	7	4.9	10	5.9	17	5.5	
Media	3	2.1	26	15.4	19	6.1	
Regular gynecological controls once							
6 months	1	1.9	17	11.4	18	5.8	0.72
a year	14	26.9	30	20.1	44	14.1	
> a year	4	7.7	18	12.1	22	7.1	
Having complaints	33	63.5	84	56.4	117	37.5	

test accounted for the higher scores obtained on the test by the physician group (Table 2).

Insufficient knowledge was the main barrier identified by non-physicians against HPV vaccination. While side effects were mentioned more frequently by non-physicians for vaccination consent for themselves and their sons, parental anxiety for the side effects of the vaccine were similar for the consent for daughters (Table 3).

Regression analysis concerning comparison of physician and non-physician group revealed that the primary difference

Table 2. Knowledge about HPV infection among physicians and non-physician healthcare providers

Knowledge about HPV infection	Occupational status						p value
	Physician (n=142)		Non-physician (n=169)		Total (n=311)		
	n						
Patient with HPV is usually symptomatic	104	74.8	38	26.0	142	49.8	<0.001
HPV infection risk increases with the number of sexual partners	138	97.9	157	98.1	295	98.0	0.99
Most types of HPV do not heal spontaneously	33	23.9	11	7.0	44	14.9	<0.001
Certain types of HPV may cause cervical cancer	141	100.0	153	99.4	294	99.7	0.99
HPV may cause genital warts	137	97.2	146	93.0	283	95.0	0.10
Abnormality in smear test may indicate HPV	132	94.3	124	85.5	256	89.8	0.01
Total Score (mean±SD)	4.88±0.77		4.07±0.73		4.49±0.85		<0.001

Table 3. Barriers against willingness to receive HPV vaccination among physicians and non-physician healthcare providers

	No consent for HPV vaccine						p value
	Physician		Non-physician		Total		
Barriers to vaccination for him/herself	n	%	n	%	n	%	
Insufficient knowledge	17	28.3	32	47.8	49	38.6	0.019
Side effects	6	10.0	12	17.9	18	14.2	
Cost	5	8.3	2	3.0	7	5.5	
Other	32	53.3	20	29.9	52	40.9	
Total	60	100.0	67	100.0	127	100.0	
Barriers to vaccination for his/her daughter							
Insufficient knowledge	11	50.0	34	63.0	45	59.2	0.180
Side effects	5	22.7	13	24.1	18	23.7	
Cost	0	0.0	2	3.7	2	2.6	
Other	5	22.7	5	9.3	10	13.2	
Total	22	100.0	54	100.0	76	100.0	
Barriers to vaccination for his/her son							
Insufficient knowledge	29	50.0	52	65.0	81	58.7	0.028
Side effects	5	8.6	13	16.3	18	13.0	
Cost	3	5.2	3	3.8	6	4.3	
Other	21	36.2	12	15.0	33	23.9	
Total	58	100.0	80	100.0	138	100.0	

between two groups was the variable questioning symptomatic nature of HPV related disease and the main determinant of the obtained score was the occupation of the subject.

Discussion

Published reports on HPV vaccination signified that intention to immunize was associated with the characteristics of the provider, knowledge about HPV and attitudes towards HPV vaccination (2). In the present study, we evaluated the awareness and attitudes towards HPV infection and vaccine among healthcare providers from a variety of specialties other than obstetrics and gynecology in Istanbul, Turkey.

Owing to the advantages of physicians to address and manipulate perceived barriers against HPV vaccine, physician recommendation has been considered a key ingredient of successful HPV vaccination programs (15).

Compatible with the recent data (8), healthcare providers composed of physicians and non-physicians in our study were aware of HPV infection and vaccine but awareness of HPV vaccination was more significant in the physician population just like knowledge about HPV infection. Concerning knowledge

level, correct answers concerning symptomatic nature of HPV, healing process of the disease and the value of smear test accounted for the higher scores obtained by the physician group. Accounting for their significant role in vaccine recommendation, awareness of HPV infection and vaccination in our population were much higher than documented in general populations published in recent cross sectional studies (13, 16, 17). Anyhow, insufficient public knowledge regarding HPV; parental intention regarding vaccination, cost, and the multiple dosages required for administration are the main barriers to the widespread use of the HPV vaccine include (8).

Being much more significant for the physicians, healthcare providers in our study were determined to be enthusiastic about vaccination of their daughters rather than sons. Refusal of HPV vaccine was reported to range from 15 to 20% among patients mostly due to cost of the vaccine which was also confirmed by a third of physicians as a commonly stated barrier to patient acceptance of the HPV vaccine (12, 15, 18). However, insufficient knowledge about the vaccine and side effects to some extent especially in the non-physician group were the main barriers identified in the present study rather than the cost of action.

The present study revealed a high (84.3%) level of acceptance of the HPV vaccine among physicians which is higher than the acceptability rates documented previously for health professionals in general as 79.7% and specific to gynecologists as 79% (3, 9, 19). In agreement with the data concerning nurses' lower level of conviction about the usefulness of vaccines when compared to other health providers (11), the frequency of healthcare providers other than physicians favoring HPV vaccine was lower than physicians in our study as well as nurses reported elsewhere in the literature (9).

In accordance with previous multivariable analyses confirming provider and practice characteristics, knowledge about HPV, and attitudes were independently associated with intention to recommend HPV vaccination and showing an association between knowledge and the intention to recommend a vaccine (2), awareness of, knowledge about and the attitude towards HPV infection and vaccine were better for physicians when compared to non-physicians. Indeed, the similar discrimination has also been shown among physicians with different specialties so that physicians who focus on women's health issues or work were suggested to have a better approach for the disease including potential health benefits of an HPV vaccine (2).

In this regard, since the knowledge about HPV disease and its prevention varies across specialties with superiority of obstetrician/gynecologists (3), moderate level of knowledge about HPV infection and vaccine among our healthcare providers composed of non-obstetrician physicians and non-physician healthcare providers seems proper.

Concerning the general population, it was documented that those who believed that HPV is an STD were three times more likely to support state-mandated vaccination, but no relation of knowledge to vaccination consent was obtained among who believed HPV causes cervical cancer (13). In our population, physicians were more likely to support HPV vaccination for their children despite similar awareness of HPV as a STD and superiority of cervical cancer awareness when compared to non-physician participant. The main barrier against vaccination was identified to be insufficient level of knowledge in overall population with higher percentages in non-physician subjects. Therefore, based on significantly higher rates of vaccine related awareness among our physicians, consent of vaccine seems to be dependent on vaccine related issues rather than the long term effects of the HPV infection at least among our population composed of healthcare providers. Indicating the value of educational intervention barriers against vaccination was shown to be handled via provision of information to people who were against vaccination (14, 20).

While parental intention to vaccinate was higher among physicians regardless of the gender of child, most of our subjects favored the vaccination for girls with much lower consent rates for boys in agreement with other papers (2, 9). In a recent study (21) concerning attitudes of nurse practitioners, lack of preference for vaccination of female adolescents among nurse practitioners was interpreted as the likelihood of their attitudes to differ from physicians who were more willing to vaccinate girls than boys due to the fact that cervical cancer affects women only and thus will have a greater impact on women's health. In fact considering past studies suggesting that vaccinating men and women will be more effective in reducing HPV prevalence than vaccinating women only gender related prepossession among healthcare providers was suggested to be reconsidered (2).

Compatible with the previously shown association between HPV awareness, knowledge and formal education (22) noting educational status as independent predictor of HPV knowledge and awareness (13), occupation was identified to be the major determinant of knowledge level related to HPV infection and vaccine in our present study.

Unfortunately compatible with moderate level of knowledge about HPV in our study, overall ignorance of HPV has been reported to be common even in 'educated' populations especially when compared with other STIs (22). Nevertheless, it must be remembered that recognition of a term does not necessarily imply an ability to understand its implications or to be able to summon it without prompt in the correct context (22).

Accounting for higher awareness of HPV vaccine among physicians leading to higher willingness of vaccination among them as parents, information source for awareness of HPV vaccination was identified to be medical publications among physicians but media by non-physicians. Likewise, physicians were reported to look at their professional organizations for information about vaccination in a past study, so communication strategies should target professional organizations and journals to provide information about the safety and efficacy of vaccines and giving general recommendations for HPV immunization (23).

One of the limitations of our study was using of a simple short item evaluation of knowledge level with the possibility of lower sensitivity. A second limitation was that the evaluation of intention to HPV vaccination among healthcare providers in

relation to themselves and their children as parents rather than the actual prescription of the vaccine for the patients. Finally, because of the small sample and the qualitative nature of the study, the findings may not be representative of the views of all healthcare providers in Turkey.

In conclusion, compatible with the identification of the occupation as the major determinant of knowledge level related to HPV infection and vaccine, physicians in our study were more competent about the relation of HPV infection to cervical cancer and the presence and types of HPV vaccination which may lead to significantly higher willingness of vaccination among them compared with non-physician healthcare providers. Larger scale studies concerning provider attitudes, intentions and barriers concerning HPV vaccine and increase in medical awareness programs and publications for healthcare providers addressing full information on vaccine properties and benefits may contribute in enhancing vaccination coverage and the design of effective STI vaccine delivery programs for physicians as well as other providers who care for children and adolescents.

Conflict of interest

The authors declare that they have no conflict of interest.

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Risk of malignancy index is not sensitive in detecting non-epithelial ovarian cancer and borderline ovarian tumor

Malignite risk endeksi borderline ve epitelyal olmayan over tümörlerinin tanısında duyarlı değildir

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Abstract

Objective: To determine the value of risk of malignancy index in detection of ovarian cancer and referral of adnexal masses.

Material and Method: Patients scheduled for surgery due to adnexal mass between May 2008 and August 2009 were prospectively included in the study. Risk of malignancy index (RMI) was calculated for each patient with a published formula (RMI=Ultrasonic score X menopausal status X Ca-125 (IU/ml) level). RMI >200 was accepted as positive for malignancy and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of RMI in detecting malignant cases were calculated.

Results: One hundred consecutive patients of whom 80 (80%) had benign ovarian cyst, 4 (4%) had borderline lesion and 16 (16%) had invasive ovarian cancer were included in the study. Forty-five percent (9/20) of malignant cases were epithelial ovarian cancer, 20% (4/20) were borderline ovarian tumor, 30% (6/20) were non-epithelial ovarian tumor and 5% (1/20) was a metastasis from the appendix. All the cases with epithelial ovarian cancer had positive RMI but only 1 of 4 borderline lesions, 2 of 6 non-epithelial ovarian cancers had positive RMI. The sensitivity of RMI was 60%, specificity was 88.8%, PPV was 57.1% and NPV was 89.9% for all cases. When the cancer cases other than epithelial ovarian cancers were excluded, the sensitivity, specificity, PPV and NPV of RMI was 76.92%, 88.75%, 52.63% and 95.95% respectively.

Conclusions: RMI is not adequate in detecting malignant cases in a population with high non-epithelial ovarian cancer and borderline ovarian tumor prevalence.

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Key words: Risk of malignancy index, Malignant, Benign, Ovarian cancer, Ultrasonography

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Özet

Amaç: Adneksiyal kitlelerin değerlendirilmesinde ve over kanserini tanımada malignite risk endeksinin değerini araştırmak.

Materyal ve Metod: Mayıs 2008 ve Ağustos 2009 tarihleri arasında adneksiyal kitle nedeniyle cerrahi uygulanması planlanan hastalar prospektif olarak çalışmaya dahil edildi. Malignite risk endeksi (MRE) daha önce yayınlanmış olan formül ile hesaplandı (MRE= ultrason puanı x menapozal durum x Ca-125 (IU/mL) seviyesi). MRE>200 olduğunda malignite pozitif olarak kabul edildi bu kestirim değerinin malign olguları saptamada ki duyarlılığı, özgüllüğü, pozitif öngörme değeri ve negatif öngörme değeri hesaplandı.

Bulgular: Çalışmaya alınan 100 hastanın 80 tanesinde (%80) benign over kisti saptanırken, 4 tanesinde (%4) borderline over kanseri ve 16 tanesinde de (%16) invaziv over kanseri saptandı. Malign hastaların %45'i epitelyal over kanseri iken, %20'si (4/20) borderline, %30'u (6/20) epitelyal olmayan over kanseri ve %5'i de (1/20) appendiksten metastazdı. Tüm epitelyal over kanseri olgularının MRE pozitif iken borderline olguların dörtte birinin ve epitelyal olmayan over kanserli olguların altıda ikisinin MRE'si pozitifti. MRE' nin tüm adneksiyal kitleler içinde over kanserini saptamadaki duyarlılığı %60, özgüllüğü %88.8, pozitif öngörme değeri %57.1 ve negatif öngörme değeri %89.9 idi. Epitelyal olmayan over kanserleri dışlandığında MRE'nin over kanserlerini tanımadaki duyarlılığı, özgüllüğü, negatif ve pozitif öngörme değerleri sırasıyla %76.9, %88.7, %52.6 ve %95.9 idi.

Sonuç: Epitelyal olmayan kanser ve borderline over kanseri olgularının sıklığının yüksek olduğu bir toplulukta MRE, malign olguları tanımada yeterli değildir. (J Turkish-German Gynecol Assoc 2010; 11: 22-6)

Anahtar kelimeler: Malignite risk endeksi, malign, benign, over kanseri, ultrasonografi

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Introduction

Ovarian cysts are a common reason for admission to hospital (1). Due to the routine use of transvaginal ultrasonography as a part of gynecological examinations; even asymptomatic ovarian cysts in patients admitted for other complaints have been detected incidentally, increasing the incidence of ovarian cysts. However, differentiation of ovarian carcinomas from benign ovarian tumors is the major diagnostic problem. Preoperatively, the knowledge of the malignant nature of the adnexal mass would enable the optimum timing and conditions for the surgical treatment.

Malignant ovarian tumors, unlike other gynecologic cancers, are mostly asymptomatic and are diagnosed at advanced stages (2). These patients undergo extensive surgical debulking followed by combination chemotherapy and have high mortality rates. Appropriate primary surgery may greatly improve the prognosis of these patients (3-4). Therefore, the surgical intervention of malignant ovarian tumors should be done by gynecologic oncology surgeons who have special skill and experience.

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It is not practical for oncology surgeons to treat all adnexal masses to favor the prognosis, in case the mass is malignant. instead some referral criteria should be created to differentiate malignants from benigns. Individual diagnostic tools used to differentiate malignant cases are not adequate. The ultrasonographic findings such as multilocularity, presence of solid parts and irregularity of the cyst wall have been regarded in favor of malignancy (5). However, 1.6 to 9.6% and 0.73% of unilocular simple cysts were found to be malignant in postmenopausal and premenopausal women, respectively (6-7). Serum level of Ca-125 is a well recognized marker of epithelial ovarian cancer and it increases in >80% of epithelial ovarian cancer. However it increases in only 50% of stage I ovarian cancer and it can also increase in benign conditions like endometriosis, fibroma, pregnancy, menstruation, pelvic inflammatory disease, peritonitis and liver cirrhosis. Assesment of vasculature of the adnexal masses with Doppler ultrasonography was also investigated. Presence of central vessels and low vascular resistance was found to be in favor of malignancy (8). However, use of Doppler ultrasonography in the preoperative evaluation of the adnexal masses had a low sensitivity in detecting malignant ovarian tumors (9). Also, when combined to the gray scale morphologic evaluation, it did not increase the number of correct diagnosis (10, 11).

For the accurate preoperative diagnosis of ovarian cancers, Jacobs et al. (12) originally developed the risk of malignancy index (RMI) in 1990. They calculated the RMI based on menopausal status, ultrasonographic morphology of the adnexal mass and serum level of Ca-125. The sensitivity and specificity of RMI was found as 85% and 97%, respectively. They also found RMI to be more sensitive and specific from individual parameters used in calculation **o**f it, in detecting malignant cases. With this study we aimed to evaluate the value of RMI in the preoperative evaluation and referral of women with adnexal mass for optimal treatment.

Materials and Methods

The institutional ethical committee approved this study. We prospectively included the patients who were scheduled for surgery with the diagnosis of adnexal mass after they signed the written consent form, between May 2008 and August 2009. Age, parity, medical history, pelvic and physical examination findings were noted for all patients. Venous blood samples were taken from each patient and centrifuged in 4000 rpm for 3 minutes. The serum was taken to determine Ca-125 level. Ca-125 level was determined by using electrochemiluminescence technique (Immulite 2000 DPC®, Siemens, Los Angeles, CA, USA with Immunolyte 2000 kit, Medical Solutions Diagnostic, Los Angeles, CA, USA). Preoperatively, menopausal score (M), ultrasonographic score (U) and RMI were calculated for each patient, according to Tingulstad et al. (13).

Patients who had amenorrhea for at least 1 year and hysterectomized patients aged 50 years or older were accepted as menopausal. Premenopausal cases got 1 and postmenopausal cases got 3 points as menopausal score (13).

Sonographic examination was undertaken by the same physician, who is the first author (O.M.). Five-10 Mhz trans-vaginal and trans-abdominal probes (PVT-375AT, Toshiba Xario®, Toshiba Medical Systems, Tokyo, Japan) were used for evaluation. Ultrasonographic scoring system evaluating multilocularity, bilateralism, presence of solid area, findings supporting intra-abdominal metastasis and presence of ascites was used (13). Each criterion got 1 point if present or got 0 point if not present. The scores of each criterion were added to find out the total score. U was determined as 3 if the total score was ≥ 2 or as 1 if the total score was ≤ 1 (13).

RMI was calculated as: RMI = (M)x(U)x(Ca-125 IU/ml). Cut off value for RMI was taken as 200 which was originally used by Jacobs et al (12) and later confirmed by others as the optimal cut off point (14-15).

Intra-operative findings were noted for all patients. Surgical specimens were evaluated with frozen section intra-operatively. Because 20-25% of borderline ovarian tumors have the final diagnosis of malignant ovarian tumor after the evaluation of paraffin embedded sections (16), cases that had borderline and malign ovarian tumor diagnosis in frozen sections underwent comprehensive surgical staging. Surgical procedure of all the borderline and malignant ovarian tumors was accomplished by a specialized gynecologic oncology surgeon, who is the third author (M.M.M). Histopathologic examination of the specimens was then carried out in paraffin embedded sections and the diagnosis was accepted as the final histopathology diagnosis. All the findings were evaluated in respect of the final histopathology diagnosis.

Statistical analysis

Statistical Packages for Social Sciences (SPSS) 13.0 for Windows and Medcalc version 7.4.4.1 for Windows were used for statistical analysis. Measurable variables were given as mean±standard deviation (SD) and un-measurable variables were given as number and percentage (%). RMI and final histopathology diagnosis were compared with chi-square test. Menopausal scores and ultrasonographic morphological findings were compared with Pearson chi-square and Fisher's Exact chi-square tests. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of RMI and U was determined. Sensitivity was calculated as the ratio of true positives to true positives + false negatives, specificity was calculated as the ratio of true negatives to true negatives + false positives, PPV was calculated as the ratio of true positives to true positives + false positives and NPV was calculated as the ratio of true negatives to true negatives + false negatives. The level of significance was set at $P<0.05$.

Results

Between May 2008 and August 2009, a total number of 100 consecutive patients were included in the study. Final histopathologic diagnosis was benign in 80 cases (80%), borderline in 4 cases (4%) and malignant in 16 cases (16%). The mean ages of cases were 40.2±14 years (range 16-79) and

46.7±15.8 years (range 16-77) in benign and malignant groups respectively (p=0.073).

Cases with benign adnexal mass had the diagnosis of endometrioma most frequently (n=24, 30%). The second most frequent diagnosis was mature teratoma (n=15, 18.5%). Histopathologic diagnosis of benign cases is given in Table 1.

Borderline ovarian tumors (BOT) accounted for 20% (4/20) of malignant ovarian tumors.

Among malignant tumors, epithelia originated tumors were the most frequent (13/20, 65% including the BOT). Germ cell tumors (3/20, 15%) and sex cord stromal tumors (3/20, 15%) were the second most frequently diagnosed tumors. In one case (1/20, 5%) a metastatic ovarian tumor which originated primarily from appendix was diagnosed. Characteristics of malignant cases are given in Table 2.

Seventy five percent of the cases were premenopausal (75/100), whereas 25% (25/100) were postmenopausal. Eighty-eight percent of premenopausal cases (66/75) were diagnosed with benign adnexal mass, whereas 12% (9/75) was diagnosed with malignant adnexal mass. For postmenopausal cases, 40% (10/25) was diagnosed with benign adnexal mass and 60% was diagnosed with malignant adnexal mass. Malignant cases were significantly more frequent in postmenopausal cases (p<0.001).

Among the morphologic criteria used for sonographic scoring, the presence of solid area (17/20, 89.4% vs 35/80, 43,2%; p<0.001), ascites (7/20, 36.8% vs 1/80, 1.2%; p<0.001), findings supporting intraabdominal metastasis (6/20, 31.57% vs 1/80, 1.2%; p<0.001) were found significantly more frequently in malignant cases compared to benign cases. However, sonografically, the rate of multilocularity (9/20, 47.3% vs 27/80, 33.3%; p=0.3485) and bilaterality (2/20, 10% vs 10/80, 12.3%; p=1) were found to be similar in malignant and benign cases, respectively (Table 3).

Sonographically, out of 100 cases 22 cases had a simple adnexal mass (total score=0, U=1), 51 cases had a semicomplex

Table 1. Histopathology diagnosis of benign adnexal masses

Histopathology diagnosis	N (%)
Endometrioma	24 (30%)
Mature teratoma	15 (18.75%)
Serous cystadenoma	13 (16.25%)
Corpus luteum/corpus hemorrhagicum/ follicular cyst	12 (15%)
Paratubal cyst	6 (7.50%)
Mucinous cystadenoma	5 (6.25%)
Tubo-ovarian abcess	4 (5%)
Fibroadenoma	1 (1.25%)
Total	80 (100%)

Table 2. Characteristics of cases with malignant adnexal tumors

Patient No:	Age	U	CA-125(IU/ml)	M	RMI	Histopathology Diagnosis
1	55	3	52,6	3	473	Serous Cyst Adenocarcinoma
2	60	3	49,7	3	447,3	Serous Cyst Adenocarcinoma
3	39	3	500	1	1500	Serous Cyst Adenocarcinoma
4	68	3	50,1	3	450,9	Serous Cyst Adenocarcinoma
5	48	3	43,3	3	389,7	Serous Cyst Adenocarcinoma
6	55	3	347	3	3123	Serous Cyst Adenocarcinoma
7	43	3	179	1	537	Serous Cyst Adenocarcinoma
8	50	3	500	1	1500	Serous Cyst Adenocarcinoma
9	38	1	17,1	1	17,1	Granulosa Cell Tumor
10	52	1	5,8	3	17,4	Granulosa Cell Tumor
11	77	3	23,1	3	207,9	Granulosa Cell Tumor
12	62	3	255	3	2295	Clear Cell Adenocarcinoma
13	17	3	77,3	1	695,7	İmmature Teratoma
14	16	3	46,5	1	139,5	Endodermal Sinus Tumor
15	51	3	19	3	171	Carsinoid Tumor
16	36	3	26	1	78	Metastasis from Appendix
17	28	3	77,9	1	233,7	Serous Borderline Tumor
18	44	1	7,6	1	7,6	Serous Borderline Tumor
19	34	1	37	1	37	Serous Borderline Tumor
20	60	1	30	3	90	Serous Borderline Tumor

adnexal mass (total score = 1, U = 1) and 27cases had a complex adnexal mass (total score = 2-5, U = 3). Malignant adnexal mass was diagnosed in 10.1%, 5.9% and 51.8% and benign adnexal mass was diagnosed in 90.9%, 94.1% and 48.1% of simple, semicomplex and complex adnexal masses respectively. Sensitivity, specificity, PPV and NPV of finding a complex adnexal mass sonographically in the detection of malignant cases was 75%, 83.75%, 53.57% and 93.06%, respectively.

When sonographic findings were combined with the menopausal status and Ca-125 value (RMI), sensitivity, specificity, PPV and NPV in the detection of malignant cases were found as 60%, 88.8%, 57.1% and 89.9% respectively, when the cut off value of RMI was set as 200. (Table 4)

When epithelial ovarian tumors only were taken into consideration (8 serous cystadenocarcinoma, 1 clear cell carcinoma and 4 serous borderline tumor) sensitivity, specificity, PPV and NPV of RMI score in detecting malignant cases were found as 76.92%, 88.75%, 52.63% and 95.95% respectively, with the cut off value of 200 (Table 5).

Discussion

In the current study, the overall prevalence of malignancy was 20%, including the borderline ovarian tumors (60% and 12% in post and premenopausal patients, respectively), reflecting the unselected nature of the study population. However, although the non-epithelial ovarian cancer constitutes 10% of ovarian cancers in the general population, its prevalence is 30% in our study population.

We found RMI to be successful in identifying the benign cases (specificity = 88.8%). This finding was in accordance with the findings of other studies (specificity ranged between 77 to 97%) (12-15, 17-19). However, apart from other studies we found the sensitivity of RMI as 60% which was similar to the findings of Tanriverdi et al (20). RMI was positive in all invasive epithelial ovarian cancers, however it was positive in only 1 out of 3 germ cell tumors, 1 out of 3 endodermal sinus tumors and 1 out of 4 borderline ovarian tumors. Others also found RMI negative in most of non-epithelial ovarian cancers and borderline ovarian tumors (19). Therefore the low sensitivity of RMI for our population can be attributed to the high prevalence of non-epithelial ovarian cancers and borderline ovarian tumors. When we excluded the non-epithelial ovarian cancers, the sensitivity of RMI increased to 76.92%, which is in accordance with the other studies (sensitivity ranged between 70.6 to 90%) (12-15, 17-19, 21).

We found the PPV of RMI as 57.1%. However, others found the PPV between 66.1 and 96% (14, 15, 17-19, 21). In our study population, endometrioma was the most common diagnosis among benign adnexal masses comprising 30% (24/80). Fifteen out of 24 endometrioma cases (62.5%) had a Ca-125 level more than 30 IU/ml and 25% of cases (6/24) had a false positive RMI. Yamamoto et al (22) also found the PPV of RMI as 52.5% in a population in which 40% of benign adnexal masses was diagnosed with endometrioma and 20% of endometrioma cases had false positive RMI.

RMI, after originally being developed by Jacobs et al (12) and modified as RMI-2 (17) and RMI-3 (13) by Tingulstat et al, has been tested in prospective and retrospective studies (14, 15, 18, 19). Studies found the sensitivity of RMI as 70.6 to 90% and the specificity as 77 to 97%. It is found to be more sensitive and specific from individual parameters used in calculation of RMI in detecting malignant cases. With these findings, RMI is currently being used as a referral criterion of adnexal masses to oncology centers by some gynecology units (19, 21). However we found it inadequate in detecting ovarian cancers in a population which has a high prevalence of non-epithelial ovarian cancer and borderline ovarian tumors.

Table 3. Frequency of morphologic findings in malignant and benign adnexal masses

	Malignant	Benign	p
Solid Area	89.4%	43.2%	< 0.001
Ascites	36.8%	1.2%	< 0.001
Findings supporting intraabdominal metastasis	31.57%	1.2%	< 0.001
Multilocularity	47.3%	33.3%	0.3485
Bilaterality	10%	12.3%	1

Table 4. RMI scores according to the final histopathology diagnosis

RMI Score	Final Histopathology Diagnosis		Total
	Benign	Malignant	
< 200	71	8	79
> = 200	9	12	21
Total	80	20	100

Table 5. RMI scores when malignant tumors other than epithelial ovarian tumors were excluded

RMI Score	Final Histopathology Diagnosis		Total
	Benign	Malignant	
< 200	71	3	74
> = 200	9	10	19
Total	80	13	94

Conclusion

Although RMI has high sensitivity in detecting epithelial ovarian cancers, it is not adequate in detecting non-epithelial ovarian cancers and borderline ovarian tumors.

Conflict of interest
None declared

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Experience in stage IB2 cervical cancer and review of treatment

Serviks evre IB2 kanserinde tecrübe ve literatürün gözden geçirilmesi

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Abstract

Objective: The aim of the study is to evaluate and compare the efficacy of neoadjuvant chemotherapy (NACT), radical hysterectomy (RH) and radiotherapy (RT) in the treatment of stage IB2 cervical cancer.

Material and Methods: Medical records of 86 patients with stage IB2 cervical cancer between 1993 and 2006 were evaluated. Patients who underwent type III RH ± bilateral salphingo-oophorectomy and para-aortic and pelvic lymphadenectomy constituted the RH group (n=18). Patients who received radiotherapy constituted the RT group (n=20). Patients who underwent any of the combination chemotherapies (cisplatin/5-fluorouracyl, cisplatin/UFT® or paclitaxel/carboplatin) followed by RH or RT constituted the NACT group (n=36).

Results: Seventy-four patients were included in the study. The median follow-up was 48.5 months and the mean tumor size was 51.4mm. The groups were similar in terms of follow-up duration and tumor size. However, the mean age of the patients was higher in the RT group and nonsquamous type cervical cancer was more frequent in the RH group. Disease free survival (DFS) and overall survival (OS) were 75.7%. DFS rate was 65% in the RT group, 77.8% in the RH group and 80.6% in the NACT group. OS rates were 65%, 77.8% and 83.3% respectively. The groups were similar in terms of DFS and OS rates.

Conclusion: In our study, none of the treatment modalities were shown to be superior in terms of efficacy. There is need for additional prospective studies comparing multimodal treatment regimens in stage IB2 cervical cancer.

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Key words: Cervical cancer, neoadjuvant chemotherapy, radical hysterectomy, radiotherapy

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Özet

Amaç: Bu çalışmada ever IB2 serviks kanserinde neoadjuvant kemoterapi (NAKT), radikal histerektomi (RH) ve radyoterapinin (RT) tadavi başarısının karşılaştırılması amaçlandı.

Gereç ve Yöntemler: 1993-2006 yılları arasında ever IB2 servikal kanser tanısı olan 86 hastanın tıbbi kayıtları değerlendirildi. RH ± bilateral salpingo-ooforektomi + para-aortik ve pelvik lenfadenektomi yapılan hastalar RH grubunu (n=18), radyoterapiyle tedavi edilen hastalar RT grubunu (n=20) ve kemoterapi kombinasyonlarından (cisplatin/5-fluorourasil, cisplatin/UFT® or paklitaksel/carboplatin) herhangi birini alan ve takiben RH veya RT uygulanan hastalar NAKT grubunu oluşturdu (n=36).

Bulgular: Çalışmaya 74 hasta alındı. Ortanca takip süresi 48.5 ay ve ortalama tümor boyutu 51.4mm'ydi. Gruplar takip süreleri ve tümör boyutu açısından benzerdi. Ancak hastaların ortalama yaşı RT grubunda daha yüksekti ve nonskuamöz tip kanser RH grubunda daha sıktı. Tüm grupta hastalıksız yaşam süresi (HYS) ve tüm yaşam süresi (TYS) %75.7'ydi. HYS RT grubunda %65, RH grubunda %77.8 ve NACT grubunda %80.6'ydı. TYS sırasıyla %65, %77.8 ve %83.3'dü. Gruplar HYS ve TS açısından benzerdi.

Sonuçlar: Bu çalışmada etkinlik açısından tedavi modalitelerinden herhangi birinin diğerine üstün olmadığı görüldü. Evre IB2 serviks kanserinde multimodal tedavi rejimlerinin karşılaştırıldığı prospektif çalışmalara ihtiyaç vardır.

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Anahtar kelimeler: Servikal kanser, neoadjuvant kemoterapi, radikal histerektomi, radyoterapi

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Introduction

There is an ongoing uncertainty about the treatment of early stage cervical cancer. The efficacy of radical hysterectomy and radiotherapy with a 5-year overall survival for stages IB-IIA, estimated to be around 90% in both, are comparable (1, 2). Surgery, the preferred mode of treatment, preserves ovarian function, has fewer adverse effects and allows establishment of radiotherapy as a treatment choice in case of recurrence. However, Landoni et al. showed that 84% of patients with early stage disease who underwent radical surgery also received adjuvant radiotherapy (3).

Chemotherapy given together with radiotherapy (concurrent chemoradiotherapy, [CCRT]) increases the efficacy of radiotherapy. It has been observed that CCRT is associated with an increase in treatment response and improvement in survival rates (4-7). Decrease in distant metastasis rates as well as achievement of local control made neoadjuvant chemotherapy (NACT) more popular. Theoretically, the aim of neoadjuvant chemotherapy is reduction of tumor volume,

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elimination of micrometastases and accomplishing optimal tumor size for surgery. Radical hysterectomy or radiotherapy may be applied after chemotherapy to improve survival rates in locally advanced cervical cancer. However, some studies have shown that radiotherapy administered after neoadjuvant chemotherapy did not improve survival rates (8-10), and even displayed a negative effect (11, 12). This effect has been explained by the cross-resistance between chemotherapy and radiotherapy as well as the intracellular changes caused by chemotherapy itself (13). In contrast, these problems do not appear with radical hysterectomy in addition to achievement of excision of focal residual tumor. Hence neoadjuvant chemotherapy followed by radical hysterectomy is expected to improve survival rates. In a meta-analysis of 21 phase III studies, it has been shown that neoadjuvant chemotherapy followed by radical hysterectomy reduced disease specific death rates by 35% and increased survival rates by 14% when compared with radiotherapy only (14). However, in a study by the Gynecologic Oncology Group (GOG) where neoadjuvant chemotherapy followed by radical hysterectomy was compared with radical hysterectomy only, no improvement in surgical-pathologic risk factors or survival rates has been observed (15).

The choice of initial treatment in early stage bulky tumor is not certain. The aim of this study is to evaluate and compare the efficacy of different treatment modalities in stage IB2 cervical cancer.

Material and Methods

Medical records of 86 patients diagnosed with stage IB2 cervical cancer and treated between 1993 and 2006 were evaluated retrospectively. All patients were assessed by pelvic and rectovaginal examination under general anesthesia, computerized tomography of upper abdomen, pelvic magnetic resonance imaging or intravenous pyelography. Measurement of the tumor size was the product of the two greatest tumor diameters. Patients staged clinically according to the FIGO 1988 criteria were treated with radical hysterectomy, radiotherapy or neoadjuvant chemotherapy as the initial treatment. According to the treatment modality, patients were classified into three groups; RH group (radical hysterectomy), RT group (radiotherapy) and NACT group (neoadjuvant chemotherapy).

Patients who underwent type III radical hysterectomy ± bilateral salphingo-oophorectomy and para-aortic and bilateral pelvic lymphadenectomy constituted the RH group. Para-aortic lymphadenectomy was performed up to the level of the inferior mesenteric artery. High-risk patients received postoperative radiotherapy. Until year 2001, criteria for postoperative adjuvant radiotherapy were presence of at least one major factor (positive lymph node, parametrial involvement, presence of tumor within surgical border and tumor size ≥4cm) or two minor factors (lymphovascular space involvement [LVSI], stromal invasion greater than ½, tumor size >2-≤4cm, three or more lymph nodes with microscopic metastasis). After year 2001, only patients who had positive lymph node and/or parametrial involvement and/or tumor within surgical border received adjuvant radiotherapy.

The chemotherapy group were initially treated with one of the cisplatin / 5-fluorouracyl (CF) or cisplatin / UFT (CU) or paclitaxel / carboplatin (CbP) combination chemotherapies. CF protocol was administered with 28 day intervals. Patients received cisplatin (75mg/m^2) on the 1st day and 5-fluorouracyl (5-FU) (500mg/m^2) on the 1st-5th day. CU protocol was administered with 21 day intervals. Patients received cisplatin (75mg/m^2) on the 1st day and UFT™ (uracyl [224mg]-tegafur [100mg] capsule, Bristol-Myers Squibb) orally during the first 14 days. CbP protocol was administered with 21 day intervals. Patients received paclitaxel (175mg/m^2) by intravenous infusion in three hours and carboplatin (AUC=6) o the 1st day of therapy. All patients were evaluated prior to therapy and those who had a performance score above two according to the Gynecologic Oncology Group (GOG) criteria, bone marrow suppression or hepatic/renal dysfunction did not receive chemotherapy.

Following two or three courses of chemotherapy, patients were re-evaluated under general anesthesia and those with a tumor size less than 40mm underwent type III radical hysterectomy, while other patients with tumor size ≥40mm received radiotherapy. Clinical response to chemotherapy was evaluated according to World Health Organization criteria (16). Complete clinical response (CCR) was defined as absence of clinically gross tumor; partial clinical response (PCR) was defined as reduction in tumor size of greater than 50%; stable disease (SD) was defined as reduction in tumor size of less than 50% or an increase in size by less than 25% and finally progressive disease (PD) was defined as an increase in tumor size of greater than 25% or appearance of new tumoral foci. Pathological complete response (PatCR) was defined as absence of tumor in postoperative pathological examination of the surgical specimen (type III hysterectomy, ovaries and lymph nodes).

In the RT group, radiotherapy was administered alone or in combination with chemotherapy (CCRT) as the initial treatment. Following radiotherapy, patients who had a tumoral lesion in the cervix underwent adjuvant surgery (type I hysterectomy).

Primary or adjuvant radiotherapy had been the sole treatment until the National Cancer Institute announcement in 1999, after which CCRT was accepted as the standard therapy. Radiotherapy was administrated by the radiation oncology department. External radiotherapy was in the form of four field box technique with 6-18 MV photon beams to a total dose of 4500-5040cGy with conventional daily fractionation. In patients with para-aortic lymph node metastases, 45Gy para-aortic radiotherapy was also added. In case of a close surgical vaginal margin, 21Gy high dose rate vaginal brachytherapy in three fractions was applied. Dose prescription was made 0.5cm below the vaginal mucosal surface and the first 4cm of the vagina was treated.

Patients were evaluated every 3 months for the first two years, every six months for the following three years and annually thereafter. Follow-up included recto-vaginal examination, Pap smear test, abdominal sonography, complete blood count and serum biochemistry. Disease free survival (DFS) and overall

survival (OS) rates during the follow-up period were evaluated. All of the mentioned death events were disease specific deaths. Prognostic factors affecting survival rates within each group were evaluated and groups were compared in terms of survival rates. Statistical analysis was performed with the Chi-Square test and ANOVA Table Test using SPSS (Statistical Package for Social Sciences) 12.0 statistical software. Differences between the groups were considered significant at $p \leq 0.05$.

Results

A total of 86 patients had been treated for stage IB2 cervical cancer. Of these, five patients who had been operated in a different clinic and seven patients who had incomplete follow-up data were excluded. The data of the remaining 74 patients were analyzed.

The mean age of the patients was 48.7 years (range: 29-73, median: 47) and the mean duration of follow-up was 52.5 months (range: 3-167, median: 48.5) (Table 1).The mean pre-treatment tumor size was 51.7mm (range: 40-75, median: 50). Thirty-six patients (48.6%) received neoadjuvant chemotherapy, while 20 patients (27.1%) received radiotherapy and 18 patients (24.3%) underwent radical hysterectomy as the initial treatment. Recurrence developed in 18 patients, hence the DFS rate was 75.7%. The interval between initial treatment and recurrence ranged between 2-80 months (mean: 18.6). Isolated pelvic recurrence developed in 11 patients (61.1%). The localizations of recurrence in relation with modality of treatment are displayed in Table 2.

During follow-up, 18 patients died; hence the OS rate was 75.7%. The interval between initial treatment and death ranged between 6-84 months (mean: 20.8). Of the remaining patients, data about the most recent medical condition of seven patients (9.5%) was missing, one patient (1.4%) was alive with disease and 48 patients (64.9%) were alive without disease. Follow-up duration of patients with unknown latest medical condition ranged between 12-96 months, therefore they were included in the survival analyses.

Radiotherapy group

There were 20 patients in this group. The mean age of these patients was 52.3 years (range: 41-73) and the mean duration of follow-up was 61.9 months (range: 3-127, median: 55). Seventeen patients (85%) had squamous cell carcinoma. < < the mean pre-treatment tumor size was 51.7mm (range: 40-75) (Table 1).

While six patients received CCRT, eleven patients received only radiotherapy. It is not possible to evaluate the acute complications of radiotherapy since it was administrated by a number of radiation oncology departments belonging to other hospitals. Three patients underwent extraperitoneal lymph node dissection followed by CCRT. Two of these patients were node-positive.

Table 1. General characteristics of patients

Parameter		Initial treatment			Total mean / n
		RH mean / n	NACT mean / n	RT mean / n	
Number of patients		18	36	20	74
Age (year)		49.4 (38-62) median:49	46.3 (29-66) median:44.5	52.3 (41-73) median:47.5	48.7 (29-73) median:47
Duration of follow-up (months)		53.9 (9-167) median:49.5	46.5 (6-97) median:44	61.9 (3-127) median:55	52.5 (3-167) median:48.5
Pre-treatment tumor size (mm)		52 (40-70) median:50	51.4 (40-70) median:50	51.8 (40-75) median:50	51.7 (40-75) median:50
Pathology	Squamous cell carcinoma	11	34	17	62
	Adenocarcinoma	3	2	2	7
	Adenosquamous carcinoma	4	-	1	5
Presence of recurrence		4	7	7	18
Interval between initial therapy and recurrence (months)		15.5 (6-36)	9 (2-17)	29.6 (6-80)	18.6
Interval between initial therapy and death (months)		25.3 (9-69)	18.8 (6-34)	39.6 (22-84)	20.8
Latest medical condition	No evidence of disease	9	27	12	48
	Alive with disease	-	1	-	1
	Dead	3	8	7	18
	Lost to follow-up	6	-	1	7

RH: Radical hysterectomy, NACT: Neoadjuvant chemotherapy, RT: Radiotherapyn, number of patients

Following radiotherapy, four patients underwent type I hysterectomy + bilateral salphingo-oophorectomy + para-aortic and bilateral pelvic lymphadenectomy as adjuvant surgery. Two of these patients had a tumor in the cervix but all were node-negative. Postoperative pathologic diagnosis was squamous cell carcinoma in these patients and radiotherapy was administered with CCRT preceding type I hysterectomy. Among patients undergoing adjuvant surgery, recurrence developed in one patient 80 months after radiotherapy, who then received palliative treatment but died four months later. Two patients are still alive without disease. Follow-up duration of these patients is 105 and 122 months respectively. One patient was lost to follow-up 12 months after surgery.

Seven patients developed recurrence. During follow-up, the DFS rate was 65%. The duration of the interval between radiotherapy and recurrence ranged between 22 and 84 months (mean: 39.6). The localization of recurrence was only the pelvic region in five patients while it was only the lung in one patient and both pelvis and the lung in another (Table 2). Four of six patients who had recurrence in the pelvis had received only radiotherapy. However, CCRT did not seem to affect pelvic recurrence rate ($p=0.550$). Of the patients who developed recurrence, four received palliative treatment, two received chemotherapy and one patient underwent surgery.

During the follow-up period, seven patients (35%) with recurrence died and the OS rate was 65%. Twelve patients (60%) were alive without disease. The latest medical condition of one patient was unknown but we had data of 12 months of follow-up.

During follow-up, DSF and OS rates were 66.7% among patients receiving only radiotherapy. These rates were 87.5% and 75% respectively, among patients receiving CCRT. When the two groups were compared, there was no statistically significant difference in terms of DFS ($p=0.312$) and OS ($p=0.707$). However, the mean interval between radiotherapy and death was 82.1 months for CCRT, while it was 43.3 months for only radiotherapy.

Radical hysterectomy group

There were 18 patients in this group. The mean age of the patients was 49.4 years (range: 38-62) and the mean duration of follow-up was 53.9 months (range: 3-167, median: 49.5). Postoperative pathology revealed squamous cell carcinoma in 11 patients (61%). The mean pre-treatment tumor size was 52 mm (range: 40-70) (Table 1).

None of the patients died due to surgery-related complications. An intraoperative bladder injury was repaired successfully. During the postoperative period, wound dehiscence was observed in one patient and urinary tract infection was observed in another patient. Postoperative intraabdominal bleeding occurred in one patient but it was not serious and was managed by observation and blood transfusion. Routine suprapubic catheterization was performed intraoperatively and no bladder atonia was observed. Postponement of radiotherapy due to surgery-related complications did not occur.

Postoperative pathology report was unsatisfactory in two patients. Parametrial tumor invasion was detected in 35.3% (6/17), presence of tumor within the surgical border in 23% (4/17), lymph node metastasis in 44.4% (8/18) and deep stromal invasion in 46.2% of patients. The mean number of nodes removed was 51.7 (range: 25-80, median: 48) and the mean number of metastatic lymph nodes was 4.3 (1-19, median: 1). Seventeen patients (94.4%) received adjuvant radiotherapy (14 CCRT and three only radiotherapy) following radical surgery. The histopathologic diagnosis in the patient who did not receive adjuvant radiotherapy was adenocarcinoma.

Information about the current status was not available in six patients. These patients had follow-up durations of 12, 12, 13, 18, 47 and 96 months and were included for survival analyses. Four patients (22.2%) developed recurrence and the interval between radiotherapy and recurrence ranged between 6-36 months (mean: 15.5). Recurrence was detected in only the pelvic region in one patient, only the upper abdomen in one patient, only the lung in one patient and both pelvis and upper abdomen in one patient (Table 2). Three of these patients received palliative treatment, one patient received chemotherapy.

Of the patients who developed recurrence, three died. The fourth patient could not be contacted. Overall survival was 9, 11 and 69 months for the three patients. Parametrial tumor invasion, lymph node metastasis and positive surgical border did not affect survival rates (Table 3) in RH group. However 50% of patients who had a tumor within the surgical border developed recurrence, while this rate fell to 7.7% for those who did not have a tumor within the surgical border ($p=0.052$). Thirty percent of patients with lymph node metastasis died, while none of the patients without lymph node metastasis had died during follow-up ($p=0.090$).

Table 2. Localizations of recurrence in relation with modality of treatment

Treatment groups	Pelvic	Upper Abdomen	Lung	Pelvic + Upper Abdomen	Pelvic + Lung	Upper Abdomen + Lung	Total
RH group	1	1	1	1	-	-	4
RT group	5	-	1	-	1	-	7
NACT group	5	-	-	1		1	7
Total	11	1	2	2	1	1	18

RH: Radical hysterectomy, NACT: Neoadjuvant chemotherapy, RT: Radiotherapy

Neoadjuvant chemotherapy group

There were 36 patients in this group. The mean age of the patients was 46.3 years (range: 29-66) and the mean duration of follow-up was 46.5 months (range: 3-97, median: 44). Postoperative pathology revealed squamous cell carcinoma in 34 patients (94.4%). The mean pre-treatment tumor size was 51.4mm (range: 40-70) (Table 1).

Thirty patients (94.4%) received CF, four patients (11.1%) received PC and two patients (5.6%) received CU as neoadjuvant chemotherapy. Following neoadjuvant chemotherapy, the mean tumor size was reduced to 32.7mm and the type of chemotherapy protocol did not affect the reduction in tumor size ($p=0.158$).

Toxicity of CF combination was tolerable. Only one patient developed grade 3-4 toxicity leading to postponement of chemotherapy for one week. The most common side effect encountered was acute nausea and vomiting, observed in 74% of the cycles (Table 4). Chemotherapy was not cancelled and dose reduction was not indicated in any of the patients because of toxicity. Toxicity of the other two chemotherapy protocols was not evaluated because of the small number of patients. Assessment of toxicity was done according to the criteria of the World Health Organization (16).

Following neoadjuvant chemotherapy, 27 patients (75%) became suitable for surgery in terms of tumor size, but two patients were inoperable for medical reasons and received CCRT. The remaining 25 patients underwent type III radical hysterectomy + bilateral salphingo-oophorectomy + para-aortic and bilateral pelvic lymphadenectomy. Eleven patients were not suitable for surgery after neoadjuvant chemotherapy. Of these patients, six received CCRT and five underwent extraperitoneal lymph node dissection followed by CCRT.

The overall clinical response rate was 33.3% (CCR: 11.1%, PCR: 22.2%). Stable disease was detected in 61.1% of patients while 5.6% had progressive disease. Pathological complete response rate was 8.3%.

The surgical border was tumor-free in all 25 patients who underwent radical surgery, however, five patients (20%) had parametrial tumor invasion and 11 (44%) had lymph node metastasis. Three of five patients (60%) who underwent extraperitoneal lymph node dissection also had positive lymph nodes.

Sixteen (64%) out of 25 patients who underwent radical surgery received postoperative radiotherapy (12 CCRT and four only radiotherapy). So, it was calculated that a total of 27 patients (75%) in this group received radiotherapy.

During follow-up, seven patients (19.4%) developed recurrence; hence the DFS rate was 80.6%. The interval between neoadjuvant chemotherapy and recurrence ranged between 2-17 months (mean: 9). There was recurrence in only the pelvis in five patients while there was both pelvic and upper abdominal recurrence in one patient and upper abdominal and lung recurrence in another patient (Table 2). Of these patients with recurrence, two received radiotherapy and five received

Table 3. The effect of surgical-pathologic risk factors on DFS and OS rates during follow-up in the RH group

Prognostic Factors		DFS	p	OS	p
Parametrial invasion	Negative	%81.8	0.938	%81.8	0.266
	Positive	%83.3		%100	
Lymph node metastasis	Negative	%87.5	0.375	%100	0.090
	Positive	%70		%70	
Positive surgical border	Negative	%92.3	0.052	%92.3	0.347

DFS: Disease free survival, OS: Overall survival, n: Number of patients

Table 4. Toxicity of CF combinations per courses

Parameters	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	%88.3	%10.4	%1.3	-	-
Leucopenia	%97.4	%1.3	%1.3	-	-
Thrombocytopenia	%97.4	-	%1.3	-	%1.3
ACINV	%26	%54.5	%19.5	-	-
Diarrhea	%89.6	%5.2	%3.9	%1.3	-
Mucositis	%81.8	%13	%3.9	%1.3	-
Elevation of liver enzymes[1]	%98.7	%1.3	-	-	-
Proteinuria	%94.8	%5.2	-	-	-
Hematuria	%88.3	%11.7	-	-	-

ACINV: Acute Chemotherapy Induced Nausea and Vomiting, [1]SGOT/SGPT elevations

chemotherapy.

Six out of seven patients with recurrence died; hence the OS rate was 77.8%. The mean duration between detection of recurrence and death was 21 months (range: 6-34). One patient is still alive 31 months after recurrence and is receiving chemotherapy.

Two patients (5.6%) not responding to NACT showed progression of disease. These patients died 11 and 14 months after neoadjuvant chemotherapy respectively. During follow-up, eight patients died and the OS rate was 77.8%. The interval between neoadjuvant chemotherapy and death ranged 6-34 months (mean: 18.8).

The effect of chemotherapy type and lymph node metastasis on survival rates was not significant statistically. However factors such as being able to perform radical surgery after neoadjuvant chemotherapy, presence of parametrial involvement, tumor size after chemotherapy and the reduction rate of tumor size had prognostic value for survival (Table 5). The presence of parametrial involvement decreased the OS rate from 95% to 40% (p=0.003). Lymph node metastasis,although being statistically not significant, worsened DFS and OS rates clearly (92.9% vs. 62.5% and 85.7% vs. 50% respectively) (Table 5).

When the three groups were compared, duration of follow-up and pre-treatment tumor size was not different statistically. However, patients in the radiotherapy group were older and the incidence of adenocarcinoma or adenosquamous carcinoma was higher (Table 6).

None of the initial treatment protocols were superior to one another statistically in terms of DFS and OS rates. Responsiveness to neoadjuvant chemotherapy provided no further advantage in

Table 5. The effect of surgical-pathologic risk factors on DFS and OS rates during follow-up in the NACT group

Parameter		DFS	p	OS	p
Neoadjuvant chemotherapy modality	Cisplatin/5-fluorourasil	%83.3	0.346	%80	0.473
	Other	%66.7		%66.7	
Treatment after neoadjuvant chemotherapy	Surgery	%80	0.899	%84	0.176
	Radiotherapy#	%81.8		%63.6	
Parametrial involvement	Negative	%90	0.012*	%95	0.003*
	Positive	%40		%40	
Lymph node metastasis	Negative	%92.9	0.076	%85.7	0.070
	Positive	%62.5		%50	
Pre-neoadjuvant chemotherapy tumor size (mm)	≤50	%81.8	0.297	%78.8	0.629
	>50	%66.7		%66.7	
Post- neoadjuvant chemotherapy tumor size (mm)	≤30	%82.4	0.797	%88.2	0.153
	>30	%78.9		%68.4	
Post- neoadjuvant chemotherapy reduction in tumor size	None	%85.7	0.944	%71.4	0.460
	<%25	%75		%62.5	
	≥%25 - <%50	%77.8		%77.8	
	≥%50	%83.3		%91.7	

DFS: Diesase free survival, OS: Overall survival, #RT or CCRT, *: Statistically significant

Table 6. Comparison of age, tumor size and duration of follow-up between the groups

Treatment groups	Age (years), mean	Tumor size (mm), mean	Duration of follow-up (mo's), mean	Histopathology	
				Squamous cell	Others
RH group	49.4 (median: 49)	52 (median: 50)	53.9 (median: 49.5)	%61.1	%38.9
NACT group	46.3 (median: 44.5)	51.4 (median: 50)	46.5 (median: 44)	%94.4	%5.6
RT group	52.3 (median: 47.5)	51.8 (median: 50)	61 (median: 55)	%85	%15
p	0.036*	0.978	0.294	0.007*	

RH: Radical hysterectomy, NACT: Neoadjuvant Chemotherapy, RT: Radiotherapy (RT or CCRT), *: Statistically significant

terms of survival (Table 7).

Discussion

While radiotherapy is the contemporary modality of cervical cancer treatment for stage IIB or later stages, surgery is the choice of treatment for earlier stages. However, treatment of locally advanced early stage tumor (IB2 and bulky IIA) is still controversial; in consequence a multimodal approach is generally preferred. The efficacy of radical hysterectomy and radiotherapy in early stage (IB-IIA) cervical cancer is similar. Five-year OS is approximately 90% in both modalities (1, 2). Neoadjuvant chemotherapy is also associated with similar five-year OS rates (nearly 90%) (17, 18). In the present study, OS rates during follow-up were 77.8% (median follow-up:55 months) in the RT group, 77.8% (median follow-up:44 months) in the NACT group and 83.3% (median follow-up:49.5 months) in the RH group. Survival rate was high in the RH group, although non-squamous type cervical cancer, which is known to have a worse prognosis, was more frequent in this group. The RT group was older. It is known that, with advancing age, survival decreases in cervical cancer. Death rate at age 60 was twice as high as at age 30 (relative index: 1.9) (19). This might explain the recurrence and death rates in the RT group. Despite a higher incidence of recurrence and death in patients receiving radiotherapy, the interval between initial treatment and recurrence and death was longer in this group (for RT group, RH group and NACT group; DSF 29.9 months, 15.5 months and 9 months respectively, OS 39.6 months, 25.3 months and 18.8 months respectively). The limited number of patients or the relationship between treatment modality and cellular kinetics might be the cause of this finding.

Surgical approach has priority in the treatment of early stage tumor as radiotherapy is associated with ovarian and sexual dysfunction. In addition, in case of treatment failure with surgery and recurrence, radiotherapy will be an effective treatment option. However, the likelihood of receiving adjuvant radiotherapy after radical surgery is quite high for stage IB2 tumor. A retrospective analysis by Yessaian et al showed that 52% of patients with stage IB2 tumor had to receive radiotherapy after radical hysterectomy according to GOG criteria (20). In patients with stage IB1 and IB2 cervical cancer treated with radical hysterectomy, Finan et al. found that the rate of adjuvant RT was 72.3% in the stage IB2 group (21). Similarly, another study by Landoni et al comparing radical hysterectomy and radiotherapy in the treatment of stage IB-IIA cervical cancer, demonstrated that 84% of patients with tumor size greater than 4cm received adjuvant radiotherapy (3). In the present study, nearly 95% of patients received adjuvant radiotherapy, which might be explained by the high incidence (40%) of non-squamous cell type cancer in the RH group. Nevertheless, all the patients with squamous cell type cancer (n: 11) received adjuvant radiotherapy in the RH group.

CCRT has been used for the last 20 years to increase the efficacy of radiotherapy. Five studies performed towards the end of 1990s, in which cisplatin based chemotherapy was used, concluded that CCRT improved survival rates (GOG#85, GOG#120, GOG#123, SWOG#8797, RTOG#9001) (22-26). Thereupon NCI made an emergency declaration in 1999 and since then the addition of chemotherapy to radiotherapy has become standard practice (http://rex.nci.nih.gov/massmedia/pressreleases/cervicalcancer.html). Green et al. presented a meta-analysis of 19 studies performed between 1981 and 2000 (n: 4580). They showed that the improvement in the OS rate in the CCRT group was 12% and this was independent of having undergone surgery or not. This effect was most prominent in early stage disease (27). These results were further supported by other studies. In a study by Cetina et al., including 294 patients with stage IB2-IVA cervical cancer treated with weekly cisplatin (40mg/m^2, maximum dose=80mg), the OS was 76.5% during a median 28 month follow-up. This was 86% for stage IB2-IIB (28). In 2007, the long-term results of the GOG#123 study, which evaluated the effect of weekly cisplatin (40mg/m^2) on survival rates in stage IB2 cervical cancer, were presented (29). Preliminary results have demonstrated a reduction rate of 49% for recurrence and 46% for death (25). These rates were 39% and 37% respectively according to the new long-term results. The efficacy of chemoradiotherapy seemed to be diminished in a long-term result of the GOG#123study (29). In the present study, the DFS rate was improved by 20% and the OS rate by 9%, and the OS was increased by two-fold in the CCRT group when compared with the radiotherapy only group. Despite all these results, in the phase III study by the National Cancer Institute of Canada including 259 patients with stage

Table 7. The effect of treatment modality on disease-free survival and overall survival rates during follow-up

Treatment modality		Disease-free survival	p	Overall survival	p
NACT vs RT	NACT	%80.6	0.198	% 77.8	0.301
	RT	%65		%65	
NACT vs RH	NACT	%80.6	0.537	%77.8	0.463
	RH	%77.8		%83.3	
RT vs RH	RT	%65	0.307	%65	0.200
	RH	%77.8		%83.3	

RH: Radical hysterectomy, NACT: Neoadjuvant chemotherapy, RT: Radiotherapy (RT or CCRT)

IB-IVA tumor, weekly cisplatin-based CCRT was not found to be superior to radiotherapy only. Five-year OS was 62% in the CCRT group, while it was 58% in the radiotherapy only group (p=0.42) (30). However, the duration of radiotherapy in that study was shorter than the other studies. Besides, the discrepancy in results is considered to occur as a result of evaluation of the para-aortic region solely with computed tomography and the high incidence of anemia in the chemotherapy group.

The improvement in survival rates with CCRT is explained theoretically by the inhibition of recovery of sublethally damaged cells, the change in cellular kinetics and the increase in radiosensitivity as the result of the reduction in tumor volume (31). The success of CCRT is not limited to prevention of local recurrences only. Studies have also shown that the incidence of distant recurrence was reduced (27). In the present study, 75% of recurrences in the RH group were distant, while 28.6% of recurrences in the NACT and RT group were distant (Table 2). The reduction in distant metastasis is thought to be due to the cytotoxic effect of chemotherapy. In addition to this, it was shown that adjuvant chemotherapy after CCRT did not improve survival (32).

There is an ongoing debate about executing adjuvant type I hysterectomy after radiotherapy. Keys et al., in the GOG#71 study, compared adjuvant hysterectomy after radiotherapy with radiotherapy alone in stage IB2 cervical cancer (19). CCRT was not administered in the two groups. As a result, it was shown that adjuvant hysterectomy improved survival in patients with tumor size smaller than 7cm. Gallion et al. also obtained similar results (stage IB barrel-shaped cancer) (33). However, in the GOG#123 study comparing CCRT followed by adjuvant hysterectomy with radiotherapy followed by adjuvant hysterectomy, it was shown that the incidence of persistent disease decreased significantly in the chemotherapy group. Similarly the DFS and OS were higher in the chemotherapy group (25). As a result, the GOG#123 study states that for patients receiving CCRT, adjuvant hysterectomy has no place in treatment. In the present study, although the number of adjuvant hysterectomies was not high, it was observed that this type of treatment produced improvement in DFS and OS rates by 12% (37.5% vs. 25%, p=0.634).

Neoadjuvant chemotherapy is the standard treatment in many solid tumors, particularly breast tumors and tumors of the head and neck. However, the role of this treatment in cervical cancer is still unclear, even after 25 years. Theoretically, by reducing the size of the tumor, neoadjuvant chemotherapy is expected to increase the chance of resectability. Additionally, surgical prognostic factors are improved by eliminating micrometastases. Some clinical studies and phase II studies with large sample sizes support this hypothesis by demonstrating improvement of surgical prognostic factors with neoadjuvant chemotherapy (34-36). However, more recent studies comparing neoadjuvant chemotherapy followed by radical hysterectomy and only radical hysterectomy did not find any improvement (15, 37).

Complete response rate with neoadjuvant chemotherapy varies between 0-50% (OCR 25-95%) (15, 38-59). After neoadjuvant chemotherapy, surgery became suitable for 28-100% of patients (18, 35, 37-43, 53, 55-58, 60-66). One of the reasons for the diversity of results is the heterogeneity of the study populations. Patients had clinical stage IB2-IIIB locally advanced cervical cancer in most of the studies, although the response to neoadjuvant chemotherapy is directly correlated with the stage of the disease. In the meta-analysis by Eddy et al, CCR was 28% in stage IB2-IIA but fell to 7% in stage IV (67). Similar results have also been reported in other studies (50-52).

The factor that determines operability is the stage of disease. Duenas-Gonzales et al. showed that the operability rate fell from 83% in stage IB2 to 60% in stage IIB and 40% in stage IIIB (52). As a result neoadjuvant chemotherapy, not indicated in the treatment of advanced stage cervical cancer since the need for subsequent radiotherapy is high, should be limited to the treatment of early stage. In the present study, OCR rate with neoadjuvant chemotherapy was 33.3% (CCR: 11.1%, PCR: 22.2%) and 75% of patients became suitable for operation. 75% of patients in the NACT group received adjuvant radiotherapy.

Survival rates are also diverse as are the response and operability rates. Five-year DFS and OS vary between 29-80% and 21-81% respectively (15, 18, 34, 37, 38, 42, 48, 51, 57, 60, 66). Results of this study are within these ranges (median follow-up:44 months, DFS: 80.6%, OS: 77.8%). Prognostic factors found to be important were tumor size following chemotherapy, radiotherapy administration after neoadjuvant chemotherapy and parametrial involvement.

Because of the diversity in the reported results it is difficult to appreciate the status of neoadjuvant chemotherapy. Heterogeneity of disease stages in the studies is one of the reasons. In advanced stages, survival rate with neoadjuvant chemotherapy is lower (63, 64, 68) with no additional benefit (52). However, results of studies including only stage IB2 patients are also variable (15, 17, 18), mainly because of uncertainty of clinical staging. Another reason for the diversity may be the neoadjuvant chemotherapy protocol selected to be administered. Because most neoadjuvant chemotherapy protocols are cisplatin-based, it is considered that chemotherapy protocols do not have any effect on response and survival rates (66). However, in an Italian phase III study which compared cisplatin/iphosphamide/paclitaxel with cisplatin/iphosphamide, it was shown that triple neoadjuvant chemotherapy combination improved CCR significantly (9% vs. 20%) (50). Nevertheless ,there was no difference in terms of operability and survival rates between the two chemotherapy protocols. In the present study, chemotherapy protocol did not affect survival, however CF protocol improved the DFS by 16% and the OS by 13% (p=0.346, p=0.473 respectively).

Neoadjuvant chemotherapy for Cervical Cancer Meta-Analysis Collaboration re-evaluated 21 phase III studies performed between 1975 and 2000 and presented a meta-analysis (14). In this meta-analysis, two groups were created. In the first group, neoadjuvant chemotherapy followed by radiotherapy was compared with radiotherapy only (16 studies, n: 2074) while in the second group neoadjuvant chemotherapy followed by radical hysterectomy was compared with radiotherapy

only (five studies, n: 872). In the latter group, neoadjuvant chemotherapy + radical hysterectomy reduced death rate by 35% and increased survival rate by 14%. Only 2 studies in this group consisted of stage IB2 tumor (49, 66). Benedetti-Panici et al., in their subgroup evaluation, observed that neoadjuvant chemotherapy was advantageous in terms of survival in stage IB2 (66), while Chang et al. did not (49).

Aoki et al., in their study comparing neoadjuvant chemotherapy followed by radical hysterectomy with radiotherapy only (locally advanced stage IB-IIB); they observed that, with neoadjuvant chemotherapy, surgical-pathologic risk factors and survival were improved (45). A similar result was reported by Namkoong et al. (locally advanced stage IB-IIB) (69). On the other hand, Serur et al. (stage IB2, squamous cell carcinoma) detected an improvement in surgical-pathologic risk factors but no influence on survival (18). Recently, two studies were reported, one retrospective (37) and a prospective phase III GOG study (15) comparing neoadjuvant chemotherapy followed by radical hysterectomy with radical hysterectomy only in locally advanced early stage cervical cancer. These studies suggest that neoadjuvant chemotherapy has no place in the treatment of locally advanced early stage cervical cancer. In the GOG study, it was shown that neoadjuvant chemotherapy did not improve surgical-pathologic risk factors and survival. Five-year OS was 60.7% in patients receiving neoadjuvant chemotherapy, while it was 63.3% in patients undergoing radical hysterectomy only.

Uncertainty about cervical cancer arises from staging of tumor clinically and debate concerning treatment of stage IB2 tumor continues. It is difficult to create a homogenous patient group and to make a comment about the extent of tumor according to clinical stage. Neoadjuvant chemotherapy, initially a hopeful adjuvant, may be disappointing. In the present study, recurrence developed earlier in the group of patients undergoing neoadjuvant chemotherapy and surgery. However, survival rates were higher in NACT and RH group than in RT group. The percentage of patients receiving adjuvant radiotherapy in RH group and NACT group was quite high (94.4% and 75% respectively). Thus, it was concluded that radical hysterectomy or neoadjuvant chemotherapy as initial treatment had suboptimal efficacy. The comparison of RT and RH groups may be considered as the comparison between radiotherapy versus primary radical surgery followed by radiotherapy, owing to the high rate of adjuvant radiotherapy (94.4%) in the RH group. In this case, it can be concluded that primary radical surgery might be an overtreatment in stage IB2 cervical cancer because the improvement observed in survival was statistically insignificant. On the other hand, the limitations of the present study (retrospective, nonrandomized and relatively small number of patients) must be kept in mind. CCRT and adjuvant hysterectomy improved survival in the RT group.

In conclusion, this retrospective analysis showed that none of the treatment modalities had any superior effect on survival. However, CCRT should be added if radiotherapy will be given as the initial therapy. Furthermore radiotherapy followed by adjuvant hysterectomy must be investigated by further studies and indecision about neoadjuvant chemotherapy should be overcome.

Conflict of interest

None declared

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Comparison of single and double courses of antenatal corticosteroid administration on neonatal mortality and morbidity

Neonatal mortalite ve morbidite üzerine tek doz ve çift doz antenatal kortikosteroid uygulamasının etkisi

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Abstract

Objective: We aimed to evaluate the effects of single and double courses of antenatal corticosteroid administration on neonatal mortality and morbidity.

Materials and Methods: 232 preterm babies delivered between 01. April 2007 and 31. March 2008 with gestational ages of 26- 34 weeks were evaluated prospectively. Infants were divided into three groups. The first group did not receive any antenatal betamethasone therapy. The second group received single (two doses of 12 mg betamethasone administered at 24 hour intervals) and the third group received double (repeated course after one week) courses of betamethasone therapy.

Results: 156 (67.2%) infants received at least one dose of corticosteroid treatment whereas 76 (37.8%) did not. Of 156 infants who had received antenatal betamethasone, 36 (23.1%) developed respiratory distress syndrome (RDS), while the incidence of RDS was 35.5% in 76 preterms who received no antenatal betamethasone (27/76) ($p<0.05$). When single and double courses of bethamethasone administration were compared, 20 (24.7%) infants with single course and 16 (21.3%) infants with two course developed RDS ($p>0.05$).

Conclusion: When single and two courses of antenatal steroid therapy were compared, there was no statistically significant difference between groups regarding the incidence of RDS and mechanical ventilator treatment. (J Turkish-German Gynecol Assoc 2010; 11: 38-43)

Key words: Antenatal betamethasone therapy, respiratory distress syndrome, preterm delivery

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Özet

Amaç: Tek ve çift doz antenatal kortikosteroid uygulamasının neonatal mortalite ve morbiditesi üzerine olan etkisini incelemeyi amaçladık.

Gereç ve Yöntemler: 1 Nisan 2007 ve 31 Mart 2008 tarihleri arasında gestasyonel yaşları 26-34 hafta arasında olup doğurtulan 232 preterm bebek prospektif olarak değerlendirildi. İnfantlar üç gruba ayrıldı. Birinci grup antenatal betametazon tedavisi almadı. İkinci grup yirmidört saat arayla iki doz 12 mg betametazon alırken üçüncü grup bir hafta arayla ikinci betametazon tedavisi aldı.

Bulgular: 156 (%67.2) infant en az tek doz kortikosteroid tedavisi alırken 76'sı (%37.8) kortikosteroid almadı. Antenatal betametazon alan 156 infanttan 36'sında (%23.1) respiaratuar distres sendromu (RDS) gelişirken antenatal betametazon almayan 76 pretermden 27'sinde (%35.5) RDS gelişti ($p<0.05$). Tek ve çift doz betametazon uygulaması karşılaştırıldığında, tek doz betametazon alan 20 (%24.7) infantta, çift doz betametazon alan 16 (%21.3) infantta RDS gelişti ($p>0.05$).

Sonuç: Tek kür ve iki kür betametazon uygulaması karşılaştırıldığında, RDS insidansı ve mekanik ventilasyon ihtiyacı yönünden iki grup arasında istatistiksel olarak anlamlı bir fark saptanmadı ($p>0.05$).

(J Turkish-German Gynecol Assoc 2010; 11: 38-43)

Anahtar kelimeler: Antenatal betametazon tedavisi, respiratuar distres sendromu, prematüre bebek

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Introduction

Preterm birth and associated complications are one of the leading causes of neonatal mortality and morbidity (1). Antenatal corticosteroids have been used for the prevention of RDS and other complications of prematurity for nearly thirty years. Yet, the debate still exists on the timing and frequency of antenatal steroid administration. It is still unclear whether a single or double course of antenatal steroid is more effective. It has been shown that a single course of antenatal steroid administered to women at risk for preterm delivery reduces neonatal mortality and morbidity (2). The effects of repeated doses are uncertain. They might improve pulmonary complications, but there is concern about the

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reduction of birth weight and adverse neurological outcome. The results of two studies on the long term effects of repeated doses of antenatal steroids are also controversial (3, 4).

In this study we aimed to evaluate the effects of single and two courses of antenatal betamethasone treatment on neonatal mortality and morbidity and to compare these groups with preterm babies who did not receive any antenatal corticosteroids.

Materials and Methods

This prospective study was conducted in the Ondokuz Mayıs University Faculty of Medicine, Department of Obstetrics and Gynecology between 01. April 2007 and 31. March 2008. Women in preterm labor with a gestational age of 26- 34 weeks were eligible for the study. Women admitted for preterm delivery on odd days received a single course and those admitted on even days of the month received a double course of betamethasone. Women in whom delivery was imminent, without time for the administration of betamethasone ,constituted the control group. Women in the single course group received betamethasone (Celestone®) 12 mg intramuscularly at 24 hour intervals (2x12 mg). The scheduled dose was repeated the next week if the patient still did not deliver and she remained at risk for preterm delivery before 34 weeks of gestation (Double course group). Women who were included in the double course group but delivered before the second dose were included in the single dose group. All women at risk for preterm delivery received ritodrine starting with a dose of 50 μgr/min. When contractions continued, ritodrine infusion was increased by 50 μgr/minute up to 350 μgr/min. The infusion was continued for 24 hours after the cessation of contractions. Babies with major congenital and/or chromosomal abnormalities were excluded from the neonatal outcome data analysis. Recorded maternal clinical parameters were: age, chronic illness (diabetes mellitus, hypertension) and complications of pregnancy (pregnancy induced hypertension, preeclampsia, eclampsia, gestational diabetes), preterm premature rupture of membranes, multiple pregnancy, antenatal corticosteroid administration and courses of antenatal corticosteroids. Recorded neonatal parameters were: method of birth, gestational age, sex, birth weight, 5th minute Apgar score, surfactant administration, requirement for mechanical ventilation (MV) and duration of MV, respiratory distress syndrome (RDS), complications of prematurity [bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leucomalasia (PVL), patent ductus arteriosus (PDA)], length of hospitalization and whether the baby was discharged or died.

During the study period, of 239 babies born before 34 weeks of gestational age, 7 were excluded due to major congenital and/or chromosomal abnormalities and 232 were eligible for the analysis. 156 (66.8%) of these babies were exposed to antenatal corticosteroids 81 (51.9%) received a single course and 75 (49.1%) received double courses of antenatal betamethasone; where 76 (33.2%) babies did not receive antenatal betamethasone.

Respiratory distress syndrome was diagnosed with compatible chest x-ray images and arterial blood gas analysis results in babies with respiratory insufficiency. Surfactant treatment was indicated by the results of arterial blood gas analysis and chest x-ray and a mean alveolar pressure equal to or higher than 7 cmH_2O measured by the attending neonatologist. Survanta® in a dose of 4 ml/kg was used as an early rescue treatment in babies with RDS. Bronchopulmonary dysplasia was defined as oxygen requirement with a duration of 28 days or more in the presence of typical chest x-ray. The diagnosis of PVL and IVH were based on cranial ultrasound examination. Sepsis was diagnosed according to the Töllner score and blood culture results (both clinical and culture proven) (5). Patent ductus arteriosus was diagnosed with echocardiography by a pediatric cardiologist. Necrotising enterocolitis was diagnosed via physical examination, Guiac positive/ bloody stools and abdominal x-ray findings and classified according to Modified Bell's staging criteria (6).

''SPSS for Windows 13.0'' was used for statistical analysis. The data were checked for normal distribution using normality tests. Mann-Whitney U and Chi-square tests were used for group comparisons where data were not normally distributed and the Student-t test was applied for data with normal distribution. A p value <0.05 was considered as significant. The Local Ethics Committee approved the study.

Results

232 preterm babies, with gestational ages of 26- 34 weeks, born in the obstetrics clinic between 01. April 2007- 31. March 2008 constituted the study group. Twenty- six (11.2%) of these were twins. Clinical characteristics of the study group are shown in Table 1.

156 (66.8%) babies had received antenatal corticosteroids: 136 (87.1%) singletons and 20 (12.9%) twins. Of 76 (33.2%) babies who did not receive antenatal betamethasone, 70 (96%) were singletons and 6 (4%) were twins.

Table 1. Clinical characteristics of the study group

	Antenatal steroid (+) (n=156)	Antenatal steroid (-) (n= 76)	p
Birth weight (grams)	1580± 460 (630-2500)	1473± 500 (740-2480)	>0.05
Gestational age (weeks)	30.4± 2.4 (26-34)	29.8± 2.6 (26-34)	>0.05
Male/ Female (%)	49 / 51	47 / 53	>0.05
Vaginal/Caesarean birth (%)	78 / 22	83 / 17	>0.05
Maternal age (years)	27.6± 5.2	27.3± 5.7	>0.05
Values are given as average ± standard deviation (minimum- maximum)			

RDS was diagnosed in 36 (23.1%) babies who received antenatal corticosteroids and in 27 (35.5%) who did not ($p<0.05$). Surfactant use was also statistically different between antenatal steroid administered and non- administered groups (23.1% vs. 35.5%, $p<0.05$).

The incidence of BPD, sepsis, NEC, grade 3 / 4 IVH, PVL and PDA did not differ between babies receiving antenatal corticosteroid treatment and those who did not, as shown in Table 2 (7.7% vs.13.2%, 12.2% vs.17.1%, 4.5% vs.5.3%, 3.8% vs. 6.6%, 9% vs. 13.2%, and 15.4% vs.19.7% respectively; for all $p>0.05$).

Mechanical ventilation was required in 64 (43%) infants who received antenatal betamethasone and in 42 (57.5%) infants who did not ($p<0.05$). The average period for MV was 4.1±2.2 days (1-14 days) for babies receiving antenatal steroid therapy and 7.7±6.3 days (1-28 days) for babies not receiving steroids ($p<0.05$).

The 5th minute Apgar score was above 7 in 120 babies (79.5%) receiving antenatal steroid therapy and in 31 (40.8%) babies having no antenatal steroids ($p<0.01$).

The length of hospitalization was 11.7±11.4 (1-65) days in infants who received antenatal betamethasone, whereas this was 17.5±16.4 (1-78) days in infants who did not ($p<0.01$).

Regarding mortality, three (1.9%) babies exposed to antenatal corticosteroids died, whereas eight (10.5%) babies among the ones not receiving antenatal corticosteroids died. The difference was statistically significant ($p<0.05$) (Table 2). In the group receiving antenatal steroid, death was due to IVH in one and due to RDS in the others. In babies not being exposed to antenatal steroids, the reasons for death were IVH in two, sepsis in one and RDS and related complications in the others.

When the effect of antenatal steroids on RDS according to gestational age was analyzed, it was observed that antenatal steroids significantly reduced the incidence of RDS in babies born between 29-31 weeks and 32-34 weeks ($p<0.05$). When the incidence of RDS was analyzed in babies born between 26-28 weeks, there was no statistically significant difference between steroid receiving and not receiving groups ($p>0.05$) (Table 3).

81 (51.9%) babies received a single course and 75 (49.1%) babies received double courses of antenatal betamethasone. The clinical characteristics of single and double course steroid groups are shown in Table 4. Two groups were similar regarding gestational age, birth weight and method of birth ($p>0.05$).

RDS was observed in 20 (24.7%) babies receiving a single dose and in 16 (21.3%) babies receiving two doses of antenatal corticosteroids and they all received surfactant. The incidence

Table 3. The effect of antenatal corticosteroid treatment on RDS according to gestational age

Gestational age (weeks)	Antenatal steroid (+) (n=156)	Antenatal steroid (-) (n=76)	p
26-28 wk (n=65)			
RDS (+)	18 (45%)	13 (52%)	>0.05
RDS (-)	22 (55%)	12 (48%)	
29-31 wk (n=76)			
RDS (+)	10 (19.6%)	9 (36%)	<0.05*
RDS (-)	41 (80.4%)	16 (64%)	
32-34 wk (n=91)			
RDS (+)	8 (12.3%)	5 (19.2%)	<0.05*
RDS (-)	57 (87.3%)	21 (80.8%)	

RDS: Respiratory distress syndrome , *: $p<0.05$

Table 2. Neonatal problems in babies with and without antenatal corticosteroid treatment

	Antenatal steroid (+) (n= 156)	Antenatal steroid (-) (n= 76)	P
RDS	36 (23.1%)	27 (35.5%)	<0.05*
Surfactant use	36 (23.1%)	27 (35.5%)	<0.05*
Bronchpulmonary dysplasia	12 (7.7%)	10 (13.2%)	>0.05
Sepsis	19 (12.2%)	13 (17.1%)	>0.05
Necrotising enterocolitis	7 (4.5%)	4 (5.3%)	>0.05
Intraventricular hemorrhage	6 (3.8%)	5 (6.6%)	>0.05
Periventricular leukomalacia	14 (9%)	10 (13.2%)	>0.05
Patent ductus arteriosus	24 (15.4%)	15 (19.7%)	>0.05
MV use	64 (43%)	42 (57.5%)	<0.05*
Days on MV	4.1± 2.2 (1- 14)	7.7± 6.3 (1- 28)	<0.05*
5th minute Apgar score >7	120 (76.9%)	31 (40.8%)	<0.01*
Hospitalization days	11.7± 11.4 (1- 65)	17.5± 16.4 (1- 78)	<0.01*
Mortality	3 (1.9%)	8 (10.5%)	<0.01*

RDS: Respiratory distress syndrome, MV: Mechanical ventilator

Values are given as average ± standard deviation (minimum- maximum) *: $p<0.05$

for RDS and surfactant use did not differ between the groups (p>0.05). Mechanical ventilation was required in 39 (48.1%) of single course and 31 (41.3%) in double course groups (p>0.05). There was no statistically significant difference regarding days on MV, BPD, sepsis, NEC, IVH, PDA, PVL, 5th minute Apgar scores, length of hospitalization and mortality between single and double course antenatal steroid groups (p>0.05) (Table 4).

Discussion

Complications related to preterm labor have a great impact on neonatal morbidity and mortality; with RDS as the leading cause (7). Antenatal corticosteroids have been shown to promote fetal pulmonary maturation and reduce perinatal mortality, pulmonary and cerebral morbidity in preterm babies (8, 9). In the meta-analysis by Crowley et al. (10) antenatal steroids have been shown to reduce the incidence of RDS 50%. In the study by Kari et al (11) and in another study conducted by Brazilian Neonatal Research Network, antenatal steroid treatment reduced both the incidence of RDS and surfactant use and the requirement for MV (12). In the present study, it has also been observed that antenatal corticosteroid administration significantly reduced the incidence of RDS and surfactant use, as well as the need and duration of MV.

Gardner et al. have shown that antenatal corticosteroid treatment improved Apgar scores in babies born <1000 grams (13). In our study, 5th minute Apgar scores were significantly higher in babies receiving antenatal steroids compared to the ones not receiving steroids. There was no difference between single and double course steroid groups regarding 5th minute Apgar scores. The results were in accordance with the data that antenatal steroid administration improves early postnatal adaptation in preterm babies.

Gestational age is one of the main topics of disagreement regarding antenatal corticosteroid administration. Liggins and Howie (14) were the first investigators who, in 1972, showed that antenatal corticosteroid administration reduced the incidence of RDS by 60% in preterm babies with gestational ages between 26-32 weeks. Ballard et al. (15) have stated that antenatal corticosteroid administration to hasten pulmonary maturation may be effective even at >34 weeks of gestational age. The NIH consensus report published in 1994 advised that all fetuses at the risk for preterm birth between 24-34 weeks of gestation are candidates for antenatal corticosteroid treatment (9). In the study by Modarek and Najati (16), including 300 preterms of 29- 34 weeks, it was shown that antenatal corticosteroids prevented RDS. In the present study, we have also shown that antenatal corticosteroid administration reduced the incidence of RDS between 29- 34 weeks.

Although antenatal steroids reduce the incidence of RDS in preterm babies 50%, there is no net reduction in the incidence of BPD. Besides, there are studies showing that

Table 4. The comparison of single and double courses of antenatal corticosteroid treatment groups

	Single course steroid (n=81)	Double course steroid (n=75)	P
Maternal age	28.0± 5.2 (18- 40)	2728± 5.4 (18- 42)	>0.05
Gestational age (weeks)	30.5± 2.4 (26-34)	30.4± 2.4 (26-34)	>0.05
Birth weight (grams)	1567.9± 453 (630-2500)	1593.0± 470 (810-2420)	>0.05
Vaginal/cesarean birth (%)	19.7/80.3	13.5/ 86.5	>0.05
Respiratory distress syndrome	20 (24.7%)	16 (21.3%)	>0.05
Surfactant treatment	20 (24.7%)	16 (21.3%)	>0.05
Mechanical ventilator treatment	39 (48.1%)	31 (41.3%)	>0.05
Days on mechanical ventilator	4.2± 2 (1-10)	3.9± 2.3 (1- 14)	>0.05
Bronchpulmonary dysplasia	7 (8.6%)	5 (6.7%)	>0.05
Sepsis	10 (12.3%)	9 (%12)	>0.05
Necrotising enterocolitis	4 (4.9%)	3 (4%)	>0.05
Intraventricular hemorrhage	4 (4.9%)	2 (2.7%)	>0.05
Patent ductus arteriosus	13 (16%)	11 (14.7%)	>0.05
Periventricular leukomalacia	8 (9.9%)	6 (8%)	>0.05
5th minute Apgar score >7	62 (76.5%)	58 (77.3%)	>0.05
Hospitalization days	12.9± 12.5 (1-50)	10.5± 9.8 (1-65)	>0.05
Mortality	2 (%2.5)	1 (%1.3)	>0.05

Values are given as average ± standard deviation (minimum- maximum)

antenatal exposure to three or more doses of corticosteroids might increase the risk for BPD (17). In the present study, the incidence of BPD was 8.6% in single and 6.7% in double dose groups; without statistical difference. In the ACTORDS study, multiple doses of antenatal steroids have been shown to decrease the risk for BPD in babies < 32 weeks of gestation (20% in the single dose and 12% in the multiple dose group; RR: 0.6). These controversial results might be due to different patient selection criteria in these studies.

Liggins and Howie reported the reduction in the incidence of IVH after antenatal corticosteroid use (14). Garite et al. (18) have also shown that antenatal steroids reduced the incidence of IVH from 25% to 3% in 24-28 week preterms and they stated that betamethasone had a stabilizing effect on fragile germinal matrix capillaries. In another retrospective study including 514 preterms of 23-34 weeks, there was no difference regarding IVH among babies receiving antenatal steroids and not (12). In the present study, the incidence for IVH was 3.8% in babies receiving antenatal steroids, whereas this was 6.6 % in babies not receiving them. Although the difference was statistically insignificant, this minor difference might be important, since IVH is a major concern for neonatal mortality and long term handicaps.

Halac et al. (19), in a prospective study including 960 newborns, concluded that the incidence of NEC decreased by antenatal betamethasone use. This reduction was also shown by Bauer et al (7.1 % vs 2.0 %) and in the in the meta-analysis by Crowley (reduction by 65%) (20, 21). Conversely, there are studies in the literature showing that they do not influence the incidence of NEC (12,22). In the present study, antenatal corticosteroids did not reduce the incidence of NEC in preterms born between 26- 34 weeks.

Compared to the non-treated group, in babies receiving steroids during the antenatal period, the incidence of RDS, the need for MV and invasive interventions as well as occurrence of other neonatal complications are less frequently observed. As shown in our patient population, shorter hospitalization time in babies of steroid-treated mothers can be considered as an objective parameter supporting this observation.

The present study showed that length of hospitalization decreased significantly in babies receiving antenatal steroids (11.7 vs. 17.5 days). The six day reduction in hospitalization is important both in order to minimize the risk for nosocomial infection and to reduce hospital costs.

Since Liggins and Howie (14) have shown that antenatal steroids were most effective following 48 hours to 7 days of steroid administration and the effect was attenuated after 7 days, some authors have advised weekly courses of antenatal steroid administration to reduce the incidence of RDS and complications of prematurity in women who did not deliver seven days following steroid administration (23).

Ellimian et al. have shown that multiple course steroid treatment reduced the incidence of RDS and surfactant use without affecting growth and without increasing the risk for neonatal sepsis (24). In another study conducted by Pratt et al, when single and multiple course antenatal steroid treatment was compared, multiple course treatment reduced the incidence of RDS, surfactant use and the requirement for MV; although not statistically significant (25). On the contrary, in the present study, we did not show a difference in the incidence of RDS, surfactant use and need for mechanical ventilator among single and double course steroid groups.

The effect of multiple doses of antenatal steroids on birth weight is controversial. In some studies, it has been reported that repeated doses of betamethasone leads to birth weight reduction (5, 17, 26). Conversely, in the study by Guinn et al, no significant difference in birth weight has been observed with multiple courses of steroid therapy (27). In a similarly planned study, a proportional increase of on birth weight in the presence of increasing frequency of betamethasone therapy has been observed (28). We did not observe a difference in birth weight in single and double course antenatal steroid exposed groups; but the number of babies in the present study is too low to reach a conclusion on the reduction of birth weight.

Abbasi et al. (26), French et al. (17) and Crowther et al. (3) have shown that repeated dose steroid treatment not only reduces birth weight, but also leads to a reduction in head circumference. Contrarily, other studies have shown that the weight and head circumference of the babies exposed to repeated doses of antenatal steroids did not differ from the normal population both at discharge (4) and also at the age of three (17).

Belteki and Smith in their review on single and multiple doses of antenatal steroids concluded that, when compared with a single course, weekly repeated doses of antenatal steroids seem to reduce neonatal respiratory morbidity and some of its complications, especially when the delivery was before 32 weeks of gestation (28).

No significant difference has been reported between single and multiple courses of steroid therapy regarding the morbidity and mortality parameters, such as neonatal death, sepsis, IVH, NEC, BPD and PDA (27, 28, 29); similar to the results of the present study.

We conclude that single course antenatal corticosteroid therapy reduces the incidence of RDS, surfactant use, MV requirement, days on MV, duration of hospitalization and mortality; with an improvement of 5th minute Apgar score compared to non antenatal steroid exposed babies. Double course corticosteroid therapy was not superior to single course regarding complications of prematurity.

Conflict of interest

None declared

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The impact of cervical dilatation on pregnancy outcomes after cerclage placement in women with a short cervical length

Kısa serviks nedeniyle serklaj atılan kadınlarda servikal dilatasyonun gebelik sonuçları üzerine etkisi

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Abstract

Objective: The aim of the study was to compare the outcome of pregnancies with cerclage placement in which cervical length was <15 mm and 15-25 mm. We further investigated the impact of cervical dilatation on delivery at <34 weeks.

Material and Methods: Women with singleton gestations with cerclage placement due to cervical insufficiency were enrolled into the study. The data were collected prospectively between September 2004 and February 2009. We divided patients into two categories: (group I) cervical length below 15 mm, (group II) cervical length between 15-25 mm. We compared the pregnancy outcomes of the two groups and also analyzed the independent impact of cervical dilatation on delivery <34 weeks.

Results: The cervical cerclage group <15 mm had a similar incidence of preterm delivery <34 weeks gestation to the cerclage group 15-25 mm (p=0.4). No significant difference in rate of neonatal survival (p=0.6) was found between the two groups. Increased cervical dilatation in centimeters was found to be a significant predictor of delivery before 34 weeks gestation (OR: 3.4, 95% CI: 1.3-8.5, p=0.009).

Conclusions: The extent of cervical shortening did not have a significant independent effect on the perinatal outcome of patients with cerclage placement. However, the presence of cervical dilatation prior to cerclage placement in cases of cervical insufficiency may worsen perinatal outcomes by increasing the rate of delivery before 34 weeks.

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Key words: Cervical insufficiency, cerclage, pregnancy outcomes, preterm delivery

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Özet

Amaç: Bu çalışmanın amacı serviks uzunluğu <15 mm ve 15-25 mm arasında olan serklaj yapılmış gebeliklerin sonuçlarının karşılaştırılmasıdır. Ayrıca, serviks dilatasyonunun 34 haftanın altında doğum yapma üzerine etkisi araştırılmıştır.

Gereç ve Yöntemler: Bu çalışmaya serviks yetersizliği nedeniyle serklaj atılmış tekil gebeler kaydedilmiştir. Veriler Eylül 2004 ile Şubat 2009 arasında prospektif olarak toplanmıştır. Hastalar iki kategoriye ayrılmıştır: serviks uzunluğu 15 mm. nin altında olanlar (grup I), serviks uzunluğu 15–25 mm olanlar (grup II). Bu iki grubun gebelik akıbetleri karşılaştırılmış ve servikal dilatasyonun 34 haftanın altında doğum yapma üzerine bağımsız etkisi incelenmiştir.

Bulgular: Serviks uzunluğu 15 mm. nin altında serklaj yapılan olgularda 34 haftanın altında erken doğum yapma insidansı 15-25 mm de serklaj atılmış grupla benzer bulunmuştur (p=0.4). İki grup arasında yenidoğan sağkalım oranları anlamlı farklı bulunmamıştır (p=0.6). Artmış servikal dilatasyon, 34 haftanın altında doğum yapma açısından anlamlı bir belirteçtir (OR: 3.4, 95% CI: 1.3- 8.5, p=0.009).

Sonuçlar: Servikal kısalma derecesi, serklaj konulmuş hastalar için perinatal sonuçlar açısından belirgin bağımsız etkiye sahip değildir. Bununla birlikte, serviks yetersizliği olan olgularda serklaj öncesi serviks dilatasyonunun varlığı 34 haftadan önce doğum yapma oranlarını artırarak perinatal sonuçları kötüleştirebilir.

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Anahtar kelimeler: Servikal yetersizlik, serklaj, gebelik sonucu, erken doğum

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Introduction

Mid trimester miscarriage and premature delivery remain a significant cause of perinatal morbidity and mortality presenting an important challenge in perinatal medicine. Cervical incompetence is defined as the inability to support a term pregnancy because of a functional or structural defect of the cervix in which painless, progressive cervical dilatation occurrs in the second trimester and results in recurrent pregnancy loss. Placement of a cervical suture may be useful when there is cervical weakness in a woman at risk of miscarriage or premature birth. A transvaginal cervical cerclage can be inserted prophylactically before pregnancy or during the first trimester, or therapeutically after detection of progressive cervical changes during pregnancy (1). The efficacy of prophylactic and therapeutic cervical cerclage for prevention of preterm deliveries is still controversial. However, there is some evidence of a positive role for cerclage placement in women considered to be at very high risk, with more than one second trimester loss (2).

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Transvaginal ultrasound examination of the cervix can predict patients who are at risk of cervical insufficiency. Sonographic observation of shortening of the endocervical canal length, dilatation of the internal os, funneling of the fetal membranes into the endocervical canal (funnel length ≥16 mm or funneling of ≥40 percent) have been defined as sonographic signs for this obstetrical condition (3).

The purpose of the presented study was to compare the outcome of pregnancies with cerclage placement in which cervical length was <15 mm and between 15 and 25 mm. We also investigated the impact of cervical dilatation on delivery at <34 weeks as an independent prognostic factor.

Material and Methods

The study was carried out at Acibadem Hospital, Kadikoy, Istanbul, between September 2004 and February 2009. The transvaginal ultrasound follow-up of the cervix was performed during antenatal care visits of patients with a history of suggestive or suspicious cervical insufficiency, previous preterm labor, and of those with symptoms such as a feeling of pelvic pressure or increased vaginal discharge. The women were asked to empty their bladder before examination and were placed in the dorsal lithotomy position. Cervical length was measured along a closed endocervical canal. Fundal pressure was applied for 30 seconds to detect cervical shortening and funneling. The patients were considered as being at high risk for preterm delivery when the cervical length was measured as under 25 mm before 26 weeks of gestation, which is below the 10th percentile in a population delivering at term (4). We divided patients into two categories: [1] cervical length below 15 mm, which was suggested as the lowest critical value for practicing cerclage procedure (5), [2] cervical length between 15-25 mm. We also analyzed the outcome of patients with cervical dilatation with or without membrane bulging of the intact amniotic sac into the vagina. In all patients, vaginal microbiological culture and ureaplasma, mycoplasma culture investigations, vaginal pH measurement, whole blood test, and C-reactive protein assessment were performed to exclude active vaginal infection and chorioamnionitis. Patients with symptoms of clinical chorioamnionitis such as fever (temperature ≥38°C), uterine tenderness, fetal tachycardia, marked leukocytosis (≥15 nLO¹), and/or elevated C-reactive protein (≥1.5 mg/dL) were not included into the study group. Five cases were excluded from the study because of the clinical and laboratory evidence of chorioamnionitis which resulted in second trimester abortion. We performed amniocentesis and amnioreduction in cases of membrane bulging in order to diminish intraamniotic pressure and to facilitate the procedure. Leukocyte count, gram staining and amniotic fluid culture were studied to rule out intrauterine infection in these cases before cerclage placement (6, 7).

Women with multifetal gestations, significant vaginal bleeding, preterm premature rupture of the membranes or persistent uterine contractions were excluded from the study group.

Cerclage placements were performed as a single purse-string suture by using the Cervix-Set (B.Braun, Aesculap, Tutlingen), similar to the technique of Mc Donald. After placement of the cervical suture, women received 100 mg indomethacin suppository, ampicillin 1 gram intravenously every 6 hours and metronidazole 500 mg intravenously every 12 hours for 24 hours after the surgery. Patients were restricted to bed rest for 48 hours. Prophylactic tocolysis was not used. Cervical cerclage sutures were removed at 37 weeks gestation or when the membranes were ruptured.

Statistical analysis

Analysis was performed using the SPSS statistical Package for Windows 13.0 (SPSS, Chicago, IL, USA). The Chi-square test was used to compare categorical variables between the two groups. The Mann-Whitney U test was used to compare continuous variables between the two groups. Logistic regression analysis was used to identify possible predictors of pregnancy prolongation beyond 34 weeks as a dichotomous variable. Variables entered into the logistic regression model were presence or absence of previous preterm delivery, previous recurrent abortion (>2 abortions), tobacco use, infertility treatment in the present pregnancy, first trimester threatened abortion in the present pregnancy, uterine anomaly, conisation history, gestational age at cerclage placement, cerclage placement as emergency or elective, cervical length of <15mm and 15-25mm, cervical dilatation in centimeters, amniodrainage before cerclage placement (done or not done), ureaplasma, trichomonas or chlamydia isolation from the vagina. The results of logistic regression analysis are presented as odds ratio and 95% confidence interval. A *P* value <0.05 was considered to be significant.

Results

A total of 34 pregnant women with a cerclage placement after detection of short cervical length were enrolled into the study. Maternal demographic characteristics, obstetrics and gynecologic histories of the study population are presented in Table 1. Median maternal age was 29.82±4.14 (range, 23-41 years) years old. Mean gestational age at cerclage procedure was 20.38±4.18 (11.7-28) weeks. Mean cervical length at surgery was 14.61±5.93 (5-25) mm. Mean gestational age at delivery was 34.05±5.31 weeks. Mean birth weight was 2399.8±970 (210-3890) grams. Four women (11.8%) had one previous preterm birth and four (11.8%) women had >2 previous preterm birth histories. Five women (14.7%) had first trimester vaginal bleeding, three women (8.8%) were cigarette smokers and five (14.7%) had hereditary thrombophilia. Amniodrainage was performed in four cases and their amniotic fluid cultures were negative. Maternal complications such as sepsis, cervical laceration during pregnancy or at parturition did not occur.

Pregnancy prolongations beyond 34 weeks gestation occurred in 21 cases (61.7%). The mean cervical lengths for group I and group II prior to placement of the cerclage were 9.88±2.88 mm and 19.9±3.3 mm respectively. Maternal and perinatal

outcomes between the two groups were shown in Table 2. Women with cervical lengths of 15-25 mm underwent significantly earlier cerclage placement and their pregnancy was significantly prolonged when compared with those with a cervical length less than 15 mm (18±4 weeks vs. 22.5±3 weeks respectively, p=0.001 for gestational age at cerclage and 18.1±5.5 vs.10.2±6.2 respectively, p=0.001 for delayed delivery). Mean gestational age at delivery in the group whose cervical length <15 mm was 32.7±6.2 weeks of gestation which was not significantly lower than 36.1±3.48 weeks of gestation in the group whose cervical length was 15-25 mm (p=0.06), probably due to the small sample size of the study. Neonatal survival rate did not differ significantly between the groups (p=0.6). In group I, two fetal wastages were detected soon after the cerclage placement because of the preterm premature membranes ruptures. In group II, one neonatal death occurred in a homozygote Factor V Leiden mutation carrier patient complicated with preeclampsia and ablation placenta at 28 weeks gestation.

Table 1. Baseline demographic and obstetric characteristics

Characteristics	n=34
Maternal age (years)	29.82±4.14 (23-41)*
Number of prior births, n (%)	9 (26.6)
Number of prior preterm births, n (%)	8 (23.5)
Prior induced abortions, n (%)	11 (32.4)
Prior cerclage, n (%)	2 (5.8)
Cervicovaginal microbiology, n (%)	
Ureaplasma urealyticum	4 (11.8)
Chlamydia trachomatis	1 (2.9)
Trichomonas vaginalis	1 (2.9)
Gestational age at vaginal sonogram (weeks)	20.17±4.13 (11-28)*
Cervical length at vaginal sonogram (mm)	14.76±6.13 (5-25)*
Cervical length between 15-25 mm, n (%)	16 (47)
Cervical length less than 15 mm, n (%)	18 (53)
Patients with bulging membranes, n (%)	5 (14.3)

*Mean±SD (minimum-maximum)

Every centimeter increase in cervical dilatation was found to be a significant predictor of delivery before 34 weeks gestation (OR; 3.4 95% CI -1.3-8.5, p=0.009) (Table 3). We detected that there was no significant contribution of cerclage placement between cervical length <15 mm and 15-25 mm to delivery before 34 weeks gestation even with the higher incidence in group I than group II (44% (n=8/18) *vs.* 31% (n=5/16), respectively, p=0.4)

Conclusions

Sonographic cervical length measurement is an effective prognostic indicator of cervical insufficiency and preterm birth (PTB) which has been evaluated and studied up to the present. Cervical shortening is accepted as an early asymptomatic phase in the occurrence of PTB rather than as a sign of innate or acquired cervical weakness (8). A shortened cervical length can predict 61% of PTB cases, whereas the combination of cervical shortening and a history of PTB predict only an additional 4.4% cases at the same false positive rate of 5% (9).

A cervical length of less than 25 mm before 28 weeks gestation has been found to have the best predictive accuracy for PTB in most populations (8). Owen et al. concluded that the overall sensitivity, specificity and positive predictive value for preterm birth were 69, 80 and 55 percent respectively when the optimum threshold for cervical length was considered below 25 mm (10). A recent metaanalysis by Berghella et al. demonstrated that cerclage does not prevent preterm birth in all women with a short cervix, but they detected a significant reduction in preterm birth <35 weeks in the subgroup of patients with a cervical length of <25 mm before 24 weeks gestation only if they had a prior PTB. Interestingly, this significance was lost in the subgroup of patients with cervical length <15 mm (11). More recently, reports of a multicenter randomized trial demonstrated that pre-viable birth rates less than 24 weeks occurred in 14% of the no-cerclage group vs 6.1% of the cerclage group (p=0.03), and perinatal mortality reduction was statically significant in the cerclage group, but cerclage did not prevent birth after less than 35 weeks of gestation unless the cervical length was less than 15 mm (12).

In the presented study, the prevalence of PTB before 34 weeks of gestation increased significantly with increased cervical dilatation. Women with a cervical length of 15-25

Table 2. Delivery outcomes between cervical length <15 mm and 15-25 mm groups

Variables	Group I Cervical length <15 mm	Group II Cervical length 15-25 mm	P value
Gestational age at cerclage placement (weeks)	22.5±3	18±4	0.001
Gestational age at delivery (weeks)	32.7±6.2	36.1±3.4	0.06
Delayed delivery (weeks)	10.2±6.2	18.1±5.5	0.001
Fetal body weight at delivery (gram)	2123±1083 (210-3890)	2710±738 (870-3615)	0.1
Delivery rate <34 weeks	8/18 (44%)	5/16 (31%)	0.4
Neonatal surveillance	16/18 (88.9%)	15/16 (93.8%)	0.6

Table 3. Characteristic of patients delivered before 34 weeks gestation

Variables	Odds ratio	95% CI	p value*
Cervical length <15 mm	0.26	0.01-5.3	0.38
Cervical dilatation in cm	3.4	1.3-8.5	0.009
Previous preterm birth	0.8	0.2-3.8	0.8
Previous second trimester abortion	1.2	0.3-4.5	0.7
*Delivery <34 weeks gestation			

mm underwent earlier cerclage placement when compared with those less than 15 mm. Although there was no significant difference in the rate of the PTB prior to 34 weeks, mean gestational age at delivery and pregnancy prolongation were higher in women with a cervical length of 15-25 mm. Neither obstetrical and gynecological history nor cervical length was found to have a significant impact on the effect of cerclage on PTB before 34 weeks. The limitation of our study is the small sample size and interobserver and even intraobserver variability of cervical dilatation evaluations by manual examination. As cervical effacement and dilatation first occur at the level of the internal os which cannot be assessed by the manual vaginal examination, transvaginal ultrasound screening of the cervical length is an important strategy for preventing PTB regardless of the underlying cause (13). Fox et al. studied the additional benefit of serial follow-up measurement of the cervical length in patients already diagnosed with a short cervix. They concluded that patients with an unstable cervix, that is, shortening over time delivered earlier when compared with short but stable cervix (14). On the other hand, weekly or biweekly transvaginal ultrasound follow-up of the short cervix between 16 and 24 weeks gestation may result in acute cervical insufficiency in high-risk patients. If cerclage could be placed before exposure of the membranes, there is a greater opportunity to reinforce the cervical barrier and prevent irreversible cervical changes (5). Positive fetal fibronectin test results and/or increased interleukin-8 levels in the cervical mucus could be a marker for procedure failure in these cases. Cerclage may be used for patients with a high-risk obstetric history when the cervical length is detected as <25 mm before the development of cervical dilatation.

We choose 15 mm as an alternate cutoff to introduce the benefit of the cerclage procedure when the cervical length is very short. In our study, women whose transvaginal cervical length was less than 15 mm delivered earlier and presented more frequently with acute cervical insufficiency. Since the emergency cerclage had the poorest obstetrical outcomes with a high rate of chorioamnionitis and PPROM (6), these cases may have benefitted from earlier cerclage procedure. On the other hand, operative management for emergency cases with membranes bulging significantly improves perinatal outcomes when compared to the conservative treatment modalities such as bed rest and/or tocolysis (15, 16).

Although the cervical length is important, absence of the cervical dilatation prior to cerclage placement in cases of cervical insufficiency may improve perinatal outcomes by increasing delivery rate after 34 weeks. Larger numbers of patients and prospective randomized trials are needed to verify our findings.

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Conflict of interest

None declared

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Claudin and ovarian cancer

Klaudin ve over kanseri

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Abstract

Claudins are a family of proteins and the most important component of the tight junction. They constitute a paracellular barrier that controls the flow of molecules in the intercellular space of an epithelium. Although it seems that claudin should be down regulated in cancer cell, some claudins are, in fact highly elevated in various human cancers, including ovarian cancer. Whereas the functional significance of claudin overexpression in ovarian carcinoma is unclear, these proteins are important for migration, invasion, and survival of ovarian cancer cells. They clearly represent a general pathway in tumorigenesis, are a novel marker for ovarian cancer and may become a target for therapy or diagnosis of this disease.

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Özet

Klaudinler bir protein ailesidir ve konneksonların en önemli üyeleridir. Moleküllerin epitelin hücrelerarası boşluğuna geçmesini kontrol eden bir engel oluştururlar. Klaudinlerin kanser olgularında azalması beklenirken bazı klaudinler ise over kanserini de içeren farklı insan kanserlerinde yüksek oranlarda artmıştır. Bu proteinlerin over kanserlerinde artmış bulunmasının fonksiyonel önemi bilinmemekle birlikte bu proteinler migrasyon, invazyon ve over kanserlerinin hayatta kalaması için önemlidir. Tümör oluşumunda genel bir yolu temsil ettiklerinden over kanserleri için yeni bir belirteçtirler ve bu hastalığın tanı ve tedavisinde yeni bir hedef olmaya adaydırlar.

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Introduction

Claudins are 20-27 kDa transmembrane proteins spanning the cellular membrane 4 times, with the N-terminal end and the C-terminal end both located in the cytoplasm, and two extracellular loops which show the highest degree of conservation. The first extracellular loop consists on average of 53 amino acids and the second one, being slightly smaller, of 24 amino acids. The N-terminal end is usually very short (4-10 amino acids), the C-terminal end varies in length from 21 to 63 and is necessary for the localisation of these proteins in the tight junctions. It is suspected that the cysteines of individual or separate claudins form disulfide bonds. All human claudins (with the exception of Claudin 12) have domains that let them bind to PDZ domains of scaffold proteins.

Work from several groups has now confirmed the over expression of these proteins in ovarian cancer. To find the subtypes based on a specific marker is a lucrative idea in diagnosis and specific managements including targeting and prognosis, such as ER, PR and HER *neu* in breast cancer, cyclin D and some translocations in leukemias. Ovarian cancer is a killer disease of unknown aetiology. It is detected late and has no good treatment. So, effort is concentrated on the use of claudin for diagnosis and target of therapy in ovarian cancer. It is worthwhile to study claudin in detail to know its significance in ovarian cancer.

Tight junction

Specialized intercellular junctions, known as desmosomes and terminal bars were recognized as local modifications of the surface of adjacent yet separate cells, rather than as intercellular bridges (1,2) with an effect on cell-to-cell adhesion and epithelial permeability.

In the nineties, mammalian intercellular junctions were described and were categorized into four types: adherens junctions (AJ), desmosomes (DS), gap junctions (GJ), and tight junctions (TJ) (3). The major integral membrane proteins in AJ are glycoprotein, cadherins. The desmosomal integral membrane proteins are called desmogleins and desmocollins ,similar in amino acid sequence to cadherins, and they fall into the cadherin superfamily. The integral membrane protein in GJ is a dense aggregation of multimeric channels, each of which consists of six identical proteins named connexins. TJ is an element of the epithelial and endothelial junctional complex. It seals cells to create the primary barrier to the diffusion of solutes through the paracellular pathway. It also works as a boundary between the apical and basolateral plasma membrane domains to create the polarization of epithelial and endothelial cells. It remains controversial whether the particles in the strands of TJ are predominantly lipidic in nature. However, detergent stability of TJ strands as

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visualized by negative staining and freeze fracture proves that these elements are not composed solely of lipids

Tight junctions, together with adherens junctions and desmosomes, form the apical junctional complex in epithelial and endothelial cellular sheets. Adherens junctions and desmosomes are responsible for the mechanical adhesion between adjacent cells, whereas tight junctions are essential for the tight sealing of the cellular sheets, thus controlling paracellular ion flux and therefore maintaining tissue homeostasis. Tight junctions also play a crucial role in the maintenance of cell polarity by forming a fence that prevents lateral diffusion of membrane proteins and lipids, thereby maintaining the differential composition of the apical and basolateral domains.

Occludin

In the late nineties, ZO-1, a tight junction-associated protein, was derived from chick liver. This protein was not extractable from plasma membranes without detergent, suggesting that it is an integral membrane protein. When its cDNA was cloned and sequenced a new 504-amino acid, 55.9 kDa polypeptide with a hydrophilicity plot very similar to that of connexin was found. A search of the data base identified no proteins with significant homology to this membrane protein. Furuse et al. (3) designated this integral membrane protein localizing at tight junctions as "occludin."

Claudin

Identification of claudin was regarded as the Holy Grail in this field. Although successive studies emphasized the importance of occludin in the structure and functions of TJs, it gradually became clear that the molecular architecture of TJ strands is more complex than expected. Especially, the fact that the occludin-deficient visceral endoderm cells still bear a well developed network of TJ strands indicated that membrane proteins or lipid molecules as yet unidentified may constitute TJ strands (4). Another two distinct peptide sequences of 211 and 230 amino acids of about 22-kD were obtained in a similar experiment on chick liver. Hydrophilicity analysis suggested that both bore four transmembrane domains (Fig.1), although they did not show any sequence similarity to occludin. Immunofluorescence and immunoelectron microscopy revealed that both proteins were targeted to and incorporated into the TJ strand itself. Furuse et al. (3) designated them as "claudin-1" and "claudin-2", respectively (12). Gradually in humans, 23 members of the family have been described.

Claudin Expression in Cancer

Decreased tight junction protein expression in cancer is consistent with the generally accepted idea that tumorigenesis is accompanied by a disruption of tight junctions, a process that may play an important role in the loss of cohesion, invasiveness, and lack of differentiation observed in cancer cells. Down-regulation of both occludin (in gastrointestinal tumors) and claudins (in breast cancer, gastric cancer as well as in colon cancer) is noticed in cancer. Claudin-7 is down-regulated in invasive breast cancer (and in head and neck cancer). Likewise, expression of claudin-4 in pancreatic cancer cells reduces invasiveness of these cells. Phosphorylation of tight junction proteins, including claudins, may also disrupt tight junction function in cancer[5]. Claudins down regulated are listed in Table 1.

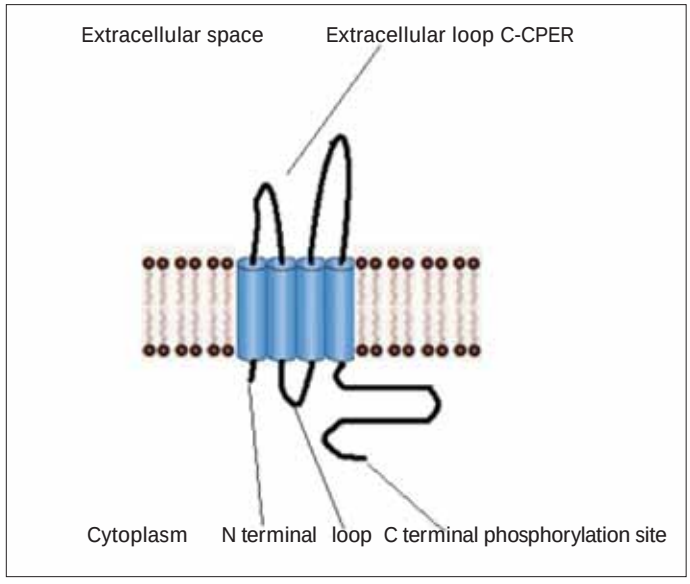

Figure 1. Claudins with four transmembrane domains. The extracellular loops target for therapy. The C-terminal is PDZ binding domain

Table 1. Down regulated claudins in various cancers

Cancer	Claudin gene	Expression	References
Breast	CLDN1	Down	7
	CLDN7	Down	8
	CLDN1, CLDN3, CLDN4	Variable	9
Breast and Paget's disease	CLDN2, CLDN3, CLDN4, CLDN5	Variable	10
Colon	CLDN1	Variable	11
Gastric	CLDN4	Down	12

Paradox

Many claudins, such as claudin-3 and claudin-4, are typically up-regulated in many cancers, suggesting that these proteins may have a positive effect on tumorigenesis. Recent work has shown that, in ovarian cells, expression of claudin-3 and claudin-4 may lead to an increase in invasion, motility, and cell survival, all characteristics important for metastasis. This was observed in advanced ovarian cancer but not in ovarian cystadenomas. Therefore, the functions of claudins may be highly tissue specific and may depend on the exact molecular circuitry of the cell. In addition, claudin-3 and claudin-4 have also been reported to be expressed in other cancers, such as breast, prostate, and pancreatic cancers. The overwhelming majority of studies published thus far report an overexpression of many claudins in various cancers (Table 2).

Thus, recent reports suggest that we may lack a full vision of the functional complexity of claudins and their possible functional connection to a larger protein family. Database searching reveals a large number of proteins with structural similarities to claudins but whose functional similarities remain largely unexplored. There was a lack of consistent nomenclature. Before their naming in 1998, three of the orthodox claudins had already been cloned and given other names and were characterized by nonbarrier functions.

All are not barrier-forming claudins, neither is it known if they have involvement in apoptosis and proliferation. Several orthodox claudins are not restricted to tight junctions; claudin-7, for example, is on the basolateral surface of cells in the kidney tubule epithelium. Many other claudins have large pools of protein on the lateral surface distinct from the barrier-forming TJ strands. The role and organization of extrajunctional claudin remain unclear. Even more enigmatic is the inclusion in the pfam0082 family of some subunits of voltage dependent calcium channels. Cytokines such as tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ) can modulate claudin. Moreover, claudins play a significant role in some autoimmune and hereditary diseases such as inflammatory bowel disease, hereditary deafness, multiple sclerosis, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), diabetic retinopathy etc (31). It seems that not only tissue specificity but inflammatory and immunological conditions prevail, and variation of the functions of claudins may be responsible for a contradictory expression of claudins in many cancer.

Claudin and Ovarian Cancer

To date, research on claudin in ovarian cancer has been both on a basic and clinical level. Basic research involing cell line or animal experiments include a) detection of expression of many claudins b) exploring the mechanism of gene expression, methylation status, epigenetic study, influence of gonadotrophin and metabolic pathways like phospholyration etc. In clinical research this effort is mainly limited to observation of tissue expressions of claudin in snap frozen or archival specimen for diagnosis and targeting by Clostridium perfringens enterotoxin, lipidoid siRNA etc.

Table 2. Up regulated claudins in various cancers

Cancer	Claudin gene	Expression	References
Breast	CLDN3	Up	13
	CLDN4	Up	13
Hepatocellular carcinoma	CLDN10	Up	14
Squamous cell carcinoma	CLDN1	Up	15
	CLDN4	Up	15
Ovarian	CLDN3	Up	16,17, 18, 19
	CLDN4	Up	16, 18, 19
	CLDN16	Up	20
Pancreatic	CLDN4	Up	21, 22,23,24
Pancreatic (intraductal papillary mucinous neoplasms)	CLDN4	Up	25
	CLDN18.2	Up	
Prostate	CLDN3	Up	26
	CLDN4	Up	26
Thyroid papillary cancer	CLDN10	Up	27
Endometrial Cancer	CLDN4	Up	28
Oesophageal tumour	CLDN18.2	Up	29
non-small cell lung cancer: Squamous cell carcinoma	CLDN1	Up	30
Adenocarcinoma	CLDN4	Up	30
	CLDN5	Up	

1. Important basic researches

Serial analysis of gene expression (SAGE) was used to generate global gene expression profiles from various ovarian cell lines and tissues, including primary cancers and ovarian surface epithelia cells, in archival material and cystadenoma cells (16) This showed upregulation of claudin-3 and claudin-4 gene and this was further validated through immunohistochemical analysis. It was only in the previous year that SAGE had detected the tag for the *Claudin-7* gene 12 times in the tumor cell lines for the first time, whereas no *Claudin-7* tags were found in the normal breast cultures (32). The earlier group tried to account for the significance of its upregulation. Although *CLDN4* overexpression is well established, the mechanisms responsible for this abnormal regulation remain unknown. In a study, they delineated a small region of the *CLDN4* promoter critical for its expression. This region contains two Sp1 sites, both of which are required for promoter activity. However, because of the ubiquitous expression of Sp1, these sites, although necessary, are not sufficient to explain the patterns of *CLDN4* gene expression in various ovarian tissues. *CLDN4* promoter is further controlled by epigenetic modifications of the Sp1-containing critical promoter region. Cells that overexpress *CLDN4* exhibit low DNA methylation and high histone H3 acetylation of the critical *CLDN4* promoter region, and the reverse is observed in cells that do not express *CLDN4*. Moreover, the *CLDN4*-negative cells can be induced to express *CLDN4* through treatment with demethylating and/or acetylating agents. Because *CLDN4* is elevated in a large fraction of ovarian cancer, they opined that the mechanism leading to deregulation may represent a general pathway in ovarian tumorigenesis and may lead to novel strategies for therapy and an overall better understanding of the biology of this disease (33).

In a recent phophorylation study, analyses using PKC inhibitors, siRNA and immunofluorescence have shown that PKC-epsilon, an isoform typically expressed in ovarian cancer cells, may be important in the TPA-mediated claudin-4 phosphorylation and weakening of the TJs (34). In *CLDN3* promoter it was possible to identify a minimal region containing a Sp1 site crucial for its activity (35). In addition, this group found that the *CLDN3* promoter is regulated through epigenetic processes as in *CLDN4*. Interestingly, in vitro binding experiments, as well as chip assays show that Sp1 binds the unmethylated promoter much more efficiently, providing a mechanism for *CLDN3* silencing in non-expressing cells. siRNA-mediated knockdown of Sp1 led to a significant decrease of *CLDN3* expression at both the mRNA and protein levels, demonstrating a crucial role for this transcription factor in the regulation of *CLDN3* (36).

Animal experiments from Canada showed that, in the absence of FSH-R signaling, claudin-3, claudin-4, and claudin-11 are selectively upregulated, whereas claudin-1 decreases in ovarian surface epithelium. In vitro experiments using a mouse ovarian surface epithelial cell line derived from wild-type females reveal a direct hormonal influence on claudin proteins. Although recent studies suggest that cell junction proteins are differentially expressed in ovarian tumors in women, the etiology of such changes remains unclear. They suggest an altered hormonal environment resulting from FSH-R loss as a cause of early changes in tight junction proteins that predispose the ovary to late-onset tumors that occur with aging (36).

2. Clinical research

a) Diagnosing ovarian cancer, tissue marker

The result of the SAGE study on ovarian cancer was established in a detailed analysis of *CLDN3* and *CLDN4* expression in a panel of ovarian tumors of various subtypes and cell lines. RNA was obtained from a panel of 39 microdissected epithelial ovarian tumors of various histological subtypes for real-time reverse transcription-PCR analysis. In addition, a total of 70 cases of ovarian carcinomas, ovarian cysts, and normal ovarian epithelium from a tissue array were analyzed and validated by immunohistochemistry (21).

Affymetrix human genome arrays (U95 series) was utilized to analyze differences in gene expression of 41,441 known genes and expressed sequence tags between five pools of normal ovarian surface epithelial cells (OSE) and 42 epithelial ovarian cancers of different stages, grades, and histotypes (17). The 3-fold up-regulated genes were analyzed using recursive descent plot analysis (RDPA), and the combination of elevated claudin 3 gene (*CLDN3*) and elevated *VEGF* distinguished the cancers from normal OSE. A combination of CLDN3, of CA125, and MUC1 (mucin-1 transmembrane) stained 99.4% of 158 cancers, and all of the tumors were detected with a combination of CLDN3, CA125, MUC1, and VEGF. Thus, a limited number of markers in combination might identify >99% of epithelial ovarian cancers despite the heterogeneity of the disease.

Total RNA was extracted and transcription profiling performed in another experiment (37) using the Eos Hu03, a customized Affymetrix GeneChip oligonucleotide microarray (Affymetrix, Santa Clara, CA). The expression patterns of three integral membrane proteins, discoidin domain receptor 1 (DDR1), claudin 3 (CLDN3), and epithelial cell adhesion molecule, all of which are involved in cell adhesion, were evaluated in a cohort of 158 primary EOC using immunohistochemistry identifying DDR1 and CLDN3 as new biomarkers of EOC. Two other DNA microarray affymetrix study results corroborated claudin 3 and 4 gene overexpression in ovarian cancer. They used Hierarchical clustering of the expression data and Youden's misclassification index for each gene marker via pairwise tissue comparisons respectively (18, 19).

No new claudins were implicated with ovarian cancer in 2005. The Professor Bast Jr. group, in search of potential markers that complement expression of CA125 in epithelial ovarian cancer, included claudin 3 with at least ten other markers at the level of tissue expression (38).

In 2006 it was substantiated by both Swedish and Italian groups that both claudin 3 and 4, even though they differ in expression during ovarian malignant transformation, might be used as novel markers for ovarian tumours (39,40). In another experiment, strong expression of claudins 1, 4, and 7 was seen in benign and malignant epithelial ovarian tumors. Expression of claudin 5, reported to be mainly present in endothelial cells, was seen in ovarian epithelial tumors, but with a significantly lower frequency than claudins 1, 4, and 7. On the contrary, sex-cord stromal tumors and cysts, such as fibromas/thecomas, Sertoli-Leydig cell tumors, granulosa cell tumors, and follicular and luteinized cysts were mainly negative for claudins 1, 4, 5, and 7 (41). Ovarian/primary peritoneal serous carcinoma (OC/PPC) and diffuse peritoneal malignant mesothelioma (DMPM) are highly aggressive tumors. Claudins 3, 4, and 6 overexpression

was noticed in them (42). Claudin 4 was among few proteins whose expression profiles correlated with cisplatin resistance in ovarian cancer cells. Several proteins may be involved in modulating response to cisplatin and have a potential as markers of treatment response or treatment targets (43).

Expression of claudin-3 or claudin-7 is specific for adenocarcinoma and rules out the diagnosis of cells as mesothelial and the absence of claudin-1 expression excludes ovarian carcinoma as the possible origin of metastatic adenocarcinoma. Claudins may, therefore, be of diagnostic value in biopsy and effusion cytology (44).

Kaplan-Meier survival analysis showed that serous ovarian adenocarcinoma patients with high CLDN3 expression had a substantially shorter survival (P=0.027). Multivariate analysis demonstrated that CLDN3 overexpression is an independent negative prognostic factor (45). Expression for all cell-junction proteins with a typical honeycomb-staining pattern in the serous adenocarcinomas and not Clear-cell and endometrioid adenocarcinomas prove that Serous adenocarcinomas form functional TJs in vitro (46).

CLDN-7 transcript was found significantly overexpressed in both primary and metastatic EOCs compared to normal human ovarian surface epithelium cell lines (fold change=111.4, P<0.001) by reverse transcription-polymerase chain reaction, regardless of the histologic type, the grade of differentiation, and the pathologic stage of the disease (47). Moreover, a strong immunoreactivity for *CLDN-7* was detected in EOC cells present in ascites fluids, whereas ascites-derived inflammatory cells, histiocytes, and reactive mesothelial cells were negative. With the exception of claudin-4, claudins are upregulated in OC effusions compared with solid tumors, in agreement with previous data for cadherins and integrins in this cancer type, suggesting a prosurvival role for these surface molecules. Claudin-3 and claudin-7 expression in effusions independently predicts poor survival in OC (48).

Increased expression of claudin-3 and claudin-4 may contribute to the aggressive phenotype of endometrial cancer of serous papillary or clear-cell histology also and suggests their potential utility as diagnostic biomarkers and possible targets for therapeutic intervention (28).

b) Targeting claudin for therapy

Clostridium perfringens enterotoxin receptor

The peptide toxin Clostridium perfringens enterotoxin (CPE) has been shown to bind to claudin-3 and -4, but not to claudin-1 or -2 (49). Claudin-1/claudin-3 chimeric molecules showed that the second extracellular loop of claudin-3 conferred CPE sensitivity on L fibroblasts. The second extracellular loop is the site through which claudin-3 interacts with CPE on the cell surface.

Claudins 3 and 4 have been described as the low- and high-affinity receptors, respectively, for the cytotoxic Clostridium perfringens enterotoxin (CPE) (50). Their sensitivity to CPE treatment was seen in vitro when 100% (17 of 17) of the primary ovarian tumors tested overexpressed one or both CPE receptors by quantitative reverse transcription-PCR. All ovarian tumors showed a dose-dependent cytotoxic effect to CPE in vitro. All primary ovarian tumors tested died within 24 hours of exposure to 3.3 microg/mL CPE in vitro. CPE therapy in SCID mouse xenografts in a highly relevant clinical model of chemotherapy-resistant freshly explanted human ovarian cancer (i.e., OVA-1) showed that multiple i.p. administration of sublethal doses of CPE every 3 days significantly inhibited tumor growth in 100% of mice harboring 1 week established OVA-1. Claudin-4 overexpression in epithelial ovarian cancer (EOC) does not correlate with survival or other clinical endpoints and was found to be associated with hypomethylation. Claudin-4 overexpression correlates with Rb and C-CPE. Treatment of EOC cells with C-CPE significantly decreased Rb in a dose- and claudin-4-dependent noncytotoxic manner. Thus, C-CPE treatment of EOC cells may lead to altered TJ function induced cytotoxicity, (51) and hence is a therapeutic measure.

Pan-cancer target

CLDN18.2 is retained on malignant transformation and is expressed in a significant proportion of primary gastric cancers and the metastases thereof. In addition, its orthotopic expression was found in pancreatic, esophageal, ovarian, and lung tumors, correlating with distinct histologic subtypes. The activation of CLDN18.2 depends on the binding of the transcription factor cyclic AMP-responsive element binding protein to its unmethylated consensus site. Most importantly, it was possible to raise monoclonal antibodies that bind to CLDN18.2. Its highly restricted expression pattern in normal tissues, its frequent ectopic activation in a diversity of human cancers, and the ability to specifically target this molecule at the cell surface of tumor cells, qualify CLDN18.2 as a novel, highly attractive pan-cancer target for the antibody therapy of epithelial tumors including ovarian cancer (52).

Claudin-3 gene silencing with siRNA

In a recent US study (53), intratumoral injection of lipidoid/*CLDN3* siRNA into OVCAR-3 xenografts resulted in dramatic silencing of *CLDN3*, significant reduction in cell proliferation, reduction in tumor growth, and a significant increase in the number of apoptotic cells. Intraperitoneal injection of lipidoid-formulated *CLDN3* siRNA resulted in a substantial reduction in tumor burden in MISIIR/TAg transgenic mice and mice bearing tumors derived from mouse ovarian surface epithelial cells. It has been reported that CLDN3 is expressed at very low levels in several normal tissues in humans including the lungs, kidneys, breast, uterus, pancreas, and thyroid. Colon, small bowel, and prostate are the only normal tissues that show appreciable expression. An i.p. administration of CLDN3 siRNA formulations may reduce the concern of adverse effects of silencing CLDN3 in healthy tissues that reside outside the peritoneum. Lipidoid-formulated *CLDN3* siRNA has potential as a therapeutic agent for ovarian cancer.

Disruption of TJs

The C terminus of claudin-3 was seen to be an excellent substrate for cAMP-dependent protein kinase (PKA) at threonine 192. Overexpression of the protein containing a T192D mutation, mimicking the phosphorylated state, resulted in a decrease in TJ strength in ovarian cancer cell line OVCA433. This may provide a mechanism for the disruption of TJs in this cancer causing cytotoxicity (54). Another report showed that the claudin-expressing ovarian epithelial cells were found to have increased matrix metalloproteinase-2 (MMP-2) activity indicating that claudin-mediated increased invasion might be mediated through the activation of MMP proteins. However,

siRNA inactivation of claudins in ovarian cancer cell lines did not have a significant effect on the high endogenous MMP-2 activity present in these cells, showing that malignant cells have alternative or additional pathways to fully activate MMP-2 (55).

Claudin crosstalk

Gene expression mediated by the promoter of claudin-2 may be regulated by factors involved in Wnt signaling (56). Moreover, a functional crosstalk between Wnt signaling and transcriptional activation related to caudal-related homeobox (Cdx) proteins could be demonstrated in the regulation of claudin-2 promoter-mediated gene expression.

Although formed by different molecules, tight junctions (TJs) and adherens junctions (AJs) are functionally and structurally linked, but the signalling pathways behind this interaction are unknown. A cell-specific mechanism of crosstalk between these two types of structure was shown when endothelial VE-cadherin at AJs upregulated the gene encoding the TJ adhesive protein claudin-5 (57). This effect required the release of the inhibitory activity of forkhead box factor FoxO1 and the Tcf-4-beta-catenin transcriptional repressor complex. Vascular endothelial (VE)-cadherin acts by inducing the phosphorylation of FoxO1 through Akt activation and by limiting the translocation of beta-catenin to the nucleus. These results offer a molecular basis for the link between AJs and TJs and explain why VE-cadherin inhibition may cause a marked increase in permeability. These findings might have bearing in ovarian cancer.

Conclusion

Unusual expression patterns of claudins suggest an utility for detection, diagnosis, and treatment of drug-resistant cancers. Hopefully, new experiments will pave the way for proper utilization of knowledge already gathered to the benefit of advancement in management of many diseases, including ovarian cancer. However, clinical trials will be required to establish these potentials. Until then, the interesting nature of the subject, and need for basic and clinical research on claudins cannot be overemphasized as claudin is likely to remain valuable for providing important insights into normal and neoplastic cellular physiology. The paradox of the findings has to be solved, and diagnosis and targeting has to be established in future.

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Conflict of interest

None declared

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Pregnancy achieved by transfer of thawed day 3 embryos that had been frozen after assisted hatching: a case report

Parsiyel zona disseksiyonu sonrası dondurulmuş 3. gün embryo transferindeki başarılı gebelik: olgu sunumu

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Abstract

Assisted Hatching (AH) is performed to increase implantation rates in assisted reproductive techniques, especially recurrent implantation failure and older age group. AH can be performed to four different techniques as laser, mechanical, enzymatic, chemical methods. In the literature, there is limited data about embryo freezing after AH. Herein, a successful pregnancy, which was achieved by transfer of thawed 3rd day embryos that had been frozen after AH, is presented.
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Key words: Assisted Hatching, Embryo Thawing, IVF

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Özet

Parsiyel Zona Disseksiyonu (PZD), yardımcı üreme tekniklerinde implantasyonu artırmak amacıyla özellikle tekrarlayan implantasyon başarısızlıklarında ve ileri yaş IVF/ICSI sikluslarında gebelik oranını artırmak amacıyla uygulanmaktadır. PZD lazer, mekanik, enzimatik ve kimyasal olarak farklı metodlarla uygulanmaktadır. PZD sonrası embryo dondurma ile ilgili bilgiler literatürde sınırlıdır. PZD sonrası dondurulmuş 3. gün embryoların, çözülmesi sonrası transferinde sağlanan gebelik, bir olgu olarak sunulmuştur.
(J Turkish-German Gynecol Assoc 2010; 11: 55-7)

Anahtar kelimeler: Parsiyel Zona Disseksiyonu, Embryo Çözme, IVF

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Introduction

The clinical application of assisted hatching (AH) has been proposed as one approach toward the enhancement of implantation and pregnancy rates following in vitro fertilization (IVF). Investigators postulated that the opening of the zona might enhance the subsequent hatching process. Assisted hatching may be clinically useful in patients with a poor prognosis, including those with 2 failed IVF cycles and poor embryo quality and older women (38 years of age) (1-2). The assisted hatching procedure is generally performed on day 3 after fertilization using various methods. These include the creation of an opening in the zona either by drilling with acidified Tyrode's solution (3, 4), PZD (partiall zona dissection) with a glass microneedle (Figure 1) (5), laser photoablation (6). In the literature, there is limited data about embryo freezing after AH. Herein, a successful pregnancy achieved by transfer of thawed 3rd day embryos that had been frozen after AH, is presented.

Case

A 24 year-old G0, P0 woman was admitted to the Baskent University Department of Obstetrics and Gynecology, Division of Reproductive Medicine and IVF Unit with 6 years infertility. On the assessment of the patient; the basal ultrasonographic findings showed that bilateral ovaries had 5-6 antral follicles, third day hormonal parameters were within the normal range (FSH: 5.4 IU/ml, LH: 4.3 IU/ml, E2: 35 pg/ml). For the evaluation of the endometrial cavity, sonohysterography has been performed which has revealed regular endometrium. Her hysterosalpingography revealed a normal uterus with bilateral patent tubes. Sperm analysis was as follows: sperm count: 1.200.000/ml (2 ml) and motility A: 0%, B:5%, C: 5% D: 0%. Another 3 sperm analyses were similar.

The patient was scheduled to the IVF/ICSI program with the diagnosis of severe oligoasthenospermia. Ovarian down regulation was initiated with daily leuprolide acetate 1 mg (Lucrin, Abbott, France), beginning on the 2st day of the preceding menstruation. After ovarian suppression was achieved, the dose was then reduced to 0,5 mg and ovarian stimulation was started using 150 IU of recombinant FSH (Gonal-F, Serono, Randolph, MA, USA) which was increased on the 5th day of stimulation to 225 IU. On the 10th day of stimulation she received 10000 IU of hCG. She had transvaginal oocyte retrieval of 8 oocytes of which 8 were mature, and underwent ICSI resulting in 6 cleaving embryos.

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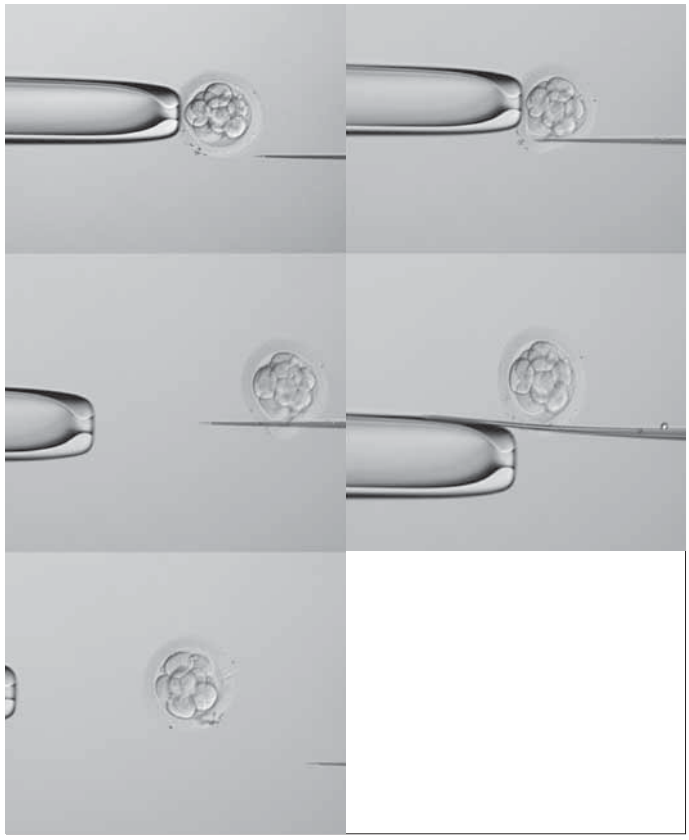

Figure 1. Representative Pictures of Assisted Hatching Procedures

Seventy-two hours after oocyte retrieval, the patient was called for embryo transfer. Three embryos were selected for transfer. During embryo selection, all embryos had thicker zona pellucida and poor embryo quality. Thereafter, assisted hatching was performed mechanically via inverted microscope with a micromanuplator before the transfer. While cervical mucus cleaning was being performed, pelvic ultrasonography showed endometrial fluid. Before embryo transfer, transfer catheter was inserted into the uterine cavity to aspirate endometrial fluid, which was purulent. Endometrial purulent fluid was cultured. Embryo transfer was postponed and embryos which assisted hatching had been performed were frozen via slow freezing.

The patient was hospitalized for antibiotic therapy. Gentamycine 2 mg/kg loading dose and 1,5 mg/kg maintenance dose together with clindamycine 900 mg tid were administered to the patient. Before antibiotics, the patient had pelvic discomfort which had been assumed to be due to oocyte retrieval. The patient's pelvic pain was relieved and her CRP and leucocytosis regressed to the normal range after antibiotherapy. Interestingly, the patient had no fever. She was discharged with oral metranidazole 500 mg bid with doxycycline 200 mg bid for two weeks.

Two months later, she was prepared for the thawing cycle, with ovarian down regulation starting with daily leuprolide acetate 1 mg (Lucrin, Abbott, France), beginning on the 21st day of the preceding menstruation. The endometrium was prepared with 2 mg/d estradiol valerate (Cyclo-Progynova tb, SCHERING) together with a transdermal patch containing 100μgr estradiol (Estraderm TTS, Novartis). The endometrial pattern was monitored with serial ultrasonography. After support with progesterone to the endometrium (Progestan kapsul, Koçak Farma), on the 16th day of the cycle, 3 embryos which had not degenerated were thawed. After embryo transfer, the luteal phase was supported by intravaginal 90 mg progesterone daily (Crinone 8% gel, Serono). 10 days after transfer, the first β HCG was 80 IU and doubling of hCG was observed 2 days later. Pregnancy was confirmed by visualization of single fetal cardiac activity appropriate to 6 weeks of gestation. The patient was delivered via caesarian section at the end of 32 weeks due to severe preeclampsia. A 1950 gr male baby was born with a 10 APGAR score. The patient was discharged on the second post-operative day. The newborn was discharged 15 days after admission to the neonatal intensive care unit.

Discussion

The assisted hatching procedure is generally performed on day 3 after fertilization using various methods with similar success rates (7). Transfer of frozen-thawed blastocysts which underwent quarter laser-assisted hatching on day 3 of the cleaving stage before freezing was previously reported in the literature (8). Herein, we presented the first case report of a successful pregnancy achieved by transfer of thawed day 3 embryos that had been frozen after AH. In this case, we performed AH to 3 selected embryos due to poor embryo quality and thick zona pellucida. Endometrial fluid visualized through ultrasonography during ovarian stimulation in IVF cycles impairs the outcome (9). On the day of embryo transfer, pelvic ultrasonography revealed a collection of endometrial fluid with absence of any symptoms of pelvic inflammatory disease. After endometrial aspiration, the presence of purulent endometrial fluid obligated us to freeze the selected poor embryos on which AH had already been performed. Although we hesitated to freeze day 3 embryos on which AH had been performed due to the risk of embryo degeneration of freezing and scarce literature, a relative good quality of thawed embryos and a successful pregnancy after thawing cycle was optimizing and interesting.

The assisted hatching procedure may be associated with specific complications independent of the IVF procedure itself, including lethal damage to the embryo and damage to individual blastomeres, with reduction of embryo viability. In addition, artificial manipulation of the zona pellucida has been associated with an increased risk of monozygotic twinning (10, 11).

This case shows that AH might have no risk for embryos if freezing is planned or obligated. The implantation and success of transfer of frozen-thawed day 3 embryos on which AH had been performed could be debated, whereas, this case report might open a horizon for further considerations.

Conflict of interest
None declared

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Angiomyxoma: a rare tumor of the umbilical cord

Anjiyomiksoma: Umbilikal kordun nadir bir tümörü

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Abstract

Tumors of the umbilical cord are rare anomalies and should be considered when using prenatal ultrasound for detection of cystic lesions. Differential diagnosis of umbilical cord tumors should comprise umbilical cord teratoma, hemangioma and angiomyxoma. It can also be an umbilical cord polyp, umbilical cord cyst, hernia into the cord and omphalocele, which are mostly isolated findings, except omphalocele. Angiomyxoma is a rare tumor of the umbilical cord and is associated with incresaed perinatal morbidity and mortality. We present a 22-year-old woman with a large umbilical cord tumor who underwent a caesarean section. As in our case, neither chromosomal aberrations nor elevated alphafetoprotein were found after amniocentesis or chordocentesis. Macroscopical and microscopical pathological examinations of the mass after delivery revealed an angiomyxoma with cystic degenerations in myxoid stroma.

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Özet

Umbilikal kord tümörleri nadir anomalilerdir ve kistik lezyonların araştırılması için prenatal ultrason kullanıldığında düşünülmelidir. Umbilikal kord tümörlerinin ayırıcı tanısı umbilikal kord teratomları, hemanjiyoma ve anjiyomiksomaları kapsamalıdır. Ayrıca omfalosel dışında çoğunlukla izole bulgular olarak izlenen umbilikal kord polipi, umbilikal kord kisti, kord içine herniasyon ve omfalosel olabilir. Anjiyomiksoma, umbilikal kordun nadir bir tümörüdür ve artmış perinatal morbidite ve mortaliteyle ilişkili bulunmuştur. 22 yaşında sezaryan ile doğum yapan geniş umbilikal kord tümörü olan olgu sunumu yapılmaktadır. Olgumuzda olduğu gibi, umbilikal kord tümörlerinde amniyosentez veya kordosentez ile kromozomal bozukluk veya yüksek alfafetoprotein değerleri bulunmayabilir. Doğumdan sonra kitlenin mikroskopik ve makroskopik patolojik incelemesinde miksoid stromada kistik dejenerasyon ile birlikte anjiyomiksoma izlenmiştir.

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Introduction

A tumor of the umbilical cord is a rare event that can be diagnosed prenatally by ultrasound examination. Only two true tumors ocur in the umbilical cord: angiomas and, more rarely, teratomas. Angiomyxoma is associated with increased perinatal morbidity and mortality. However, the management of these pregnancies in the third trimester is not clearly defined. Close follow-up is needed because some of the fetuses and newborns have fatal outcomes.

We present a 22-year-old woman with a large umbilical cord tumor who underwent a caesarean section. Serial ultrasound examinations showed an increase in the size of the mass without deterioration of the fetal condition. Macroscopical and microscopical pathological examinations of the mass after delivery revealed an angiomyxoma with cystic degenerations in myxoid stroma. Therefore, these rare umbilical cord tumors should be considered when using prenatal ultrasound for detection of cystic lesions of umbilical cord.

Case report

A 22-year-old woman, gravida 1 para 0, was referred to our clinics for routine prenatal assessment at 24 weeks of gestation. Detailed ultrasound examination showed a single live anatomically normal fetus. The pregnancy was uncomplicated regarding maternal health problems, vaginal bleeding or exposure to teratogens except that she had epileptic seizures. Because of this, she was using Trileptal treatment per oral. She and her 23-year-old nonconsanguineous spouse had an unremarkable family history. The fetal movements were normal and assesment demonstrated growth parameters appropriate for the gestational age and amnion fluid index was normal. The placenta was located at the right on the fundus. Ultrasound examination demonstrated a mass arising from the umbilical cord (Figure 1). This abnormal structure was heterogenous and composed of solid and cystic areas (Figure 2). The diameter was about 5 cm. On high-resolution ultrasound and color Doppler examination, one venous and two arterial structures were observed and Doppler indexes of umbilical arteries were normal (Figure 3). The fetal abdomen wall was intact. Chordocentesis and fetal magnetic resonance imaging were advised. At 25 weeks of gestation, chordocentesis was performed. It revealed a normal 46, XX karyotype. Magnetic resonance imaging (MRI) demonstrated a non-homogenous lesion that was clearly demarcated and located on the fundus associated with the umbilical cord and measuring about 6x5 cm in diameter. It was thought to be

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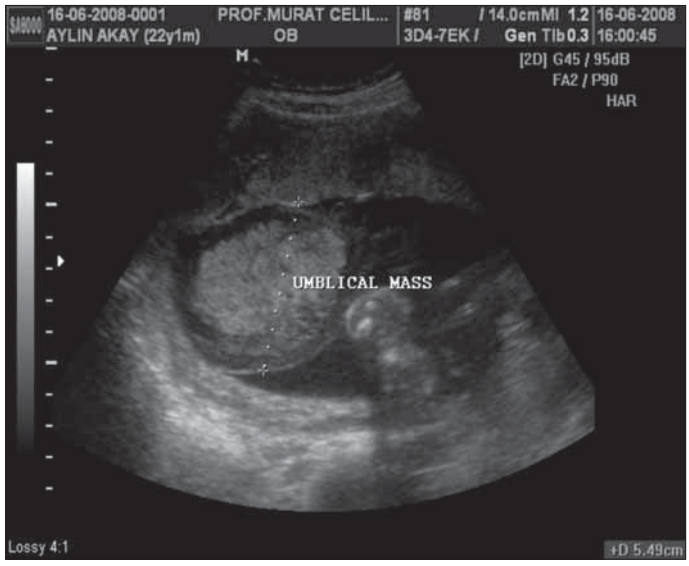

Figure 1. Umbilical mass

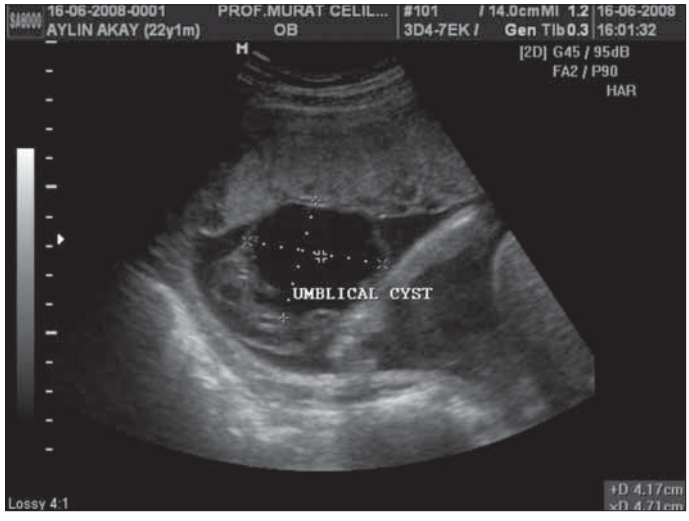

Figure 2. Umbilical cyst

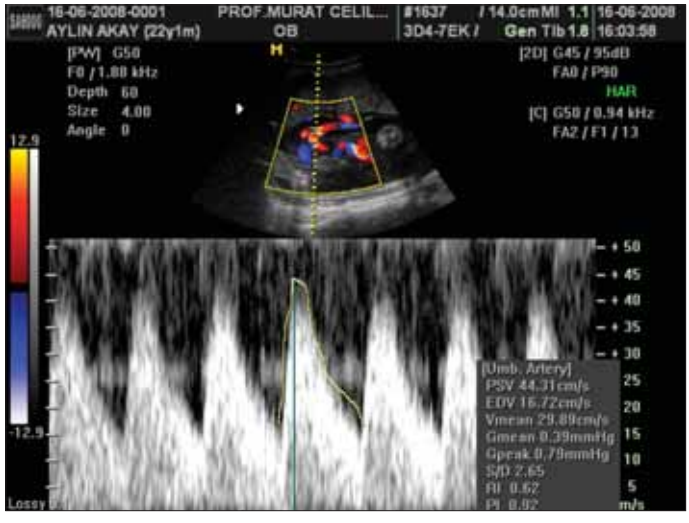

Figure 3. Doppler indexes of umbilical artery

either an angiomyxoma or hemangioma which were tumors arising from the umbilical cord.

Sequential ultrasound examination from 25 weeks to the end of pregnancy demonstrated progressive expansion of the mass. The fetal growth pattern remained normal.

At 38 weeks of gestation, a girl was delivered by caeserean section weighing 3100 gram with a length of 49 cm. Neither dysmorphism nor external malformation was observed. In the formaldehyde solution, an umbilical cord tumor of 3.5 cm was attached to the abdominal wall in a normal position. Macroscopical and microscopical pathological examinations of the mass after delivery revealed an angiomyxoma with cystic degenerations in myxoid stroma (Figure 4, 5). On the umbilical cord wall, green gelatinous and white myxoid areas were seen. On microscopic examination, one venous and one arterial structure was observed instead of one venous and two arterial structure. Around these vessels, there was expanded and degenerated myxoid stroma. The macroscopical and microscopical placental examination revealed no abnormality. The placenta weighed 272 grams and measured 9.5x6x3.5 cm. There were no clinical findings other than the umbilical tumor. The infant was discharged from hospital in a stable condition. At present, after 5 months, the infant is in good health.

Discussion

Tumors of the umbilical cord are rare anomalies and should be considered when using prenatal ultrasound for detection of cystic lesions. Nodular bulges of the umbilical cord are rare entities of polymorphous presentation that can be detected prenatally by ultrasound examination. The clinical significance common to all anomalies is determined by their size, which can potentially cause vascular compromise and affect fetal growth. After birth, referral of the newborn to a pediatric surgery clinic for revision and correction is mandatory, but not an emergency, because there may be an abdominal wall defect or any other anomalies simultaneously.

Differential diagnosis of umbilical cord tumors should comprise umbilical cord teratoma, hemangioma and angiomyxoma. It can also be an umbilical cord polyp, umbilical cord cyst, hernia into the cord and omphalocele, which are mostly isolated findings, except for omphalocele (1).

Umbilical cord teratomas have a very polymorphic presentation. They are observed along the whole length of the cord. They are frequently covered with skin and can be solid and cystic. At the histological level, there are tissues from the three germinal layers. Associated anomalies can be observed in nearly half of the cases. Despite the large volume of some tumors, few obstetrical complications have been reported (2).

With advancing technology and use of ultrasound and maternal serum alphafetoprotein evaluation in the second trimester, it may be possible to diagnose hemangiomas of the umbilical cord in early gestation. The umbilical cord hemangiomas consist of an angiomatous nodule encompassed by edema and myxomatous degeneration of Wharton's jelly. They are

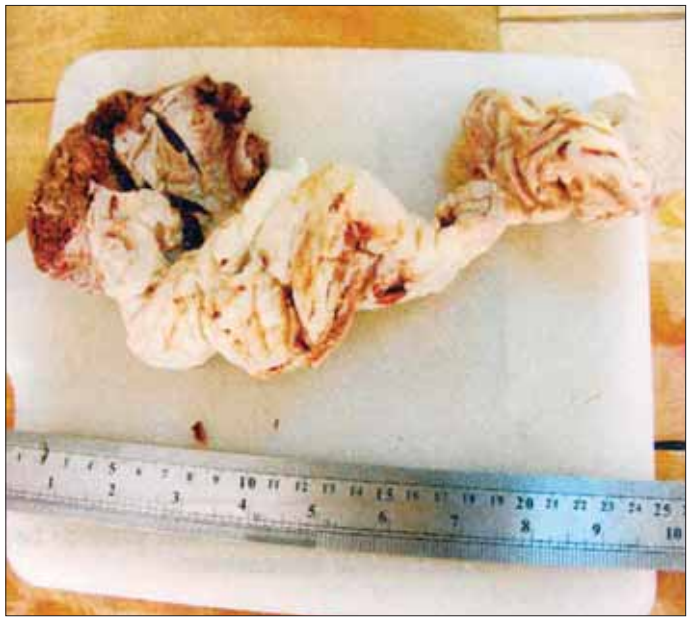

Figure 4. Increase in the size of the umblical cord

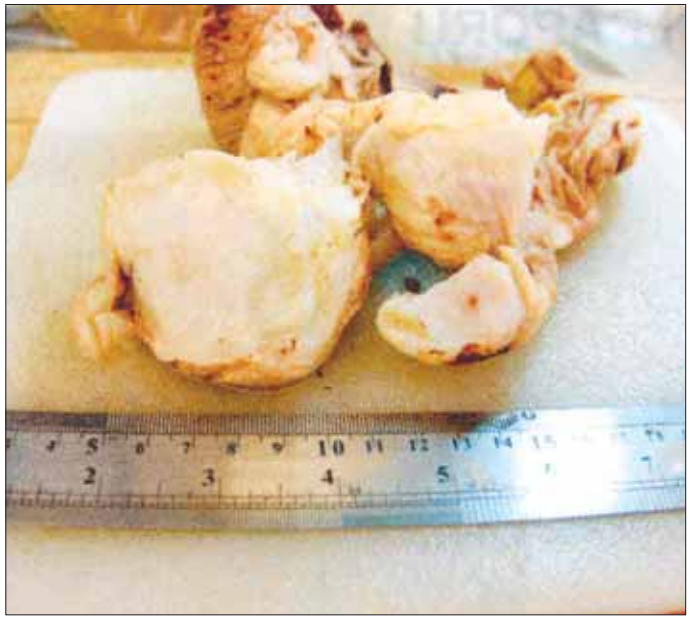

Figure 5. White myxoid areas on the macroscopic section of the umblical cord

located toward the placental end of the cord. These tumors originate from the umbilical artey, rarely from the vein or both. Morbidity and mortality rate of umbilical cord hemangiomas have been reported to be about 35% (3). They are attributed to the presence of coexisting factors, such as non-immune hidrops fetalis, intrauterine growth retardation, severe fetal hemorrhage and intrauterine fetal death as well as maternal obstetrical complications. To avoid the intrauterine and postnatal complications, an early diagnosis of umbilical cord hemangioma is necessary. A close follow-up by ultrasound examination and color Doppler is recommended to elucidate the nature of placental masses (4, 5).

Angiomyxoma is a rare tumor of the umbilical cord and is associated with increased perinatal morbidity and mortality. Therefore, it should be considered when using prenatal ultrasound for detection of cystic lesion. Color Doppler imaging can easily detect perfusion through the umbilical vessels (6), so using high-resolution ultrasound and color Doppler, the umbilical cord tumor can be suspected to be an angiomyxoma without malformations in the fetus. As in our case, neither chromosomal aberrations nor elevated alphafetoprotein were found after amniocentesis or chordocentesis (7). Fetal MRI may be advised to diagnose any other associated anomalies. In our case, fetal MRI demonstrated an exact lesion about the umbilical cord. On pathologic examinations, an angiomyxoma of the umbilical cord with massive degeneration of Wharton's jelly was revealed (8). This tumor can allow uncomplicated spontaneous vaginal delivery (9). However, we performed a caeserean section because of the size of the umbilical mass. Rarely, umbilical cord tumor is recognized in a macerated stillbirth (10). Therefore, prenatal ultrasound and Doppler ultrasound should be used for detection of umbilical cord tumors.

Conflict of interest
None declared

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First-trimester ultrasonography revealed a gestational sac featuring cystic spaces and no visible embryo: a case of trisomy 7

İlk trimester ultrasonografide kistik alanlar içeren, embriyo görülmeyen gebelik kesesi: Bir trizomi 7 olgusu

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Abstract

Ultrasound examination in early pregnancy has steadily gained importance and is now routine for most women in the first trimester. The sonographic features of early trisomy 7 pregnancies are not well characterized.

We present a case of trisomy 7 in which early pregnancy ultrasound revealed a gestational sac featuring cystic spaces and no visible embryo.

Based on comparison with a previously reported case of trisomy 7 featuring a multicystic anembryonic gestational sac we suggest that this ultrasonographic finding may be a sign of trisomy 7.

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Key words: Trisomy 7, ultrasonography, early pregnancy failure

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Özet

Erken gebelikte ultrasonografi muayenesi gittikçe önem kazanmıştır ve şu anda birçok gebeliğin birinci trimesterinde rutin uygulanmaktadır. Trizomi 7 olgularının erken ultrasonografik özellikleri tam belirlenmemiştir.

Burada erken gebelik ultrasonografisinde kistik alanları olan bir gebelik kesesinde embriyonun görülmediği bir trizomi 7 olgusunu sunuyoruz.

Daha önce rapor edilmiş olan bir trizomi 7 olgusundaki multikistik anembriyonik gestasyonel kese tanısını da göz önüne alarak bu ultrasonografik bulgunun trizomi 7 belirteci olabileceğini öneriyoruz.

(J Turkish-German Gynecol Assoc 2010; 11: 61-2)

Anahtar kelimeler: Trizomi 7, ultrasonografi, erken gebelik kaybı

Geliş Tarihi: 17 Haziran 2009 **Kabul Tarihi:** 03 Eylül 2009

Introduction

Ultrasound examination in early pregnancy is now routine for most women in the first trimester. Determination of whether some specific karyotype abnormalities are linked with distinct ultrasonographic findings is gaining importance.

Case report

A 23-year-old primigravida woman was admitted to the obstetrics unit of our hospital at 7 weeks 6 days of gestation with the complaint of vaginal bleeding. The woman and her husband were both healthy, the marriage was not consanguineous, and there was no family history of congenital malformations. Six days prior to presentation, the patient had been examined at another hospital for menstrual delay. At that time her blood beta-human chorionic gonadotropin (β-hCG) level was 9740 IU/mL. Transvaginal ultrasound showed a single intrauterine gestational sac containing a yolk sac but no fetal pole. Our ultrasonographic examination at 7 weeks 6 days of gestation showed a large gestational sac of mean diameter 38 mm, three cystic spaces in the chorionic sac (one cyst inside another, and a third tangent to these), and no visible embryo (Figure 1). The chorion appeared normal. There was no solid component in the gestational sac. The patient was diagnosed with anembryonic pregnancy. Two days later the pregnancy was terminated using the Carmen aspiration method, and two samples of the evacuated tissues were collected: one that appeared to be chorionic villi (specimen 1) and one that resembled endometrium (specimen 2). These were sent for chromosome analysis. Two weeks after termination, ultrasonography showed a normal central endometrial echo and blood testing revealed β-hCG of 3 IU/mL. The karyotyping results were 47,XX,+7 (specimen 1) (Figure 2) and 46,XX (specimen 2). The family refused any further investigation and it was thus impossible to perform molecular analyses to rule out maternal contamination. During genetic counseling, the parents were informed about the detected abnormality and prenatal diagnostic tests were recommended for any future pregnancies.

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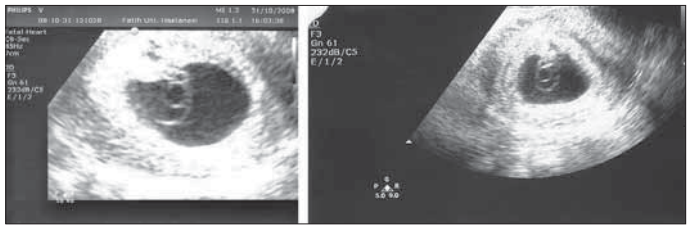

Figure 1. Ultrasonographic examination at 7 weeks 6 days of gestation showed a large gestational sac, three cystic spaces inside the chorionic sac, and no visible embryo

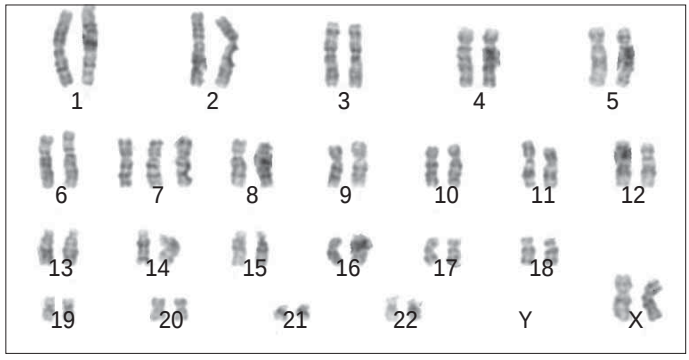

Figure 2. Representative karyotype from specimen 1, showing complete trisomy of chromosome 7

Discussion

Research indicates that nearly 40% of early pregnancies result in miscarriage, and many authors have investigated the role of chromosomal abnormalities in these embryonic losses (1). One such study looked at 144 spontaneous abortions through direct sampling of chorionic villi (2). The authors found that 100 (70%) of these specimens had abnormal chromosomes, and 64% of those 100 were autosomal trisomies. Two trials examined the correlation between karyotype and ultrasound findings in patients with failed early pregnancy. Goldstein et al. studied 102 women with ultrasound diagnosis of early pregnancy failure and found that 44 of these pregnancies (43%) featured abnormal karyotypes (3). Thirty-three (75%) of the 44 were trisomy cases. Coulam et al. examined 137 spontaneous abortions and found 86 (63%) cases with abnormal karyotypes (68 aneuploidies and 18 polyploidies) (4). Neither of these papers reported a case of trisomy 7. Both sets of authors concluded that ultrasonographic findings cannot predict karyotype in cases of spontaneous abortion, but they called for further studies to determine whether some specific karyotype abnormalities are linked with distinct ultrasonographic findings.

The second specimen from our patient appeared to be endometrium, and the karyotype for this tissue was 46 XX. Examination of tissue from curettage for reliable separation of chorionic villi from decidua was initially proposed on a clinical basis. This method allows a portion of chorionic villi to be distinguished from maternal decidua and was submitted separately for chromosomal analysis (3).

Four percent to 10% of all trisomy cases are trisomy 7, and this abnormality is generally considered to be lethal during embryogenesis. Trisomy 7 is usually detected by chorionic villus sampling due to confined placental mosaicism in an ultrasonographically normal pregnancy and the outcome is normal, without intrauterine fetal growth retardation (5). Almost all surviving children are mosaics and exhibit variable and nonspecific clinical features. A patient with typical Potter syndrome and full trisomy 7 was described in 1980 by Yunis et al. (6). Biri and colleagues presented a case of double aneuploidy, namely, trisomy 7 and X mosaicism, with characteristic features of Potter syndrome (7). The fetus survived in utero until the 32nd week of gestation. The same authors also noted four previously reported cases of trisomy 7 that survived into the third trimester and all of these exhibited features indicative of the Potter sequence.

The sonographic features of early trisomy 7 pregnancies are not well characterized. A case similar to ours was reported in 2001 by Ojha et al. (8). In that instance, ultrasonography at 8 weeks and 1 day gestation showed a heterogeneous multicystic mass with no visible embryo, and karyotyping revealed trisomy 7. The cystic appearance of that abnormal pregnancy is almost identical to what we observed in our patient. Our literature search revealed no other reports of the sonographic features of full trisomy 7 pregnancies. Based on this comparison with a previously reported case of trisomy 7 featuring a multicystic anembryonic gestational sac, we suggest that this ultrasonographic finding may be a sign of trisomy 7.

Women and couples who experience failed pregnancy need more detailed information about the reasons for the failure. In each case it is essential to assess the various causes of miscarriage. Detection of a chromosomal aberration provides a definitive diagnosis and eliminates the need for any further investigation. The ability to identify specific ultrasonographic findings that may predict abnormal karyotypes is extremely valuable and is gaining importance. Our case suggests that there may, indeed, be certain characteristic features of trisomy 7 detectable on ultrasound in early pregnancy.

Conflict of interest
None declared

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Hydatid cyst of ovary- a rare entity

Overin hidatik kisti- nadir bir durum

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Abstract

Hydatid disease is a zoonosis caused by the larval stage of Echinococcus granulosus. It is prevalent in areas where livestock is raised in association with dogs. Humans are the accidental intermediate host. Primary peritoneal echinococcosis is a rarely observed clinical condition. We report a case of peritoneal hydatid cyst diagnosed incidentally during an operation performed for suspected ovarian cyst.

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Key words: Hydatid cyst, ovary, echinococcosis

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Özet

Hidatik kist Echinococcus granulosus'un larva evresinin neden olduğu bir zoonozdur. Hayvanların köpeklerle birlikte yetiştirildiği bölgelerde sıktır. İnsanlar rastlantısal ara konaktırlar. Primer peritoneal echinococcosis nadir görülen bir klink durumdur. Burada over kisti şüphesi ile operasyona alınan bir olguda rastlantısal olarak tanı konulan bir peritoneal hidatik kist olgusunu sunuyoruz.

(J Turkish-German Gynecol Assoc 2010; 11: 63-4)

Anahtar kelimeler: Hidatik kist, over, echinococcosis

Geliş Tarihi: 25 Nisan 2009 **Kabul Tarihi:** 01 Temmuz 2009

Introduction

Echinococcosis of the ovary is a rare condition. It was found incidentally during laparotomy for an ovarian tumor. Operative and post-operative management of such a case is presented.

Case Report

A 30 yr old patient, P4, presented with amenorrhea of 3 months, intermittent bleeding P/V for 6 weeks and an abdominal mass for 8 weeks without pain in the lower abdomen or significant loss of weight. There was no alteration of bladder or bowel habits. Her past menstrual history was normal. Clinical examination revealed a large smooth surfaced mass (24×20 cm) arising from the pelvis with restricted mobility. There was no evidence of free fluid in the peritoneal cavity. Uterus was not delineated and adnexae could not be palpated on P/V examination. Urine pregnancy test was negative and laboratory investigations revealed mild neutrophilic leucocytosis, normal liver and kidney functions with normal serum CA-125. Ultrasound (USG) of the whole abdomen revealed a huge multiloculated mass occupying the pelvis with internal debris. The ovaries were not visualized. The right ureter was mildly dilated. The liver, spleen and kidneys showed a normal echo pattern. Ultrasound did not detect free fluid within the abdomen.

Exploratory laparotomy was performed and a huge cystic mass (measuring 20 x 30cm approximately) was seen arising from the pelvis (Fig 1). Uterus, left tube and left ovary appeared normal. Right ovary could not be identified separately. The mass was excised and another large cystic mass was seen occupying the pouch of Douglas. After opening the thick walled cyst, multiple cystic masses emerged (Fig 2). The cyst wall was completely dissected out. Subsequently hysterectomy with left salpingo-oophorectomy was performed. Peritoneal lavage was performed and a tube drain was placed in the cul de sac before abdominal closure. Post operative antibiotics and steroids were given and the recovery was uneventful excepting mild haematuria (macroscopic) for 3 days. Post surgery it was revealed that there was no history of contact with dogs. Albendazole (400 mg) was given twice daily for

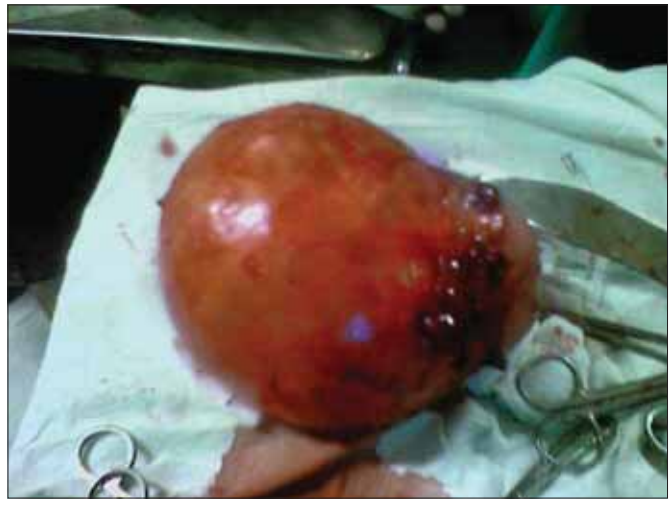

Figure 1. Encapsulated mass encountered initially during laparotomy and removed intact

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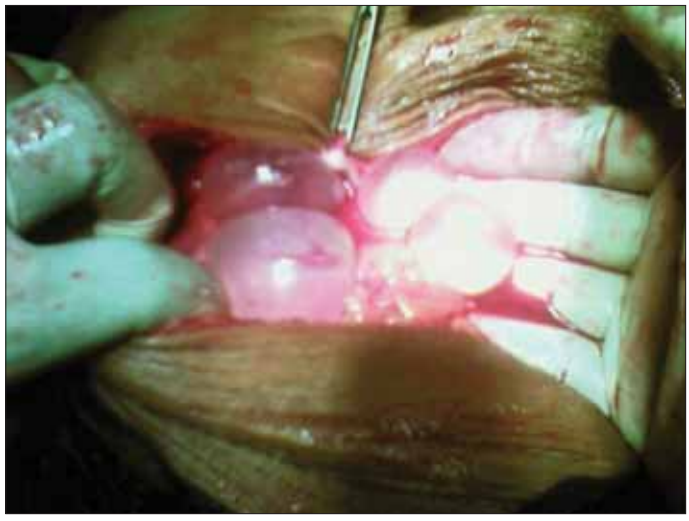

Figure 2. Multiple cystic masses emerging from the cyst in the pouch of Douglas

four weeks. Histopathology confirmed it to be hydatid disease. The patient was followed up thrice in the preceding 6 months. Abdominal USG, computerized tomography (CT) of the thorax and brain and liver function test (LFT) have been performed at each follow up visit. As yet there is no evidence of recurrence.

Discussion

The ovary is a rare primary target organ for hydatid disease. Hydatid disease is prevalent in areas where livestock is raised in association with dogs. It is found mostly in Australia, Argentina, Chile, Africa, eastern Europe, Middle East, New Zealand and Mediterranean region, particularly Lebanon and Greece (1). The organs most commonly involved in hydatid disease are the liver and lungs (2). Most of the cases of ovarian hydatidosis are diagnosed peroperatively. We also performed laparotomy in this case with an idea of encountering a multilocular ovarian cyst. Owing to its multilocular cystic appearance, a hydatid cyst may not be differentiated from ovarian lesions with septal structures such as cystadenoma (3) or cystic ovarian teratoma (with intracystic floating globules). The overall prevalence of peritoneal involvement in cases of abdominal hydatid disease is approximately 13% (1). Hydatid cyst has three layers - pericyst, germinal layer and laminated membrane. A thick pericyst is present in the liver & spleen but it is extremely thin in a peritoneal hydatid cyst. Hydatid cysts expand slowly and asymptomatically, and thus, may be large at presentation (4). Pain is the most common symptom of hydatid disease, but this was absent in our case. Fever supervenes in secondary infection and intraperitoneal rupture causes severe allergic reactions. Jaundice might develop in hepatic hydatid cysts when there is intrabiliary rupture (4). USG is a cost effective imaging modality but when available, CT scan is superior owing to its higher sensitivity (5). Serologic tests are very useful in confirming a diagnosis and usually involve a screening test such as Enzyme immunoassay or Indirect hemagglutination followed, if positive, by a confirmatory assay such as Immunoblot or Gel diffusion. Sensitivity varies from 60-90% depending on the characteristics of the case. False positive reactions may occur with cysticercosis, although disease presentation should prevent confusion (6). Fine needle aspiration cytology (FNAC) may help in establishing the diagnosis of a cystic pelvic mass. FNAC of hydatid cyst was thought to cause severe anaphylactic reactions. However, reported incidence of anaphylactic reactions was very low (7). FNAC was not done in our case as we were suspecting an ovarian tumor. Surgery remains the mainstay of treatment for hydatid disease of the peritoneal cavity (4). Albendazole may be given both preoperatively and postoperatively. It softens the cysts and facilitates removal during the operation and also prevents recurrence after the operation. The dose duration is five days before to one month after the operation. The other alternative is PAIR therapy (puncture, aspiration, injection, re-aspiration) with concomitant chemotherapy. The efficacy of sole medical therapy is limited. Antihelminthics work best when prescribed for small, unilocular, hydatid cysts. Successful treatment for such cases has been reported in up to 40% of cases. In PAIR therapy, ultrasound-guided percutaneous aspiration of cysts is carried out, followed by injection of protoscolicidal substances (such as, 20% sodium chloride solution, 95% ethanol or betadine solution). The solution is left on for a contact period of a minimum of 15 minutes and then re-aspiration of the fluid cyst content is performed. The indications of PAIR therapy are: (1) large, multiple cysts of the liver, spleen, kidney and bones; (2) inoperable cases; and (3) relapses after surgery. The contraindications are lung cysts and communicating cysts (4). Asymptomatic small cysts may be treated with anthelmintics but large and symptomatic cysts should be treated surgically to avoid complications (4). The goals of surgery are to remove all the cysts and to prevent spillage of cyst fluid (4). In extrahepatic hydatids the pericyst is very thin and hence the cyst can be dissected and excised fully along with the pericyst (4). Following surgery, the reported recurrence rate is approximately 2% and survival rate is 95% (4). Postoperative long term follow-up is essential. Early postoperative imaging provides a baseline for long term follow-up.

Conflict of interest
None declared

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Misoprostol for termination of pregnancy-can it precipitate a seizure in a well controlled secondary epileptic tuberculoma patient?

Gebelik sonlandırmasında misoprostol- iyi kontrol edilen bir epileptik tüberkülomda epilepsi nöbetini tetikleyebilir mi?

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Abstract

A 35 year woman G2P0A1L0 at 16 weeks period of gestation, underwent termination of pregnancy for a fetus having a large lumbosacral meningomyelocele and Arnold chairi II malformation. She was a known treated case of tuberculoma of the brain who was not on any antiepileptics, and had been seizure free for the past two years. She developed two episodes of seizures precipitated during pregnancy termination with misoprostol. She received intravenous diazepam and phenytoin and was safely discharged home after she aborted.

(J Turkish-German Gynecol Assoc 2010; 11: 65-6)

Key words: Seizure, misoprostol, termination of pregnancy

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Özet

Otuz-beş yaşında, G2P0A1Y0 olan bir 16 haftalık gebeye geniş bir meningomyelosel ve Arnold Chairi Tip II malformasyonlu fetus nedeniyle gebelik terminasyonu uygulandı. Beyinde tüberkülom tanısı almış olan hasta antiepileptik kullanmıyordu ve son iki yıldır epilepsi atağı yaşamamıştı. Misoprostol ile gebelik terminasyonu uygulanırken iki kez epileptik nöbet oluştu. İntravenöz diazepam ve fenitoin ile tedavi edilen hasta abort ettikten sonra sorunsuz olarak taburcu edildi.

(J Turkish-German Gynecol Assoc 2010; 11: 65-6)

Anahtar kelimeler: Epilepsi, misoprostol, gebelik terminasyonu

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Introduction

Misoprostol, a synthetic prostaglandin E1 analogue, is an important drug in obstetrics and gynecology because of its abortificient, uterotonic and cervical-ripening effects (1). The side effects are dose-related, usually transient, and well tolerated. Misoprostol in animal studies has been shown to lower the threshold for convulsions and provoke convulsions with a subconvulsive dose of pentilenetetrazol (PTZ) (2). Cumulative total daily doses of 1600 μg have been tolerated with only mild gastrointestinal discomfort. In animals, the acute toxic effects include sedation, tremor, fever, convulsions, dyspnea, diarrhea, hypotension or bradycardia (3).

Pregnancy does not affect the frequency of seizures. Women who have been seizure free and adequately controlled for many years are unlikely to have seizures during pregnancy. Antiepileptics may be discontinued in women who wish to conceive and have been seizure free for more than 2 years. The risk of recurrence is 40% by 2 years after drug withdrawal (4).

We present a case of second trimester medical termination of pregnancy induced with misoprostol in a secondary epileptic patient with healed tuberculoma of brain, who had been seizure free for the past two years not on antiepileptic drug.

Case

A 35 year pregnant woman, a $G_2P_0A_1L_0$, came to the outpatient department following a level II Ultrasound done at 16 weeks showing a large meningocele in the fetal lumbosacral spine, focal kyphoscoliosis, and Arnold chairi II malformation (“lemon sign” and “banana sign” positive) with bilateral club foot. This was a spontaneous conception; she was not on any antiepileptic drugs. Her triple screen carried out at 15 weeks revealed Down’s risk of 1 in 1,900 and neural tube defect risk of 1 in 180. She was counseled about the poor prognosis for the fetus and she opted for pregnancy termination. Patient was a known case of tuberculoma of the brain with multiple calcified granulomas and she had received a complete course of second line ATT for 18 months 10years previously. She had a ventriculoperitoneal shunt inserted in situ 8 years earlier for raised intracranial tension. Since she had not had any seizures for the past 8 years and was keen on conception, her antiepileptics (phenytoin) were stopped two years earlier. On examination, she was conscious and oriented; her general physical examination, cardiovascular, respiratory and central nervous examination were unremarkable. Her pulse rate was 86/min, her BP 130/80mm Hg , and an abdominal examination revealed a uterus 18 week in size. The investigation revealed her random blood sugar, haemogram,

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liver function, renal function and serum electrolytes to be within normal range. After proper consent and neurology evaluation and clearance for termination of pregnancy, she was planned for induction with three doses of misoprostol (Misoprost, Cipla, India.) 400mcg intravaginal 6 hours apart. She developed two episodes of generalized tonic clonic seizures following the second dose. The third dose was omitted. After securing the airway, she was started on diazepam 10mg iv stat and intravenous phenytoin 1600mg in 100ml normal saline as a slow infusion over 30 minutes and phenytoin 350mg H.S. She aborted following the second dose. Cord blood was sent for karyotyping and the fetus was sent for grossing.

Discussion

Misoprostol is a common drug in obstetric practice used in medical abortion in the 1st trimester, as a cervical ripening agent, for induction of labor and prevention of post partum hemorrhage. The toxic dose in humans has not been determined. The plasma concentration of vaginal misoprostol increases gradually, reaching a peak in 70-80 minutes and serum levels of misoprostol are sustained for longer than 6 hours (5). The second dose of misoprostol would have had an additive effect on plasma concentration, thus precipitating the seizures. Cumulative total daily doses of 1600 mcg have been tolerated with only symptoms of gastrointestinal discomfort being reported. The temporal relationship (6 hours after instilling vaginal misoprostol) strongly suggests that misoprostol was the agent directly involved in inducing the seizures. Epileptic seizures have been reported with prostaglandin analogues administered by routes other than oral. We are presenting this case as a reminder to practitioners that even well controlled epilepsy can be precipitated by misoprostol. Hence they need to be aware of the risk and take this into consideration.

Conflict of interest
None declared

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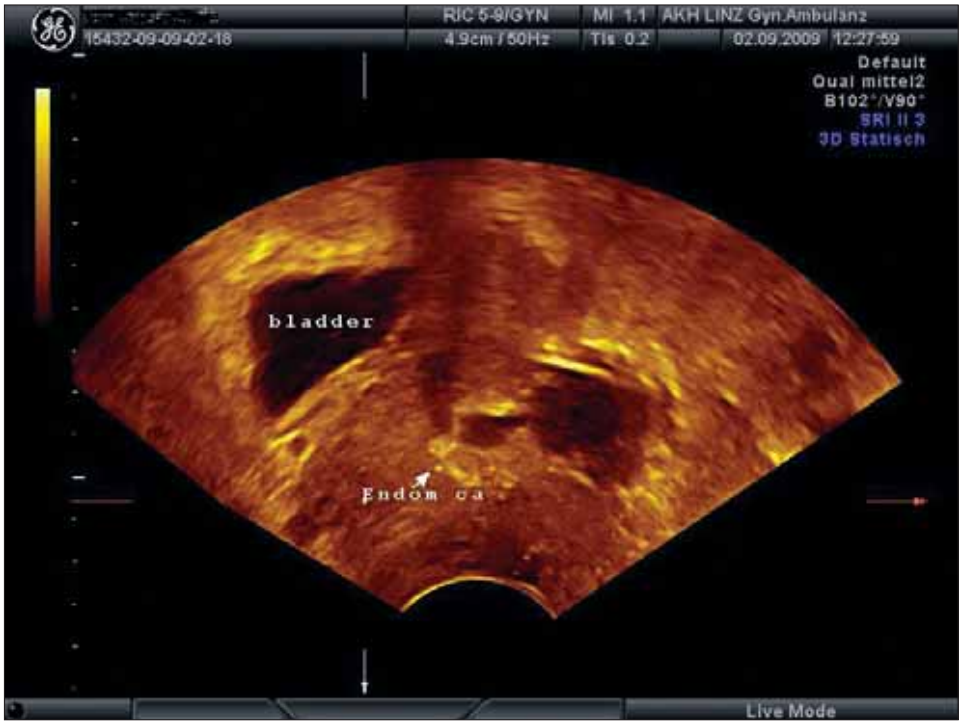
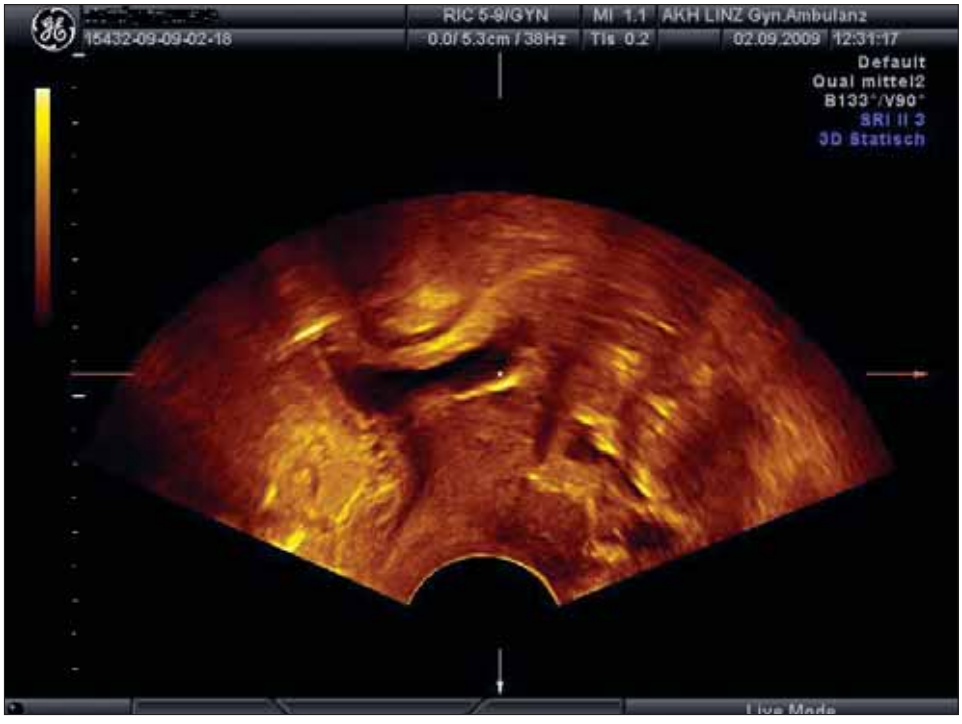
What is your diagnosis ?





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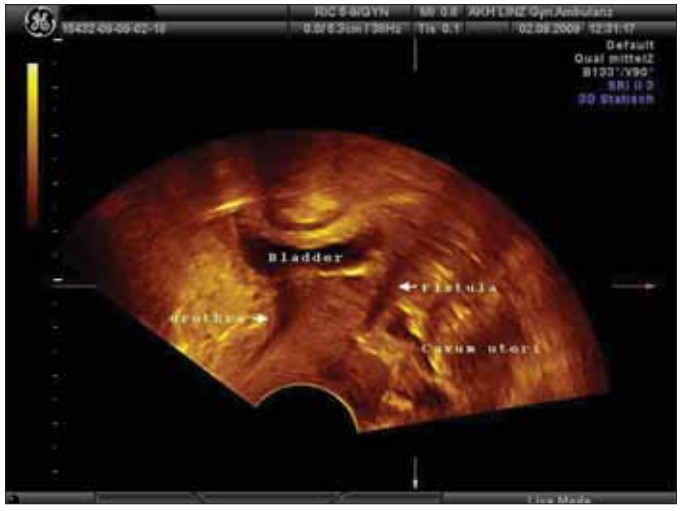
Answer

The vesicovaginal fistula is still very common in developing countries. In western Africa, its incidence in obstetrics is about 3 per 1000 births. The absence of facilities for transurethral catheterization and Caesarean section are the reasons for tissue ischemia during a prolonged second stage of labor.
In Europe, the vesicovaginal fistula most commonly occurs for iatrogenic reasons, following surgery in the lesser pelvis. In 75% of cases it occurs after gynecological procedures, especially after oncologic radical operations. Every vesicovaginal fistula with the cardinal symptom of absolute urinary incontinence signifies a major limitation of the patient's quality of life and may even lead to social isolation. Spontaneous closure is a rare occurrence. Surgical closure by means of a vaginal or transabdominal access leads to definitive closure in a large percenta-ge of cases (1).



In our case a 87 year- old woman with advanced endometrial carcinoma was referred with urinary incontinence. Her gynecologic history revealed primary chemo+radiotherapy in 2005. The diagnosis of vesicovaginal fistula was confirmed by computerised tomography. Because of her multiple morbidity surgical repair was not performed. The patient died two weeks after sonografic diagnosis of vesicovaginal fistula.
As presented in these pictures, the diagnosis of vesicovaginal fistula can also be made by so-nography. Compared to two-dimensional sonography, the additional coronarlview of three-dimensional ultrasound makes it easier to understand the complex anatomy of the patient.

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CONGRESS CALENDAR

4-7 March 2010	**ISGE (International Society for Gynecological Endocrinology)** *Firenze, Italy* http://www.isge2010.com
26 March 2010	**13th Annual Post-Graduate Course on Pediatric, Adolescent, & Young Adult Gynecology** *New York, USA* htpp://www.mssm.edu/cme
2-3 April 2010	**East and South East Region Obstetrics and Gynecology meeting on "Clinical Applications"** *Malatya, Turkey* www.kadindogumgunleri2010.org
17-18 April 2010	**1st Symposium on Controversies in Infertility, Harbiye Military Museum** *İstanbul, Turkey* irmak.gultekin@serenas.com.tr
18-23 May 2010	**8th National Congress in Obstetrics and Gynecology** *Antalya, Turkey* www.jinekoloji2010.org
19-22 May 2010	**11th Congress of the European Society of Contraception and Reproductive Health** *The Hague, Netherlands* http://www.contraception-esc.com
27-30 June 2010	**ESHRE** *Rome, Italy* http://www.eshre.com
26-29 September 2010	**7th National Congress of Turkish Maternal Fetal Medicine and Perinatology Association**
7-10 October 2010	**4th National Congress on Reproductive Endocrinology and Infertility, TSRM 2010** *Antalya, Turkey* www.tsrm.org.tr
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27-31 October 2010	**7th Congress of Obstetric and Gynecological Ultrasound, Harbiye Military Museum** *İstanbul, Turkey* www.usgkongre2010.org
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AMPUL IM/IV TABLET

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Kanıtlanmış **etkinlik**

Analjezik tedavide

ilk tercih

olarak uygulanmasını desteklemektedir.[1]

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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. 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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 üser 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 güvenirliği 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 hastalarda, 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 enfeksiyöz 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, polüri, dişide menstrüel bozukluklar; erkekte prostatik bozukluklar, sırt 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 sülfonamidler; **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-ITALYA. 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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0.5 ml İM Enjeksiyon İçin Süspansiyon İçeren Kullanıma Hazır Enjektör
[Human Papillomavirüs Tip 16 ve 18 Rekombinant AS04 adjuvanlı Aşı]

Formülü: Human Papillomavirüs Tip 16 ve 18 Rekombinant AS04 adjuvanlı Aşı, rekombinant DNA teknolojisi ile üretilen ve alimünyum hidroksit ile absorbe edilmiş infeksiyöz olmayan virüs benzeri partikül (VLP'ler) formunda L1 proteinini içerir. 0.5 ml dozu, 20 mikrogram İnsan Papillomavirüs Tip 16 L1 proteini ve 20 mikrogram İnsan Papillomavirüs Tip 18 L1 proteini içerir. **Endikasyonları:** Cervarix® aşısı, 10 yaş ile 25 yaş arası kız çocukları ve kadınlarda Human Papilloma Virüs (HPV) Tip 16 ve 18 ile nedensel ilişkisi olan yüksek gradeli servikal intraepitelyal neoplazilerin (CIN grade 2 ve 3) ve servikal kanserin önlenmesi için endikedir. **Kontrendikasyonları:** Cervarix®'in içeriğinde bulunan maddelere ve aşının kendisine duyarlı olan kişilerde yan etkilere neden olabilir. **Uyarılar/Önlemler:** Eğer sizde veya çocuğunuzda aşağıdaki durumlardan herhangi biri varsa: Aşının içerdiği maddelerden herhangi birine karşı gelişen aşırı duyarlılık (yardımcı madde listesine bakınız). Aşının bir dozunu aldıktan sonra gelişen aşırı duyarlılık. Aşırı duyarlılık belirtileri: Kaşıntılı deri döküntüsü, nefes darlığı ve yüz veya dilde şişme olarak sıralanabilir. Kanama bozukluğu olanlarda dikkatle yapılmalıdır. Bu uyarılar geçmişteki herhangi bir dönemde dahi olsa, sizin veya çocuğunuz için geçerliyse lütfen doktorunuza danışın. Bütün diğer enjektabl aşılarda olduğu gibi, aşının uygulanmasının ardından seyrek olarak anafilaktik reaksiyon görüldüğü takdirde gerekli olabilecek tıbbi tedavi olanakları hazır bulundurulmalıdır. Cervarix® 10 yaş altı çocuklarda kullanılmaz. **Gebelik ve Emzirme Döneminde Kullanımı:** Gebelik Kategorisi: C. Bu aşının hamilelik dönemindeki güvenliliği henüz tam olarak belirlenmiş değildir. Hamilelik sırasında bu aşıyı kullanıp kullanmamanıza doktorunuz karar verecektir. Cervarix®'in anne sütüne geçip geçmediği bilinmemektedir. Bu nedenle, emziriyorsanız doktorunuzu bilgilendiriniz. Emzirmenin durdurulup durdurulmayacağına ya da Cervarix® kullanımının durdurulup durdurulmayacağına ilişkin karar verilirken, emzirmenin çocuk açısından faydası ve Cervarix® kullanımının emziren anne açısından faydası dikkate alınmalıdır. Cervarix® gerekli olmadıkça gebelik döneminde kullanılmamalıdır. Aşı kesinlikle damar içine uygulanmamalıdır. **Yan Etkiler/Advers Etkiler:** Tüm ilaçlar gibi, Cervarix®'in içeriğinde bulunan maddelere ve aşının kendisine duyarlı olan kişilerde yan etkilere neden olabilir. Aşı uygulama yerinde bölgesel olarak ağrı, kızarıklık, şişlik hissedebilirsiniz. Bu belirtiler genel olarak tüm aşılarda aşılamaya bağlı olarak görülen hafif yan etkilerdir ve uzun süreli değildir. Baş ağrısı, egzersiz ile ilişkili olmayan kas ağrısı, yorgunluk, 38°C ve daha yüksek ateş, bulantı, kusma, ishal ve karında ağrı, baş dönmesi, eklem ağrısı, deride döküntü, kaşıntı diğer bildirilen yan etkilerdir. **İlaç Etkileşmeleri:** Cervarix® bağışıklık sistemini baskılayan diğer ilaçlarla birlikte kullanıldığında beklenen etkisini en iyi şekilde gösteremeyebilir. Klinik çalışmalar, Cervarix® ile elde edilen korunmanın ağızdan alınan doğum kontrol ilaçlarıyla azalmadığını göstermiştir. **Kullanım Şekli ve Dozu:** Optimal koruma sağlamak amacıyla üç intramüsküler enjeksiyon olacak şekilde 0, 1 ve 6 aylık uygulama şeması kullanılmalıdır. Cervarix® intramüsküler olarak uygulanmalıdır. Cervarix® intravenöz yoldan kesinlikle uygulanmamalıdır. **Aşırı Dozaj:** Uygulanamaz. **Saklama Koşulları:** Aşı +2°C ile +8°C arasında saklanmalıdır. Aşıyı kesinlikle dondurmayınız. Eğer aşı donmuşsa kullanmadan atınız. **Ruhsat Sahibinin Adı ve Adresi:** GlaxoSmithKline İlaçları Sanayi ve Ticaret A.Ş., 1.Levent/İstanbul. **Ruhsat Tarih ve Numarası:** 28.12.2007 - 4 Reçete ile satılır. 25.01.10 tarihi itibarıyle perakende satış fiyatı KDV dahil (%8) 129,37 TL'dir. **Kullanma Talimatı Onay Tarihi:** 28.12.2007 **Kullanma talimatı Kodu:** Cervarix_KT_PFS.10/19.12.07/v.2/C Cervarix® GlaxoSmithKline şirketler grubunun tescilli markasıdır.

CE/IL/02.10/01

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Cervarix®
Human Papillomavirüs Tip 16 ve 18 Rekombinant, AS04 adjuvanlı aşı

YAZZ 24 +4 KISA PROSPEKTÜS

YAZZ® 24+4 film kaplı tablet: Herbiri 3 mg drospirenon ve 0.02 mg etinilestradiol içeren 24 film kaplı tablet ve bunları takip eden 4 plasebo tablet. **Terapötik endikasyonlar:** ▪Gebeliği önleyici etkisinin yanısıra antimineralokortikoid ve antiandrogenik etkileri sayesinde, hormona bağlı su tutulması ve buna bağlı belirtiler gösteren kadınlarda, ▪Oral kontrasepsiyon isteyen hastalarda akne vulgaris tedavisi, ▪Premenstruel disforik bozukluk (PMDD; Premenstrual Dysphoric Disorder) semptomlarının tedavisinde endikedir. **Pozoloji/uygulama sıklığı, süresi ve şekli:** Tabletler paketin üstünde gösterildiği yönde, hergün yaklaşık aynı zamanda bir miktar su ile alınmalıdır. Tablet alımı süreklidir. Birbirini izleyen 28 gün boyunca hergün bir tablet alınır. Her bir sonraki pakete önceki kutudaki son tablet alımının ertesi günü başlanır. Tabletler normal siklusun ilk günü (kanamanın ilk günü) alınmaya başlanmalıdır. **Kontrendikasyonlar:** Kombine oral kontraseptifler aşağıdaki koşulların varlığında kullanılmamalıdır ve ilk kez kombine oral kontraseptif kullanımı sırasında bunlardan herhangi biri ortaya çıkacak olursa, tedavi hemen kesilmelidir. ▪Venöz veya arteriyel trombotik/tromboembolik olayların (örn. derin ven trombozu, pulmoner emboli, miyokard enfarktüsü) veya serebrovasküler bir olayın varlığı ya da öyküsü, ▪Tromboz prodromu varlığı veya öyküsü (örn. geçici iskemik atak, anjina 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.

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