The impact of the new Turkish regulation, imposing single embryo transfer after assisted reproduction technology, on neonatal intensive care unit utilization: a single center experience

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OBJECTIVES AND AIM: IVF has become an efficient and widely used treatment for infertile couples, however, it is responsible for an increasing number of multifetal pregnancies and adverse neonatal outcomes. This study aimed to assess a health service utilization in one neonatal intensive care unit (NICU), as a response to the 2010 Turkish reproductive regulation requiring single embryo transfer (SET).

METHODS: All assisted reproductive technology (ART) pregnancies delivered at Zekai Tahir Burak Maternity Teaching Hospital between February 2010 and October 2011 were included in this study. Subjects were divided into two groups: Group 1 consisted of infants conceived before the ART regulation, and born between February 2010 and October 2010, and Group 2 consisted of infants conceived after the ART regulation, and born between November 2010 and October 2011.

RESULTS: Upon comparing the study groups, we observed a significant decrease in the incidence of multiple births in Group 2. The mean gestational age and mean birthweight were significantly higher in Group 2. The rates of prematurity and low birthweight, very low birthweight and extremely low birthweight infants were significantly lower in Group 2. Similarly, the rates of NICU admission, respiratory distress syndrome, necrotizing enterocolitis, anemia and pneumonia/sepsis, and the need for respiratory support (mechanical ventilation and nasal continuous positive airway pressure) were significantly lower in Group 2.

CONCLUSIONS: According to our data, NICU utilization was reduced and the early post-natal outcomes of the babies were improved after the new Turkish regulation on ART imposing SET. However, multicenter studies are needed to generalize our results to the whole country.

Key words: assisted reproduction techniques / neonatal outcomes / single embryo transfer

Introduction

Assisted reproductive technology (ART) to treat infertility has developed rapidly since the first IVF baby was born in 1978. However, children born after IVF generally have poor obstetric outcomes than children born after spontaneous conception. Most of the increased risks of IVF children have been shown to be associated with multiple births (Sazonova et al., 2011). Multiple gestations may occur after ovarian stimulation or when more than one embryo is transferred during in vitro techniques. According to the results of an epidemiology study performed in Turkey, the incidences of twin and triplet deliveries were 1.86 and
0.07%, respectively. The authors observed that 75% of multiple deliveries were the product of IVF techniques (Yayla and Baytur, 2008). In a recent study from Turkey, the status of twin pregnancies, the incidence of twin births, perinatal and mortality rates associated with twin pregnancies and the problems experienced in the cases of twin and other multiple pregnancies were evaluated retrospectively. The authors concluded that preterm birth rates for twin pregnancies in Turkey were higher than that generally indicated in the literature and that prenatal and neonatal mortality rates were also similarly higher (Sezer et al., 2011).

In Turkey, on March 2010, the Ministry of Health of Turkey revised its regulations pertaining to ART. The new regulatory structure considerably extends the specifications and requirements for the practice of ART in Turkey, and introduces a range of additional prohibitions. Women under 35 in their first and second cycles of IVF can only have a single embryo transferred (SET), and a maximum of two embryos can be transferred for women over 35 and women under 35 on their third or subsequent IVF cycles (Official Gazette).

Materials and Methods

Subjects
This single center prospective study was conducted in the Zekai Tahir Burak Maternity Teaching Hospital, the largest perinatal center which serves as a referral hospital for the middle and east of Turkey. The live birth rate is ~20 000 per year in the Zekai Tahir Burak Maternity Teaching Hospital, with a birth rate of 1 300 000 per year in the whole country, i.e. ~1.5 per cent of all live births in Turkey occur in this hospital.

Between February 2010 and October 2011, all ART pregnancies delivered at the Zekai Tahir Burak Maternity Teaching Hospital were included this study. Subjects were divided into two groups; Group 1 consisted of infants conceived before the ART regulation, between February 2010 and October 2010, and Group 2 consisted of infants conceived after the ART regulation, between November 2010 and October 2011.

The study was approved by the Zekai Tahir Burak Maternity Teaching Hospital-Research Ethics Committee.

Outcomes
Primary outcomes of the study were the rates of prematurity, low birthweight and multiple birth. Secondary outcomes were Apgar scores, neonatal intensive care unit (NICU) admissions, need for respiratory support, major neonatal morbidities such as respiratory distress syndrome (RDS), significantly patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), pneumonia and sepsis, intraventricular hemorrhage (IVH) (grade >2), anemia and bronchopulmonary dysplasia (BPD), length of hospitalization and mortality rates. These variables were compared between the two groups.

Definitions
ART includes IVF and ICSI, however, it does not encompass artificial insemination or ovarian stimulation. None of the women had oocytes or sperm donation treatment as these procedures are banned in Turkey.

Gestational age was calculated by adding 14 days to the day of the embryo transfer and/or by early fetal ultrasound measures.

Preterm birth was defined as child birth occurring at <37 completed weeks. The premature babies were evaluated in three gestational week categories (<28, <32 and <37 weeks). Low birthweight (LBW) was defined as a birthweight of <2500 g, very low birthweight (VLBW) as a birthweight of <1500 g and extremely low birthweight (ELBW) as a birthweight of <1000 g.

Statistical analysis
SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The Shapiro–Wilk test was used to find out normality. Continuous data are expressed as the arithmetic mean ± standard deviation; categorical data are expressed as percentages. Differences between the two groups were analyzed by the t-test student. The χ² test was used for categorical data. P-values < 0.05 were considered statistically significant.

Results
The maternal characteristics of both groups were similar, as summarized in Table 1 and Caesarean delivery rates were similar in both groups.

Primary outcomes
A total of 413 newborns were evaluated during the study period. Group 1 consisted of 277 infants born from 188 ART pregnancies. Within this group, 102 (36.8%) newborns were born from singleton pregnancies, 141 (50.9%) were from twin pregnancies and 34 (12.3%) were from triplet pregnancies. Among the mothers who gave birth to twins or triplets after ART pregnancies, two had a fetal reduction during pregnancy and seven spontaneously lost one of the fetuses. The rates of singleton, twin and triplet pregnancies were 54.3% (n = 102), 39.4% (n = 74) and 6.4% (n = 12), respectively.

Group 2 consisted of 136 infants born from 113 ART pregnancies. In Group 2, 87 (64.0%) newborns were born from singleton pregnancies and 49 (36.0%) were born from twin pregnancies. Among the mothers who gave birth to twins or triplets after ART, three

| Table 1 | Comparison of maternal characteristics between groups. |
|---------|----------------------------------|----------------|----------------|
|         | Group 1 (before regulation) (n = 188) | Group 2 (after regulation) (n = 113) | P-value |
| Maternal age (year) (Mean ± SD) | 30.2 ± 5.1 | 31.2 ± 5.3 | 0.11 |
| ≥35 years (n, %) | 37 (19.8) | 30 (26.5) | 0.19 |
| Cesarean section (n, %) | 177 (94.1) | 106 (93.8) | 0.90 |
| Nulliparity (n, %) | 165 (87.8) | 101 (89.4) | 0.56 |
| Smoking (n, %) | 5 (2.7) | 2 (1.8) | 0.62 |
| Pregnancy-induced hypertension (n, %) | 9 (4.8) | 4 (3.5) | 0.60 |
| Pre-eclampsia (n, %) | 8 (4.3) | 6 (5.3) | 0.67 |
| Gestational diabetes (n, %) | 13 (6.9) | 15 (13.3) | 0.06 |
spontaneously lost one of the fetuses during pregnancy. The rates of singleton and twin pregnancies were 77.0% \( (n = 87) \) and 23.0% \( (n = 26) \), respectively. There were no triplet pregnancies. Comparing the study groups, we observed a significant decrease in the incidence of multiple pregnancies in Group 2 \( (P < 0.001) \).

Preterm delivery rates were 61.7% \( (n = 171) \) in Group 1 and 40.4% \( (n = 55) \) in Group 2 \( (P < 0.001) \). LBW rates were 58.5% \( (n = 277) \) and 27.9% \( (n = 136) \) respectively \( (P < 0.001) \). The mean gestational age and mean birthweight were 37.1 ± 3.1 weeks and 2790 ± 820 g, respectively \( (P < 0.001) \). The incidence of maternal complications, including anemia \( (P > 0.05) \), and breastfeeding were similar between the two groups (Table III).

Secondary outcomes

The rates of NICU admission, RDS, NEC, anemia and pneumonia/sepsis, and the need for respiratory support (mechanical ventilation and nasal continuous positive airway pressure) were significantly lower in Group 2 compared with Group 1 \( (P < 0.05) \). The incidences of PDA, IVH, BPD and mortality were similar between the two groups \( (P > 0.05) \; \text{Table III} \).

Discussion

Since March 2010, Turkish law has imposed SET after ART in patients younger than 35 years of age. We aimed to compare neonatal outcomes between babies who were conceived before and after this ART regulation. We demonstrated that babies conceived after the new ART regulation had better neonatal outcomes than those conceived before the regulation. Our analysis showed that the multiple birth rates for babies conceived after the new ART regulation was nearly 2-fold lower than for babies conceived before the new regulation.

Since Zekai Tahir Burak Maternity Teaching Hospital is a referral hospital for high-risk pregnancies and fetal-maternal care, which means that the multiple birth rates can still be considered high in both groups compared with previous Turkish data (Yayla and Baytur, 2008; Sezer et al., 2011). Caesarean section rates are similar to those previously reported. In Turkey, babies born after ART are defined as ‘precious babies’. Therefore, both the women and the physicians prefer Caesarean sections for the fear of any complications. Recently, the Ministry of Health of Turkey offered new regulations to reduce Cesarean rates in whole country.

There were no significant differences in the rates of pregnancy induced hypertension, pre-eclampsia, or gestational diabetes between the two study groups before and after the new regulation. Our center is a tertiary referral hospital for high-risk pregnancies for Central Anatolia therefore it might mask any possible effect on these factors. However, despite the high rate of maternal complications in both groups, other neonatal outcomes were better in Group 2, most probably due to a lower multiple birth rate.
Multiple pregnancies are associated with neonatal and post-natal complications, and economic and social repercussions (Gremeau et al., 2012). The mortality and morbidity of twins may differ from that in singletons because of the greater incidence of prematurity, LBW and intrauterine growth restriction (Ingram Cooke, 2010). Perinatal mortality rates are 4-fold higher for twins and 6-fold higher for triplets when compared with singleton births (Multiple Gestation Pregnancy, ESHRE, 2000). Yayla et al. (2010) reported that perinatal mortality rate in twin pregnancies is 106.9 per thousand and perinatal mortality rate in triplets is 234.2 per thousand in a multicentric study from Turkey.

The rate of multiple births continues to be the subject of discussion in many countries and the elective SET policy is increasingly being applied in some countries (Gremeau et al., 2012). For example, in 2008, the Human Fertilization and Embryology Authority in the United Kingdom required all IVF centers to reduce their multiple rates to below 10% within 3 years (Ledger, 2009); in Flanders, Belgium, because of the introduction of the Belgian law that SET is performed in first cycles for all patients younger than 36 years, the percentage of multiple pregnancies after ART has decreased from 25% in 2002 to 11.9% in 2004 (De Sutter et al., 2006); and in Sweden since 2003, an increasing number of IVF cycles are SETs owing to a change in legislation (Sazonova et al., 2011). Unfortunately, in Turkey there are no recent reliable data on the number and outcome of ART pregnancies despite mandated reporting laws. Since the Ministry of Health, Turkey, not announced figures regarding the number of couples undergoing ART in Turkey each year, there is no adequate knowledge on the rates of clinical pregnancy, multiple pregnancy and delivery after ART in Turkey (Urman and Yakin, 2010).

Until recently, the rationale for favoring double embryo transfer (DET) over SET has been that the transfer of two or more embryos results in a higher clinical pregnancy rate than the transfer of only one embryo, especially in younger women. However, outcomes of SET have shown a significant decrease in twin pregnancy rates without any decrease in cumulative pregnancy rates in a selected population (Gremeau et al., 2012). In a study from Turkey, outcomes of ART pregnancies were compared in equal periods of 2.5 months before and after the new regulation and further investigation was conducted for two different age groups: <35 and >35 years. The authors observed that the pregnancy rates were decreased from 39.9 to 34.5% and multiple pregnancy rates were decreased from 23.1 to 5.3% among all patients. With these results, the study suggested that the new regulation provided significantly lower multiple pregnancy rates while not causing an important decline in the pregnancy rates (Kutlu et al., 2011). Furthermore, the ART reports in Australia and New Zealand in 2006 have shown that the proportion of embryo transfer cycles using SET had increased from 28.4% in 2002 and to 56.9% in 2006. Over the same period, the twin pregnancy rate declined from 18.8 to 11.3% (Wang et al., 2009). In Sweden, Karlstrom and Bergh (2007) reported that SET increased from 30.6% in 2002 to 67.4% in 2004. Concomitantly, the multiple birth rates decreased dramatically from 19.4 to 5.7%. While the live birth rate per transfer was stable at 26.8% in 2002 and 25.0% in 2004. Moreover, reports from Iowa demonstrated that after implementation of SET, live birth rates improved from 51.1 to 55.9% and multiple birth rates dropped from 34.8 to 17.5% (Kresowik et al., 2011).

Research on neonatal outcomes after IVF has demonstrated a decrease in the rate of preterm births and LBW infants due to the reduction of the rate of multiple births over the last 25 years in Sweden. Additionally, there has been a decline in respiratory symptoms, use of continuous positive airway pressure and mechanical ventilation, and sepsis/pneumonia (Kallen et al., 2010). Moreover, some studies have demonstrated that the incidences of preterm and LBW births were clearly reduced when SET was compared with DET among singletons (De Sutter, 2006; Wang et al., 2009). Nevertheless, we did not compare singletons pregnancies with multiple pregnancies, because we could not reach any data about SET or DET among singletons since most women had received IVF treatment in an outside center and then came to our hospital for delivery.

In our study the differences in neonatal morbidity and NICU utilization before and after ART regulation were particularly striking. However there was not any factor that could affect NICU admission other than the new ART regulation during the study period. We showed that the average hospitalization stay was twice higher in Group 1 compared with Group 2.

There is no doubt that the vast majority of perinatal morbidity associated with ART is attributable to the conception of multiple pregnancies (Kalra and Barnhart, 2011). Although some studies have shown poorer cognitive outcomes for twins, larger and more recent studies have shown small but significant differences even when confounders were taken into account. Cerebral palsy rates are also considerably higher in twins, especially with the death of a co-twin (Ingram Cooke, 2010). Keith et al. (2000) demonstrated that long-term risks include a 300% increase in the relative risk of disability in triplets, and a 650% increase in the rate of cerebral palsy in triplets compared with singletons. In addition, multiple gestations place a greater economic and social burden on parents and on the health care system (Kjellberg et al., 2006; Mesa and Peral, 2011). A cost–benefit study comparing SET and DET showed no difference in the live birth rate, but a substantial reduction in twin births, with an additional cost of each DET at about 4000 Euros (Gerris et al., 2004). Given the data above, a need for legal surveillance of ART practices has emerged worldwide to reduce neonatal morbidities and mortalities caused by ART multiple gestations.

Our study has several limitations. First, this is a single center study and the results may not represent the whole country. Secondly, most of the mothers had received ART in an outside center and we were only able to evaluate the data on the maternal and neonatal outcomes of live born babies. These factors limited the ability to define the rates of clinical pregnancies and live births and to identify which patients were still at the greatest risk of having multiples pregnancies. Thus, our ability to make recommendations for improving legislation in the future is limited.

In conclusion, according to our data, NICU utilization is reduced and the early post-natal outcomes of the babies have improved after the new Turkish regulation on ART imposing SET. However multicenter studies are needed to generalize our results to whole country.

**Authors' roles**

N.G. was responsible for collecting substantial contributions to the conception and design and acquisition of data, drafting the article and revising it critically for important intellectual content and final
approval of the version to be published. H.G.K. was responsible for the acquisition of data, drafting the article and for the final approval of the version to be published. D.D. was responsible for analysis and interpretation of data, drafting the article critically for important intellectual content and for the final approval of the version to be published. N.U. was responsible for analysis and interpretation of data, drafting the article and for the final approval of the version to be published. O.E. was responsible for analysis and interpretation of data, revising it critically for important intellectual content and for the final approval of the version to be published. U.D. was responsible for substantial contributions to conception and design, revising it critically for important intellectual content and for the final approval of the version to be published.

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**Conflict of interest**

None.

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