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Eskişehir Milletvekili Sayın Ruhsar DEMİREL tarafından verilen "Tüp bebek tedavisine" ilişkin 7/37778 sayılı yazılı soru önergesinin cevabı ilişikte sunulmaktadır.

Arz ederim.

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Eskişehir Milletvekili Sayın Ruhsar DEMİREL tarafından verilen "Tüp bebek tedavisine" ilişkin 7/37778 sayılı yazılı soru önergesinin cevabıdır;

Üremeye Yardımcı Tedavi Uygulamaları ve Üremeye Yardımcı Tedavi Merkezleri Hakkında Yönetmelikte; "Merkezlerde ÜYTE (üremeye yardımcı tedavi) uygulamasında birden fazla embriyo transfer edilmemesi esastır. Ancak, 35 yaşa kadar birinci ve ikinci uygulamada tek embriyo, üçüncü ve sonraki uygulamalarda iki embriyo, 35 yaş ve üzerinde tüm uygulamalarda en fazla iki embriyo transfer edilebilir." İfadeleri yer almaktadır.

SORU 1- Türkiye'de ÜYTE uygulamalarında yer alan tüp bebek yönteminin 2003-2013 tarihleri arasında yıllar itibariyle başarı oranlarının, tüp bebek uygulaması yapan kamu ve özel kurumlara göre dağılımı nedir?

CEVAP 1- 2003-2012 yılları arasında yapılan tüp bebek uygulamalarına ilişkin dağılımlar aşağıda sunulmuş olup Bilim Komisyonunca değerlendirilen veriler kamu ve özel olarak ayrılmamaktadır. 2013 yılı verileri değerlendirme aşamasındadır.

YILLAR	Toplam Merkez Sayısı	Toplam Siklus Sayısı	Tüm Gebelikler	Canlı Doğumlar
2003	49	16.161	5.555	1.797
2004	54	21.025	7.648	2.721
2005	61	25.577	8.875	2.192
2006	77	32.552	12.009	3.628
2007	93	35.386	12.901	3.727
2008	107	43.928	13.464	4.073
2009	110	44.449	14.298	4.885
2010	115	48.801	15.588	6.539
2011	115	64.325	16.673	6245
2012	126	72.828	17.766	5.762

SORU 2- Tüp bebek tedavilerinde yayımlanan yönetmelikte transfer edilen embriyo sayısının azaltılmasının nedenleri nelerdir?

CEVAP 2- Anne ve bebek sağlığı açısından ve gebelik başarısı yönünden değerlendirildiğinde çoğul gebeliklerin tıbbi kabullerde istenen bir durum olmadığı bilinmektedir. Son yıllarda tüm dünyada çoğul gebelik sayısında belirgin bir artış mevcuttur ve üremeye yardımcı tedavide transfer edilen embriyo sayısı ile çoğul gebelik arasında reddedilemez bir ilişki vardır. Ülkemizdeki çoğul doğumlar; tüm canlı doğumların % 3'ünü,

erken doğumların % 17'sini, düşük doğum ağırlıklı bebeklerin % 25' ini ve neonatal ölümlerin % 20'sini oluşturmakta ve yine Bakanlığımız 2008 verilerine göre üremeye yardımcı tedavi sonucu oluşan gebeliklerin % 37'sini çoğul doğumlar oluşturmaktadır. Şüphesiz ki, bunun ana nedeni üremeye yardımcı tedavideki ovülasyon indüksiyonu ve birden fazla embriyo transferidir. Çoğul gebeliklerin anne, bebek, toplum ve sağlık hizmeti verenler için çok ciddi sonuçları vardır. Bu durum özellikle yenidoğan bakım hizmetlerinin sınırlı veya eksik olduğu yerlerde belirgindir.

Çoğul doğumlar bedensel, ruhsal ve ekonomik sorunları da beraberinde getirmektedir. Bebek açısından; asfiksi, doğum travmaları, deformasyonlar, nörogelişimsel problemler, ani bebek ölümü sendromu, konjenital anomaliler, kardiyak, ürogenital, santral ve Gastro İntestinal Sistem rahatsızlıkları şeklinde sayabiliriz. Aile bireyleri açısından ise psikososyal sorunlar, uykusuzluk, yorgunluk, anksiyete, depresyon, iş kaybı, ekonomik sıkıntı ve maalesef boşanmalara yol açabilmektedir. Ülke ekonomisine zarar ise oldukça fazladır. Ülkemizde her yıl doğan bir milyon bebeğin 85.000' i prematüre doğmaktadır. Türk Neonatoloji Derneği'nin 2004 yılında yaptığı bir araştırmada ise 24'ü üniversite hastanesi olan 26 merkezde vücut ağırlıkları 2000-2500 gram olan bebeklerin yüzde 7'si, 1500-2000 gram olanların yüzde 12'si, 1250-1500 gram olanların yüzde 14'ü, 1000-1250 gram olanların yüzde 20'si, 750-1000 gram olanların yüzde 42'si, 500-750 gram olanların yüzde 60'ı kaybedildiği belirtilmiştir. Artık IVF'de gebelik elde etmenin değil tekil gebelik elde etmenin bir başarı olduğu ve çoğul gebeliklerin de bir başarı değil bir komplikasyon olduğu dünyaca kabul edilmektedir. Bunu önlemek için Örneğin 2001 yılında Human Fertilisation and Embryology Authority (HFEA), istisnalar dışındaki üremeye yardımcı tedavide transfer edilecek embryo sayısını 2 ile sınırlandırmıştır. Keza Amerikan Üreme Tıbbı Derneği(ASRM) en son 2008' de yayınladığı makalede 35 yaşından küçük kadınlara 1 ya da 2 embriyo verilmesini tavsiye etmektedir.

Çoğul gebelikleri azaltma yöntemleri az sayıda embriyo transferi, tek embriyo transferi ve fetal redüksiyondur. Fetal redüksiyon üremeye yardımcı tedavi uygulamalarından sonra oluşan üçüz ve üstü çoğul gebeliklerde, bir veya daha fazla bebeğin kalbinin özel bir ilaçla durdurularak o bebeğin gelişiminin sonlandırılması işlemidir. Ancak fetal redüksiyon da artık bir çözüm değildir. Çünkü spontan redüksiyon sonrasında bile, sağ kalan fetuslar, başlangıçta aynı sayıda bulunan redüksiyon yapılmamış gebeliklere göre daha erken ve düşük doğum ağırlıklı doğmaktadır. Tek embriyo uygulamalarını çiftlerin zor kabullenmesinin altında, çoğunlukla çoğul gebelik ve risklerini (kanama, preeklampsi, DM, erken eylem, neonatal ölüm, serebral palsi) bilinenden daha hafife alma bilgisizliği yatmaktadır. Ayrıca çiftler, tek embriyo uygulaması sonrası sağlanacak gebelik oranları konusunda da karamsardırlar. Çiftler çoğul gebelik riskleri ve tek embriyo transferinin başarısı anlatılmamaktadır. Hâlbuki iki embriyo transferinde canlı doğum oranları yüksekken, çoğul gebelik oranları da anlamlı olarak fazladır. Tek embriyo transferinde ise transfer sonrası gebelik elde edilmezse bile aynı siklusta elde edilmiş embriyoların dondurma-çözme işlemleri sonrası transferi, kümülatif gebelik oranlarını iki embriyo transfer edilen grup ile eşit düzeylere yükseltmektedir. Böylece maliyet düşmekte, çoğul gebeliklerin maternal ve fetal komplikasyonları azalmaktadır. IVF çocuklarının miadında ve sağlıklı tek çocuk olarak doğma hakları, tek embriyo transferi politikasıyla olanaklı bulunmaktadır. Açıklanan nedenlerle yönetmelikte tek embriyo transfer edilmesinin esas olduğu hususu düzenleme alanı bulmuş bulunmaktadır ve bu düzenlemedeki asıl hedef çoğul gebeliklerin sayısının olabildiğince azaltılmasıdır.

SORU 3- ÜYTE Uygulamalarında transfer edilen embriyo sayısının azaltılmasının, gebe kalma ve gebeliğin devam etmesi ile canlı bebeğin kucağa alınmasına etkileri konusunda Bakanlık tarafından yapılan araştırma var mıdır? Varsa araştırma sonuçları nelerdir?

CEVAP 3- Son on yılda tek embriyo transferi IVF/ICSI uygulamalarında çok yüksek olan çoğul gebelik oranlarını düşürmek, erken doğumları engellemek, yeni doğan ünitelerindeki

yer sıkıntısını önlemek ve maddi kayıpları ortadan kaldırmak amacıyla tüm dünyada ve Türkiye'de uygulanmaya başlanan embriyo transfer seçim kriteridir.
Tek embriyo transferi uygulayan ülkelerde(örn. İsveç, Finlandiya, Belçika gibi) çoğul gebelik oranları dramatik şekilde düşerken, uygulamayan ülkelerde(örn. ABD gibi) çoğul yüksek gebelik oranları ve sorunlar erken doğumlar, neonatal komplikasyonlar artmaya devam etmektedir.

Türkiye'de 2009 yılında tek embriyo transferi zorunluluğu yokken 2 ve 3 embriyo transferi tercih edilmekte idi. Bu da aşağıdaki tabloda görülmektedir. 2010 yılı itibarı ile tek embriyo transferi zorunluluğu ile birlikte tek bebek doğumunun arttığı, neonatal komplikasyonların azaldığı görülmektedir. Klinik gebeliklerde azalmanın olmadığı aksine artışın olduğu gözlenmektedir.

Türkiye'de ÜYTE mevzuatında belirtildiği gibi belli koşullarda tek embriyo transferi uygulamasının başarılı sonuçlar verdiği yurt içi merkezlerin ekte sunulduğu üzere yapmış olduğu çalışmalarla da onaylanmaktadır. (Ek-1)

SORU 4- ÜYTE Uygulamalarında transfer edilen embriyo sayısının artırılması konusunda Bakanlık tarafından yapılan/yapılması planlanan çalışma var mıdır? Varsa nelerdir?

CEVAP 4- ÜYTE Uygulamalarında transfer edilen embriyo sayısının artırılması konusunda Bakanlık tarafından yapılan/yapılması planlanan çalışma bulunmamaktadır.

Göstermiş olduğunuz ilgiden dolayı teşekkür ederim.

Ek-1/1

Tablo: Türkiye'de yıllara göre İVF merkezi sonuçları

	2009	2010	2011	2012
Toplam Merkez sayısı	110	115	115	126
Toplam Siklus sayısı	44.449	48.801	64325	72828
Toplam Embriyo transferi	36.498	40.090	51989	57310
Tüm Klinik Gebelikler	14.298	15.588	16673	17766
Canlı doğumlar	4.885	6.539	6245	5762
Spontan abortuslar (<20. hafta)	1.791	2.040	1792	1790
Medikal abortuslar	241	434	243	308
Ektopik gebelikler	292	229	153	146
Takipten kaybolanlar (Kontrole gelmeyenler)	4.484	1.902	1301	1701
Tek embriyo transferi sayısı	5.367	22.141	21.293	25.040
Çift embriyo transferi sayısı	10.537	14.495	13.279	14.863
Üç embriyo transferi sayısı	18.086	2.882	54	63
Tekil doğumlar	2.929	5.143	5198	4895
İkiz doğumlar	1.714	1.734	1085	917
Üçüz doğumlar	150	73	5	4

Dördüz doğumlar	**1**	**5**	**1**	**0**
Erken neonatal ölümler	**323**	**323**	**53**	**65**
Gebelik/Siklus	**% 32.16**	**% 31.94**	**%25.91**	**%24.39**
Gebelik/ET	**%39,17**	**%38.88**	**%32.07**	**%30.99**
Canlı doğum/ET	**%13.4**	**%16.3**	**%12**	**%10**
Canlı doğum / Siklus sayısı	***% 10.99***	***% 13.39***	***%9.7***	***%7.9***
Tekiz gebe/Canlı doğum	***%61***	***%73.4***	***%82.6***	***%84.1***
İkiz gebelik/Canlı doğum	***%35.7***	***%24.9***	***%17.3***	***%15.8***

Ek-1/2

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Mandatory single embryo transfer policy dramatically decreases multiple pregnancy rates

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Abstract

Aim: The aim of this study is to determine the effect of a mandatory single embryo transfer (SET) policy on pregnancy rates and multiple pregnancy rates in intracytoplasmic sperm injection (ICSI) cycles.

Methods: One hundred and twenty-eight patients (154 cycles) underwent ICSI before the Turkish Ministry of Health's legislation, 55 patients (69 cycles) underwent ICSI after the legislation (day-3 embryo transfers only) and 35 patients (39 cycles) who underwent ICSI after the legislation (day-5 embryo transfers only).

Results: Groups were comparable regarding the women's mean age and body mass index. The number of embryos transferred (2.7 ± 0.5 vs 1.0 ± 0.0 vs 1.0 ± 0.0) was significantly higher in group I, compared to group II and group III. Clinical pregnancy per embryo transfer (40.8% vs 15.1% vs 36.1%) and live birth rate (37.7% vs 13.2% vs 30.6%) were significantly lower in group II when compared to group I and group III. Multiple pregnancy rates (39.6% vs 0.0%, vs 0.0%) were significantly higher in group I when compared to group II and III. Implantation rates were significantly higher in group III when compared to group I and group II. Miscarriage rates were comparable among the groups.

Conclusion: The mandatory SET policy caused a dramatic decrease of multiple pregnancy rates. Mandatory SET with only day-3 embryo transfers decreased the pregnancy rates but this detrimental effect was not seen in cycles with day-5 embryo transfers.

Key words: assisted reproductive technology, intracytoplasmic sperm injection, mandatory single embryo transfer, multiple pregnancies, single embryo transfer.

Introduction

Multiple pregnancies are a complication of the *in vitro* fertilization (IVF) procedure because they are associated with a dramatic increment of both fetal mortality and morbidity.[1] The most effective strategy for reducing multiple pregnancy rates in IVF cycles is to reduce the number of transferred embryos.[2]

In Turkey, before March 2010, the maximum number of transferred embryos was limited to three in normal circumstances, but more than three embryos could be still transferable if indications, such as advanced maternal age and poor quality embryos, were present and documented. In March 2010, the Turkish Ministry of Health declared legislation which restricted the number of transferred embryos. According to this legislation, single embryo transfer (SET) is mandatory for the first and second cycles in patients whose age is less than 35 years, regardless of any unfavorable factors such as poor quality embryos and absence of embryo for cryopreservation.

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Conflict of interest: None.

The aim of our study is to determine the effect of the mandatory SET (mSET) policy on pregnancy rates and multiple pregnancy rates.

Methods

Two hundred and eighteen consecutive infertile patients (262 cycles) during July 2006 to September 2011 were enrolled retrospectively through our computerized IVF database system. Inclusion criteria were: (i) first or second fresh intracytoplasmic sperm injection (ICSI) cycle; (ii) women aged less than 35 years; and (iii) patients who underwent gonadotropin-releasing hormone (GnRH) antagonist cycle. We divided these cycles into three groups based on the date of the Turkish Ministry of Health's legislation which strictly limited the number of transferred embryos to one only regardless of any unfavorable factors and the time of embryo transfer (ET; day-3 or day-5 transfers). Group I constituted 128 patients (154 cycles) who underwent ICSI before the legislation (only day-3 transfers included); group II constituted 55 patients (69 cycles) who underwent ICSI after the legislation (only day-3 transfers included); and group III constituted 35 patients (39 cycles) who underwent ICSI after the legislation (only day-5 transfers included). In group I the maximum number of transferred embryos was limited to three in normal circumstances, but more than three embryos could still be transferable if indications, such as poor quality embryos, were present and documented. In groups II and III, SET was mandatory regardless of any unfavorable factors.

All patients underwent controlled ovarian hyperstimulation consisting of cetrorelix (Cetrotide; Serono, Istanbul, Turkey) and recombinant follicle-stimulating hormone (FSH) (Gonal-F; Serono, Istanbul, Turkey) using the step-down protocol. When desensitization was achieved, as evidenced by plasma E2 levels of 50 pg/mL or less, the absence of ovarian follicles and endometrial thickness 6 mm or less on transvaginal ultrasound examination,[3] daily s.c. injection of recombinant FSH (Gonal-F) was commenced. The starting dose of gonadotropin was determined based on female age, antral follicle count at baseline transvaginal ultrasonography, day-3 FSH and estradiol (E2) levels, body mass index (BMI) and previous ovarian response, if available. Ovarian response was monitored with frequent serum E2 measurements and transvaginal ultrasonography, as described previously.[4] Flexible GnRH antagonist protocol was used. If serum E2 level was more than 600 pg/mL and/or if leading follicle exceeding 14 mm in diameter were present, cetrorelix 0.25 mg was initiated as daily injections up to the day of oocyte pick-up.

The criterion for hCG (Ovitrelle 250 μgram; Serono) administration was the presence of three or more follicles exceeding 17 mm in diameter. Oocyte retrieval was carried out under local anesthesia using vaginal ultrasound-guided puncture of follicles 36 h after hCG administration. Standard procedures were carried out for gamete-embryo handling and cleavage-stage ET, or blastocyst transfer was performed under abdominal ultrasonography guidance in all cases using a soft catheter (Wallace; PM Group, Istanbul, Turkey). The luteal phase was supported by daily vaginal progesterone suppositories (Crinone; Serono) starting 1 day after oocyte pick-up.

Clinical pregnancy was defined as the presence of an intrauterine gestational sac by transvaginal ultrasonography. Symptomatic patients with moderate or severe ovarian hyperstimulation syndrome were hospitalized.[5]

The statistical analyses were performed using SPSS ver. 17.0. The χ^2-test and Fisher's exact test were used to analyze nominal variables in the form of frequency tables. Normally distributed (Kolmogorov–Smirnov test) parametric variables were tested by one-way ANOVA. Bonferroni test was used for post-hoc multiple comparison. Non-normally distributed metric variables were analyzed by Kruskal–Wallis *H*-test. *P*-values of less than 0.05 were considered statistically significant. Values were expressed as mean ± standard deviation, unless stated otherwise.

Results

Groups were comparable regarding the women's mean age and BMI (Table 1). The total dose of FSH used (ampules) and the duration of stimulation (days) were comparable among the groups (Table 2). The mean number of follicles (>17 mm, 15–17 mm) at hCG administration were higher in group III when compared to group I and II. E2 level on the day of hCG administration and the mean number of follicles (10–14 mm) at hCG administration were lower in group II when compared to groups I and III (Table 2).

There were significant differences between each group regarding the numbers of retrieved oocyte–cumulus complexes, metaphase II oocytes and two

Table 1 Baseline characteristics of groups I, II and III

Variable	Group I	Group II	Group III	*P* value
No. of patients	128	55	35	
No. of cycles	154	69	39	
No. of canceled cycles (*n*, %)	24 (15.6)	16 (23.2)	3 (7.7)	NS
Female age (years)	28.9 ± 3.2	29.8 ± 3.6	28.5 ± 3.9	NS
Body mass index (kg/m2)	25.1 ± 4.4	25.4 ± 3.8	26.7 ± 5.0	NS
Duration of infertility (m)	67.7 ± 37.2	66.9 ± 50.7	63.4 ± 42.1	NS

NS, not significant.

Table 2 Controlled ovarian hyperstimulation response of groups I, II and III

Variable	Group I	Group II	Group III	*P*-value
Duration of stimulation (days)	9.0 ± 1.6	9.2 ± 2.0	9.4 ± 1.5	NS
Total dose of FSH used (ampules)	35.1 ± 9.5	35.0 ± 17.6	30.8 ± 11.2	NS
E2 level on the day of hCG administration (pg/mL)	1932.8 ± 1181.5	1349.8 ± 1010.7†	2411.7 ± 1424.2	<0.05
No. of follicles >17 mm in diameter at hCG administration	3.3 ± 2.0	2.9 ± 2.0	4.6 ± 3.4‡	<0.05
No. of follicles 15–17 mm in diameter at hCG administration	3.1 ± 2.1	2.5 ± 2.9	4.5 ± 2.8‡	<0.05
No. of follicles 10–14 mm in diameter at hCG administration	7.0 ± 5.2	4.6 ± 4.8†	7.6 ± 6.4	<0.05
Endometrial thickness at hCG administration (mm)	10.8 ± 2.6	10.5 ± 2.0	11.0 ± 2.4	NS

†Group II is significantly different from groups I and III. ‡Group III is significantly different from groups I and II. NS, not significant.

Table 3 Embryological data and pregnancy outcome of groups I, II and III

Variable	Group I	Group II	Group III	*P*-value
No. of oocyte–cumulus complexes	10.5 ± 3.8†	7.6 ± 6.1‡	13.5 ± 6.4§	<0.01
No. of metaphase II oocytes	8.5 ± 3.4†	6.0 ± 5.3‡	11.4 + 5.3§	<0.01
Metaphase II oocytes/total oocytes (%)	80.6	78.9	76.2	NS
2-Pronucleated/metaphase II oocytes (%)	77.7	75.2	78.4	NS
No. of 2-pronucleated oocytes	6.6 ± 3.1†	4.8 ± 4.2‡	9.0 ± 3.1§	<0.01
No. of embryos transferred	2.7 ± 0.5	1.0 ± 0.0	1.0 ± 0.0	<0.01
Rate of SET (%)	3.8†	100	100	<0.01
No. of cycles with embryo freezing (%)	29.8†	50.9	51.4	<0.05
Clinical pregnancy/embryo transfer (*n*, %)	53 (40.8)	8 (15.1)‡	13 (36.1)	<0.05
Clinical pregnancy/OPU (%)	39.3	14.5‡	35.1	<0.05
Implantation rate (%)	19.0	15.1	36.1§	<0.05
Live birth rate/embryo transfer (*n*, %)	49 (37.7)	7 (13.2)‡	11 (30.6)	<0.01
Multiple pregnancy rate (%)	39.6†	0	0	<0.01
Twins (%)	35.8†	0	0	<0.01
Triplet (%)	3.8	0	0	NS
Miscarriage rate (*n*, %)	4 (7.5)	1 (12.5)	2 (15.3)	NS

†Group I is significantly different from groups II and III; ‡Group II is significantly different from groups I and III; §Group III is significantly different from groups I and II. NS, not significant; OPU, oocyte pick-up; SET, single embryo transfer.

pronucleated oocytes (Table 3). The metaphase II oocytes/number of total oocyte–cumulus complexes ratio and fertilization rate did not differ between groups (Table 3).

As expected, the number of embryos transferred (2.7 ± 0.5 vs 1.0 ± 0.0 vs 1.0 ± 0.0) was significantly higher in group I, compared to groups II and III. Clinical pregnancy per ET (40.8% vs 15.1% vs 36.1%) and live birth rate (37.7% vs 13.2% vs 30.6%) were significantly lower in group II when compared to groups I and III (Table 3). Multiple pregnancy rates (39.6% vs 0.0% vs 0.0%) were significantly higher in group I when compared to groups II and III. Implantation rates were significantly higher in group III when compared to groups I and II. Miscarriage rates were comparable among the groups.

Discussion

The neonatal death rate of singleton pregnancies is 7.8 per 1000 live births; this number increases sevenfold in twins and 22-fold in triplet and higher order multiple pregnancies.[2] The incidence of cerebral palsy is approximately 2 per 1000 live births in the general population and is estimated to increase to 9, 31 and 111 per 1000 live births in twin, triplet and quadruplet pregnancies, respectively.[1,6] Twin pregnancies are also associated with a higher risk of maternal hypertension, cesarean section, post-partum hemorrhage and maternal death compared with singleton pregnancies.[7] Furthermore, twin pregnancies are associated with markedly increased costs to the family and society.[7,8] There is no doubt that high order pregnancies are a complication of assisted reproductive technology (ART). According to current data, twins should also be accepted as a complication of ART and their prevention should be considered.[7,8] In our study, there were no high order pregnancy (triplets and more) and twin pregnancy in groups II and III. However, in group I, 19 patients had twin (35.8%) and two patients had triplet (3.8%) pregnancies. We think that these rates are extremely high. The mSET policy (groups II and III) caused a dramatic decrease in multiple pregnancy rates in our study (39.6% vs 0.0%).

Single ET is the most effective way of reducing multiple pregnancy rates associated with ART.[9] Data from 31 countries suggest that there has been a gradual increase in SET rates over a 3-year period (2003–2005).[9] SET rates are highest in Sweden (69.4%), but are as low as 2.8% in the USA.[9] In Turkey, the overall rate of SET was less than 10% in 2004.[9] In our study, we noted that the rate of SET in group I is 3.8% which is very low when compared to the overall rate of SET in Turkey. However, in Turkey after March 2010, SET became mandatory for the first and second ICSI cycles for patients who are younger than 35 years old, regardless of any unfavorable factors. We think that highest SET rates will be evident in Turkey in the near future.

Karlstrom *et al.*[10] in 2007 analyzed the annual reports from 16 IVF clinics in Sweden for the time period 1991–2004. They noted that elective SET started as early as 1999 on a small scale (1.5% of all transfers), with a marked increase from 2002 and onwards with 21.2% elective SET and 30.6% SET in 2002; 41.3% elective SET and 54.3% SET in 2003; 51.0% elective SET and 67.4% SET in 2004. Concomitantly, the multiple birth rates decreased dramatically: 19.4% in 2002, 11.8% in 2003 and 5.7% in 2004 while the live birth rate per transfer was stable: 26.8% in 2002, 26.4% in 2003 and 25.0% in 2004. In the study of Karlstrom *et al.*, the rates of day-3 or day-5 transfers were not mentioned. But we guessed that the day-5 ET was preferred by most of the IVF clinics in which SET was performed.

According to a European Society of Human Reproduction and Embryology report in 2007 (collected from 33 European countries including Turkey), the total percentage of SET was 21.4% (22.1% in 2006), double ET (DET) 53.4% (57.3% in 2006), triple ET 22.7% (19.0% in 2006) and four or more ET 2.5% (1.6% in 2006). The highest levels were found in Sweden (69.9%), Finland (57.8%) and Belgium (50.2%).[11] The proportion of triple ET ranged from 0% in Sweden to 58.6% in Greece. Transfer of four or more embryos ranged from 0% in 10 countries and less than 1% in three to 18.3% in Macedonia. On average, pregnancy rates were 29.1% (+0.1% compared with 2006) and 28.6% (21.3%) per aspiration for IVF and ICSI. In our study, in group I (no limitation of the number of embryos transferred), the clinical pregnancy and live birth rates were 40.8% and 37.7%, respectively. But after the mSET policy started we could only achieve a clinical pregnancy rate of 15.1% and live birth rate of 13.2% with only day-3 ET (group II). However, this detrimental effect of mSET was not seen when we performed day-5 ET and we could achieve a clinical pregnancy rate of 36.1% and live birth rate of 30.6% (group III). This pregnancy rate is comparable with the average pregnancy rate of European countries. But one should not forget that all of our patients underwent mSET instead of elective SET.

Ryan *et al.*[12] in 2007 stated that mandatory single blastocyst transfer (mSBT) resulted in excellent pregnancy rates (66.2% vs 63%), similar to two-blastocyst transfer, but with markedly decreased twin rates (41% vs 2%). They underwent mSBT if the woman was under 38 years with more than seven embryos, no previous failed IVF cycles and at least one good quality blastocyst. Recently, Csokmay *et al.*[13] in 2011 noted that an impressive reduction in the multiple gestation rates in their study is similar to that reported by Ryan *et al.*.[12] The inclusion criteria (women <38 years with >7 embryos, no previous failed IVF cycles and at least one good quality blastocyst) for mSBT were similar in both studies. Csokmay *et al.*[13] stated that the clinical pregnancy rates before (67.7%) or after (63.5%) the mSBT policy were not statistically significantly different. Multiple gestation rates were statistically significantly reduced, from 43.8% to 14.6%, after the mSBT policy

was instituted. In both the above-mentioned studies, mSBT was performed in patients with good prognosis. However, in our study, SET was mandatory regardless of any unfavorable factors in groups II and III. We think that is why our pregnancy rate is low when compared to both the above-mentioned studies.[12,13] Recently, Kutlu *et al.*[14] from Turkey reported that the clinical pregnancy rate was 15.6% with mSET. We think that the new Turkish legislation is very beneficial in reducing multiple pregnancy rates, but mSET with day-3 embryos should not be performed if any unfavorable factors are present, such as poor quality embryos, loss of embryos for cryopreservation, one or more failed IVF and poor ovarian response. Day-5 ET should be preferred instead of day-3 ET in mSET cycles.

In conclusion, the mSET policy caused a dramatic decrease of multiple pregnancy rates, especially twins. This was very satisfactory and the desired result, but mSET also caused a dramatic decrease of pregnancy rates when day-3 ET were performed. However, mSET policy with day-5 transfers resulted in comparable pregnancy rates with those of cycles in which the number of embryos transferred was not restricted. According to our study, the mSET policy is reasonable. However, the selection of good quality embryos is critical in mSET, so that longer culture of embryos until day 5 is recommended whenever possible. However, in some patients, day-5 ET is impossible due to some unfavorable factors, such as poor embryo quality, and day-3 ET is mandatory for those patients. From our point of view, in patients for whom day-5 ET is impossible in the previous cycle mSET policy should be reconsidered. For these patients, day-3 DET for the second cycle could be considered. DET for these patients could improve pregnancy rates. But one should not forget that multiple pregnancies are a still problem in DET cycles.

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SINGLE EMBRYO TRANSFER

The impact of single embryo transfer policy on pregnancy outcomes after legislative change

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Abstract

We evaluated the effect of mandatory single embryo transfer (SET) on live birth rates and pregnancy outcomes in Turkey. A retrospective study was conducted in Zekai Tahir Burak Women's Health Education and Research Hospital. Four hundred and four patients undergoing intracytoplasmic sperm injection (ICSI) cycles were included in the study. In Turkey, the number of embryos to be transferred in an assisted cycle was limited to three under normal circumstances until 6 March 2010. After that, new legislation was introduced to promote the application of SET. Outcomes were compared in periods of 1 year before and after the new law. We compared pregnancy outcomes of all assisted reproductive cycles in SET cycles (group 1: $n=281$) with double embryo transfer (DET) cycles (group 2: $n=123$). There were significant differences in oocyte number, multiple pregnancy, gestational age, birth weight and perinatal fetal morbidity between the groups ($p=0.023$, 0.001, 0.001, 0.001, 0.001, respectively). But there were no differences in age, baseline FSH, infertility period, stimulation protocol, stimulation day, gonadotrophin dose, clinical pregnancy rate, abortion rate, live birth rate and cesarean rate ($p>0.05$). These results suggest that under the new legislation multiple pregnancy rates and perinatal complications are significantly reduced without causing a significant decline in the pregnancy rates.

Keywords

New legislation, pregnancy outcome, single embryo transfer

History

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Introduction

The first birth after in vitro fertilization (IVF) and embryo transfer was reported in 1978 [1]. Despite ongoing advances in the associated assisted reproductive technologies (ART), pregnancy rate remains around 20–30% per started cycle and lower implantation rates per transferred embryo than those in natural cycles remain a major problem. The increasing success of IVF in the 1990s did not just result in an increased pregnancy rate, but especially in an increase in the incidence of multiple births. Several cost studies have demonstrated the impact of multiple births on health care resources [2–4].

Compared to singletons, multiple gestations have an increased risk of pregnancy complications. Multiple births are also associated with adverse perinatal outcomes. Prematurity, which is the commonest perinatal complication, is the most frequent cause of perinatal death [5]. This complication could be eliminated by the use of a single embryo transfer (SET). There is a trend in Europe and Canada to promote SET [6].

In Turkey, new legislation regarding SET policy from 6 March 2010 permitted the transfer of only one embryo in the first and second cycles for patients under 35 years, a maximum of two embryos in the third or further cycles and for patients older than 35 years (regardless of the embryo quality). Papers presenting the clinical and multiple pregnancy rates after the new law have been published [7]. This article examines the impact of SET policy on pregnancy outcomes after legislative change in Turkey. It presents the findings and outcomes comparison with the data from 2009.

Materials and methods

A retrospective study was conducted in Zekai Tahir Burak Women's Health Education and Research Hospital, Reproductive Endocrinology Department; outcomes of 404 fresh, non-donor, unexplained intracytoplasmic sperm injection (ICSI) cycles were reviewed in periods of 1 year before and after the new law. Women were included in the study if they were aged 20–35 years. All of them had body mass index between 18 and 29 kg/m^2, regular menstrual cycles, no existence of polycystic ovaries, no presence of endometriosis or uterine abnormalities in the ultrasound, no previous adnexal surgery and normal basal hormonal levels during the cycle before stimulation. The exclusion criteria were history of recurrent pregnancy loss, any significant systemic disease or endocrine or metabolic disorder, a low or high response to gonadotrophin stimulation in a previous cycle, any indication for preimplantation genetic diagnosis or screening or concomitant medication interfering with the purposes of the study. This study was approved by the institutional review board of the hospital.

Data were collected for age, baseline day 3 FSH level, infertility period, stimulation parameters (stimulation protocol, stimulation day, total gonadotrophin dose), laboratory ART

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outcomes (oocytes, embryos available) and clinical outcomes (clinical pregnancy, multiple pregnancy, abortion, live birth rate, gestational age, birth weight, pregnancy outcome, neonatal intensive care unit (NICU) admissions).

The pituitary down-regulation was achieved and maintained using the long agonist or antagonist protocol. Recombinant (rec) FSH or human menopausal gonadotrophin was used for controlled ovarian hyperstimulation. The initial gonadotrophin dose used for ovarian stimulation was individualized according to the patient's age, baseline serum FSH concentrations on day 3, body mass index and previous response to ovarian stimulation. The starting regimen was fixed for the first three days (150–225 IU rec FSH/day), and thereafter the dose of gonadotrophin was adjusted according to the individual ovarian response. Serial estrogen levels and two-dimensional follicle measurements by transvaginal ultrasonography (LOGIC 200 PRO, GENERAL ELECTRIC, Seoul, South Korea) were performed until at least two dominant follicles reached dimensions of 18 mm or greater in diameter. Human chorionic gonadotrophin (HCG) was administered and oocytes were retrieved 36 h after HCG injection and then ICSI was applied as a result of our clinical procedure. Luteal phase support was routinely given as progesterone in the form of Crinone 8% gel (Serono, Istanbul, Turkey) 90 mg daily for 14 days, until a pregnancy test was performed. Clinical pregnancies were defined as those with fetal heart activity documented on ultrasound examination at 4–5 weeks after embryo transfer. Ongoing pregnancy was described as the presence of at least one viable fetus beyond gestation week 20 confirmed by ultrasound examination. Preterm birth was defined as child birth occurring at less than 37 completed weeks. The NICU admission criteria were same before and after the new legislation.

Statistical analysis

The data were analyzed with SPSS (Chicago, IL, USA) for Windows 15 package program. Shapiro-Wilk test was used to find out normality. Continuous data were expressed as mean ± standard deviation, or median (min–max). Categorical data were expressed as percentages. Whereas, means were compared among groups by independent samples t test, otherwise, comparison of medians was performed by Mann–Whitney U test according to the number of independent groups. A p value of <0.05 was considered statistically significant.

Results

Table 1 shows the IVF cycle outcomes in patients with SET, comparing those in the multiple embryo transfer group. In compliance with new legislation, not more than one oocyte was inseminated in each cycle. Four hundred and four ICSI cycles meeting inclusion criteria were performed in our center, with an overall clinical pregnancy rate of 35% per embryo transfer.

There were significant differences in oocyte number, multiple pregnancy, gestational age, birth weight and perinatal fetal morbidity between the groups ($p=0.023$, 0.001, 0.001, 0.001, 0.001, respectively). Twelve twin clinical pregnancies were ascertained. The mean gestational age and mean birth weight were significantly higher in SET group. But there were no differences in age, baseline FSH, infertility period, stimulation protocol, stimulation day, gonadotrophin dose, clinical pregnancy rate, abortion rate, live birth rate and cesarean rate ($p>0.05$).

Discussion

It is shown that considering the high twin pregnancy rate associated with double embryo transfers (DETs); SET is likely to be the preferred option for most women aged ≤36 years [8]. Grady et al. [9] revealed that elective SET is associated with decreased risks of preterm birth and low birth weight compared with DET but higher risks of preterm birth compared with spontaneously conceived singletons. From the point of view of cost-effectiveness, today DET is always more expensive than SET [10].

Turkey's new legislation was fully implemented in March 2010. Another study from the NICU of our hospital also assessed the 2010 Turkish reproductive regulation requiring SET [11]. But they included all ART pregnancies at different ART centers admitted to the NICU between February 2010 and October 2011. Because our center is a tertiary referral hospital, high risk pregnancies, including multiple pregnancy, from different hospitals admit us. Our study differs from that by including only ART cycles performed at our center. They found that the rates of prematurity and low birth weight, very low birth weight and extremely low birth weight infants were significantly lower in SET group. In the present study, the mean gestational age and mean birth weight were also significantly higher in SET group.

van Montfoort et al. [12] revealed that the consequence of elective SET would be a halving of the ongoing pregnancy rate

Table 1. Outcomes in patients with single embryo transfer, comparing those in the multiple embryo transfer group.

	Single embryo transfer (group 1) $n=281$	Multiple embryo transfer (group 2) $n=123$	p
Age (years)*	28 (18–34)	29 (20–34)	0.350
Baseline FSH (mIU/ml)*	6.02 (2.33–12.10)	5.7 (2.52–11.63)	0.632
Infertility period (year)*	5 (1–17)	6 (1–17)	0.227
Stimulation protocol, n	Long GnRHa: 250 Antagonist: 31	Long GnRHa: 106 Antagonist: 17	0.425
Stimulation day*	10 (6–17)	10 (7–16)	0.586
Gonadotrophin dose (IU)**	1600 (198.69)	1650 (211.21)	0.321
Retrieval oocyte**	10 (193.81)	10 (222.35)	**0.023**
Clinical pregnancy/embryo transfer, n (%)	120 (42.70)	42 (34.14)	0.106
Abortion/clinical pregnancy, n (%)	31 (25.8)	10 (23.8)	0.795
Multiple pregnancy/clinical pregnancy, n	0	12	**0.001**
Live birth rate/clinical pregnancy, n (%)	89 (74.16)	32 (76.19)	0.795
Live birth rate/transfer (%)	31.7	26	0.253
Gestational age (week)*	38 (28–41)	37 (25–40)	**0.001**
Birth weight (g)	3152 ± 433.93	2535 ± 912.97	**0.001**
Cesarean section/ongoing pregnancy, n (%)	68 (76.4)	24 (75)	0.873
Perinatal fetal morbidity/ongoing pregnancy, n (%)	7 (7.9)	19 (59.4)	**0.001**

*Values are median (minimum–maximum).
**Median (mean rank).
Bold values show significance, $p<0.05$.

when compared to applying a DET policy in all patients. They also argued that the transfer of one embryo in a selected group of good prognosis patients leads to a less drastic reduction in pregnancy rate but maintained a twin pregnancy rate of 12.9%. This was a randomized controlled trial which was conducted comparing SET and DET in an unselected group of patients. Veleva et al. [13] showed that the elective SET policy could be applied to patients aged 36–39 years, reducing the risk of multiple births and increasing the safety of ART in this age group. The Cochrane review of trials by Pandian et al. [14] found that elective SET resulted in fewer multiple pregnancies than DET, but the pregnancy and live birth rate per fresh IVF cycle was lower. They also revealed that the cumulative live birth rate associated with SET followed by a single frozen and thawed embryo transfer was comparable with that after one cycle of DET, while still maintaining a significantly lower rate of multiple births.

The results of Kutlu et al. [7], which is a multicenter study, showed that the pregnancy and clinical pregnancy outcomes after the new law had decreased by about 5% which was statistically not significant, whereas the decrease in the multiple pregnancy rates was highly significant (from 23.1% to 5.3%). Our results also suggested that SET policy reduced the twin pregnancy rate without reducing the whole pregnancy rate.

We believe that the new legislation introduced several important reforms in relation to multiple pregnancies and related complications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Pregnancy outcomes in a university hospital after legal requirement for single-embryo transfer

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ABSTRACT

Objective: To present our in vitro fertilization outcomes after implementation of the Turkish government policy limiting the number of transferred embryos to one, in women under the age of 35, and two, in women over age 35; and to demonstrate the feasibility of this policy.
Study design: We retrospectively reviewed the records of 423 patients who underwent ovarian stimulation, oocyte pick-up, intracytoplasmic sperm injection and embryo transfer due to primary or secondary infertility over a 22-month time interval. Clinical pregnancy was defined as a fetal heartbeat in the seventh gestational week. Embryo transfers were carried out on day 3 or 5. Descriptive statistics are given as the number of subjects and percentages.
Results: A total of 353 embryo transfers were performed: 261 (73.9%) were single-embryo transfer (244 (69.1%) elective and 17 (4.8%) non-elective) and 92 (26.1%) were double-embryo transfer. Of the 244 elective single-embryo transfers, 6.6% ($n = 16$) were performed using frozen-thawed embryos. The average patient age was 29.6 ± 4.5 years in the single-embryo group and 36.5 ± 2.4 years in the double-embryo group. The cumulative pregnancy rates per oocyte pick-up were similar in both groups: 41% ($n = 107$) in the single-embryo group and 43.4% ($n = 40$) in the double-embryo group ($p = 0.678$). The cumulative live birth rate of the single-embryo group (32.1%) was not statistically different from the double-embryo group (35.8%) ($p = 0.518$). The twin pregnancy rate after single-embro transfer was significantly lower than with double-embryo transfer (2.8% ($n = 3$) vs. 32.5% ($n = 13$); $p < 0.001$) and 62.5% of the twin pregnancies occurred in women 35 years or older who underwent double-embryo transfer. No significant difference in the spontaneous abortion rates was recorded between the single- and double-embryo transfer groups (16 (6.1%) vs. 6 (6.5%); $p = 0.894$).
Conclusion: Single-embryo transfer results in a pregnancy rate comparable to double-embryo transfer, with a significantly reduced multiple pregnancy rate. Double-embryo transfer in patients over age 35 should be reconsidered because of the resulting high rate of multiple pregnancy.

1. Introduction

Recent advances in assisted reproductive technology have resulted in higher pregnancy rates for patients, but iatrogenic multiple pregnancies and complications related to high-order multiples have also increased because of multiple embryo transfer (ET) strategies [1–3]. Current research into assisted reproductive technology is mainly aimed at increasing its success rate and preventing complications. The UK Human Fertilization and Embryo Authority recommends elective single-embryo transfer to lower the rate of multiple pregnancies resulting from in vitro fertilization (IVF), and targets a reduction in twin pregnancy rates to below 10% [4]. In Europe and the USA, the current reported rate of live multiple births resulting from assisted reproductive technology is 20–30%, and approximately one-third of all twin pregnancies occur after IVF or intracytoplasmic sperm injection [5–7]. As prematurity and its associated complications are 4–10 times more common in twin pregnancies compared with singletons, and as health-care costs of IVF newborns are 5.4 times

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higher than in other neonates, it is crucially important to build an IVF embryo-transfer policy with evidence-based guidelines [8,9]. At this point, the success of IVF should not be defined only by clinical pregnancy rates, but also by the ratio of healthy newborns. Elective single-embryo transfer seems to be the only way to decrease multiple pregnancies and their related complications [10].

In Europe, only 15% of all IVF cycles are characterized by elective single-embryo transfer [11]. This technique is less favoured in clinical practice because of its lower pregnancy rate compared with multiple-embryo transfer, because of inadequate information provided to couples receiving IVF treatment about multiple pregnancy and related complications, and because of health care reimbursement systems that force patients and providers to pay for a certain number of IVF cycles before coverage begins [12].

Although it may be challenging to apply elective single-embryo transfer policies without lowering the pregnancy rate, it should not prove impossible. There is evidence from current trials that single-embryo transfer shows no significant decrease in pregnancy rates compared with double-embryo transfer, as long as the best embryo is chosen for transfer and the results of subsequent frozen-embryo replacement cycles are combined with those of the fresh embryo cycles [1,13,14].

According to a new government limitation on the reimbursement system in Turkey, implemented on March 1, 2010, only one embryo may be transferred in women under age 35 for the first two IVF attempts, regardless of the embryo selection criteria. If the infertile woman is aged 35 years or older, double-embryo transfer is allowed in any cycle. The transfer of more than two embryos is no longer permitted under any circumstances.

Therefore since then the elective single-embryo transfer has been the routine IVF protocol in Turkey. We aimed to investigate the effects of elective single-embryo transfer on the twin pregnancy rate in our university hospital's IVF centre.

2. Materials and methods

2.1. Patient selection

We retrospectively examined the records of 423 patients who underwent ovarian stimulation, intracytoplasmic sperm injection and subsequent embryo transfer. The infertility diagnoses allowed for inclusion were bilateral tubal obstruction, anovulation, pelvic adhesions, endometriosis, unexplained infertility or serious male-factor infertility. All patients were treated in our institution's IVF unit between March 1, 2010 and December 31, 2011. All patients enrolled in this study gave informed consent and the study was approved by the ethical committee of our university hospital.

2.2. Controlled ovarian hyperstimulation

Leuprolide acetate (Lucrin; Abbott Laboratories S.A., Istanbul, Turkey) was used as a gonadotropin releasing hormone (GnRH) agonist and cetrorelix acetate (Cetrotide; MerckSerono S.A., Istanbul, Turkey) was used as a GnRH antagonist. Recombinant follicle stimulating hormone (Gonal-F; MerckSerono S.A., Istanbul, Turkey or Puregon; Schering-Plough, Istanbul, Turkey) were administered in all ovarian-stimulation protocols. All follicular-phase monitoring was performed in our IVF unit. Final maturation was promoted when the mean diameter of at least 3 follicles, measured in 2 planes, reached 16–18 mm: intramuscular injection of either 10,000 IU human chorionic gonadotropin (Pregynl; Schering-Plough, Istanbul, Turkey) or 250 mcg recombinant human chorionic gonadotropin (Ovitrelle; MerckSerono S.A., Istanbul, Turkey) was used for this purpose. Oocyte retrieval was performed 36 h later, using transvaginal ultrasound-guided follicular puncture under general anaesthesia.

After embryo transfer, the luteal phase support was administered vaginally, either with progesterone vaginal gel (Crinone 8%, 90 mg/day; Serono S.A., Geneva, Switzerland) or with micronized progesterone (Progestan, 600 mg/day; Koçak Farma Onkoloji, Istanbul, Turkey).

2.3. Embryo-transfer policy

Intracytoplasmic sperm injection was performed by the same embryologist (C.K.) in all cycles. Transfers were performed on either day 3 or day 5. Women under 35 years of age who were undergoing their first or second IVF cycle received elective single-embryo transfer. Women in this age group who were on their third cycle or greater underwent double-embryo transfer. If a woman was 35 years of age or older, she was able to undergo double-embryo transfer with any cycle; if only one good-quality embryo was available, she underwent non-elective single-embryo transfer.

Clinical pregnancy was defined by the presence of fetal cardiac activity on transvaginal ultrasonography during the seventh week of pregnancy.

2.4. Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPPS) for Windows software, version 11.5 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were listed as the number of subjects and the percentage for nominal variables. The differences in pregnancy outcomes according to patient age and the number of embryos transferred was evaluated using Pearson's chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

3. Results

During the course of the study, a total of 353 embryo transfers were carried out in 423 patients. Of the 353 embryo transfers, 261 (73.9%) were single-embryo transfer (244 (69.1%) elective and 17 (4.8%) non-elective) and 92 (26.1%) were double-embryo transfer. Of the 261 single-embryo transfers (elective and non-elective), 6.1% ($n = 16$) were frozen-thawed embryos. The average patient age was 29.6 ± 4.5 years in the single-embryo group and 36.5 ± 2.4 years in the double-embryo group. From the 353 embryo transfers, 147 (41.6%) clinical pregnancies were obtained, 16 of which (10.8%) were twin gestations.

Seventy cycles (16.6%) did not undergo an embryo transfer. The most common indications for cycle cancellation in the single-embryo and double-embryo transfer planned groups were no sperm extraction (34.3%) and poor ovarian response (39.4%), respectively. The indications for not performing ET are given in Table 1.

Of the 353 subjects the cumulative clinical pregnancy rate was 41% with single-embryo transfer and 43.4% with double-embryo transfer, with no statistically significant difference in clinical

Table 1
In vitro fertilization cycle cancellation rates.

	Single embryo transfer planned patients $n=32$	Double embryo transfer planned patients $n=38$
Poor ovarian response	9 (28.1%)	15 (39.4%)
Poor embryo quality	10 (31.2%)	14 (36.8%)
No sperm extracted	11 (34.3%)	2 (5.2%)
No oocytes aspirated	–	4 (10.5%)
All embryos frozen due to OHSS risk	2 (6.2%)	–
Total fertilization failure	–	3 (7.8%)

OHSS, ovarian hyperstimulation syndrome.

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Table 2
Pregnancy rates and outcomes following single- and double-embryo transfer.

	Single-embryo transfer (n=261)	Double-embryo transfer (n=92)	p-Value
Age (mean ± SD)	29.6 ± 4.5	36.5 ± 2.4	<0.001[a]
Cumulative pregnancy rate[d] (%)	107/261 (41%)	40/92 (43.4%)	0.678[b]
Cumulative live birth rate (%)	84/261 (32.1%)	33/92 (35.8%)	0.518[a]
Twin pregnancy (%)	3/107 (2.8%)	13/40 (32.5%)	<0.001[c]
Spontaneus abortion (%)	16/261 (6.1%)	6/92 (6.5%)	0.894[b]

[a] Student's t-test.
[b] Pearson's chi-square test.
[c] Fisher's exact test.
[d] Cumulative pregnancy defines the pregnancies achieved, either after fresh-embryo transfer or frozen-thawed embryo transfer.

pregnancy rates (p = 0.678). The twin pregnancy rate per clinical pregnancy was 2.8% (n = 3) in the single-embryo group and 32.5% (n = 13) in the double-embryo group ($p < 0.001$). The other statistically significant parameter was the patient age in the two groups. As expected, the patients in the single-embryo group were younger than those in the double-embryo group ($p < 0.001$). No statistically significant difference was found between the two groups in spontaneous abortion rates and live birth rates (Table 2).

A total of 244 patients (69.1%) were under 35 years of age and these women received elective single-embryo transfer; 228 (93.4%) of these were fresh embryo transfers in the first or second cycle of therapy and 16 (6.6%) were frozen-thawed ETs. Sixteen (n = 16) patients (4.5%) under 35 years of age who were in at least the third cycle of therapy, and 76 patients (21.5%) 35 years of age or greater who had two good-quality embryos, underwent double-embryo transfer. Seventeen (n = 17) patients (4.8%) were at least 35 years of age but had only one good-quality embryo and therefore underwent non-elective single-embryo transfer. In the single-embryo transfer group, the twin pregnancy rate was 2.8% in women under 35 years of age; there were no twin pregnancies in patients 35 years of age or greater who were in the category of non-elective SET. In the double-embryo transfer group, the twin pregnancy rates in women under 35 years of age and in women 35 years of age or greater were 37.5% and 31.2%, respectively. Among the 16 twin pregnancies; 37.5% (n = 6) were obtained in women aged under 35 years who underwent either single- or double-embryo transfer, and 62.5% (n = 10) were obtained in women of 35 years or older who underwent double-embryo transfer (Table 3).

4. Comment

The results of our study suggest that twin pregnancy rates may be lowered without changing overall IVF pregnancy rates, by expanding the indications for elective single-embryo transfer in infertile patients. Due to the legal restrictions placed on assisted reproductive technology applications in Turkey, making elective single-embryo transfer mandatory for the first two IVF cycles in women under 35 years of age, the largest proportion of our patients (73.9%) underwent elective single-embryo transfer, with a 2.8% twin pregnancy rate. The highest twin pregnancy rate was recorded in women less than 35 years of age who underwent double-embryo transfer. In 2003 in Belgium, the use of elective single-embryo transfer in the first cycle of therapy became mandatory for women less than 35 years of age and a 3-fold decrease in multiple pregnancy rates ensued (25.9% to 8%), without an impact on clinical pregnancy rates [15]. Debrock et al. demonstrated that this decrease in multiple pregnancy rates was most significant in the first cycle of therapy in women 35 years of age or younger; the rate was 4%, rising to 23.3% in the second cycle of therapy. We found a higher rate of twin pregnancy in women younger than 35 years of age who underwent double-embryo transfer. This can be attributed to differences in protocol: according to the Belgian legislation, patients 35 years of age or less are implanted with 1 fresh embryo, or 2 fresh embryos of poor quality, in the second cycle. In our study, patients in this age group received only elective single-embryo transfer in the second cycle. Faque et al. reported that elective single-embryo transfer does not place infertile women 35 years of age or younger at a disadvantage, provided there is normal ovarian function: they demonstrated a decrease in the twin pregnancy rate (37.5–3.5%) with the use of elective single-embryo transfer instead of double-embryo transfer [16].

The UK Human Fertilization and Embryology Authority has proposed that elective single-embryo transfer strategy should be performed in 50% of patients with a good prognosis in order to decrease the IVF twin pregnancy rate to below 10% [4]. Although our results were close to the targeted rate, we were not able to reduce the twin pregnancy rate to below 10% (10.8%), despite the general-policy use of elective single-embryo transfer; we attribute this to the fact that we still used double-embryo transfer in patients older than 35 years of age without taking into account the presence or absence of previous IVF failures. Given that more than half of the twin pregnancies (62.5%) occured in women 35 years of age or older who underwent double-embryo transfer, reducing twin pregnancy rates to acceptable levels would require targeting women over age 35 with a good prognosis as the second major group to undergo elective single-embryo transfer.

IVF is a delicate treatment and patients with a good prognosis must be defined very clearly. A good prognosis is conferred upon women aged 35 years or less, in their first or second IVF attempt, with at least two good quality embyos available for transfer [17]. It should be noted, however, that some women over age 35 have high rates of live births from IVF and are at risk of multiple pregnancies. In Canada, based on current data, double-embryo transfer occurs in 48.4% of patients, while the multiple pregnancy rate in patients aged 35–39 years undergoing fresh-embryo transfer is 27.6% [18]. In our study, 27% of all clinical pregnancies in women of 35 years of age or older resulted in twin gestation, which was similar to the Canadian data.

A study from Finland defined good prognosis and eligibility for elective single-embryo transfer in women aged 36–39 years as follows: those who respond well to stimulation, with at least one top-quality embryo and at least one additional embryo of sufficient quality to freeze. The live birth rate in this Finnish study was reported to be 26%, without any reported multiple pregnancies. In the group that underwent double-embryo transfer, live birth rates were found to be similar (22.4%) and twin pregnancy rates were higher (17.7%), due to the fact that the majority of the embryos in women of this age group were not of good quality [19]. In our

Table 3
Twin pregnancy rates according to age group and number of embryos transferred.

	Age < 35 elective single-embryo transfer (n=244)	Age < 35 double-embryo transfer (n=16)	Age ≥ 35 single-embryo transfer (non-elective) (n=17)	Age ≥ 35 double-embryo transfer (n=76)
Clinical pregnancy rate per transfer	101/244 (41.8%)	8/16 (50.0%)	5/17 (29.4%)	32/76 (42.1%)
Twin pregnancy rate per clinical pregnancy	3/102 (2.9%)	3/8 (37.5%)	–	10/32 (31.2%)

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practice, we do not perform embryo transfer in the absence of good-quality embryos because the quality of the embryo has a high impact on whether pregnancy will be achieved. This strategy helps our patients to keep their rights of reimbursement limited to two fresh-embryo transfers, but it results in high cycle cancellation rates.

The implementation of elective single-embryo transfer policies is the most logical solution for reducing multiple pregnancy rates in IVF patients. The most important considerations in planning single-embryo transfer are the quality of embryos available, and the ability to obtain adequate numbers of embryos for freezing. We found that single-embryo transfer results in comparable pregnancy rates to those of previous studies, and allows us to significantly reduce our multiple pregnancy rate from that previously obtained with double-embryo transfer. The next step in the prevention of multiple pregnancies may be to revisit the double-embryo transfer policy, and begin assessing embryo quality when deciding the number of embryos that will be transfered in women over age 35, because the high rate of multiple pregnancies is still continuing under the current legal regulation.

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