

How Many Embryos should be Transferred? The Relevance of Parity and Obstetric History

Doron Goldberg MD MHA^{1,2,3}, Avi Tsafrir MD^{1,2,3}, Naama Srebnik MD^{2,3}, Michael Gal MD PhD^{1,2,3}, Ehud J. Margalioth MD^{1,2,3}, Pnina Mor CNM PHD^{2,4}, Rivka Farkash MPH², Arnon Samueloff MD^{2,3} and Talia Eldar-Geva MD PhD^{1,2,3}

¹Reproductive Endocrinology and Genetics Unit, IVF Unit, and ²Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Jerusalem, Israel

³Hadassah-Hebrew University Medical School, Jerusalem, Israel

⁴Jerusalem College of Technology, Jerusalem, Israel

ABSTRACT: **Background:** Fertility treatments are responsible for the rise in high order pregnancies in recent decades and their associated complications. Reducing the number of embryos returned to the uterus will reduce the rate of high order pregnancies. **Objectives:** To explore whether obstetric history and parity have a role in the clinician's decision making regarding the number of embryos transferred to the uterus during in vitro fertilization (IVF). **Methods:** In a retrospective study for the period August 2005 to March 2012, data of twin deliveries > 24 weeks were collected, including parity, mode of conception (IVF vs. spontaneous), gestational age at delivery, preeclampsia, birth weight, admission to the neonatal intensive care unit (NICU), and Apgar scores. **Results:** A total of 1651 twin deliveries > 24 weeks were recorded, of which 959 (58%) were at term (> 37 weeks). The early preterm delivery (PTD) rate (< 32 weeks) was significantly lower with increased parity (12.6%, 8.5%, and 5.6%, in women with 0, 1, and ≥ 2 previous term deliveries, respectively). Risks for PTD (< 37 weeks), preeclampsia and NICU admission were significantly higher in primiparous women compared to those who had one or more previous term deliveries. Primiparity and preeclampsia, but not IVF, were significant risk factors for PTD. **Conclusions:** The risk for PTD in twin pregnancies is significantly lower in women who had a previous term delivery and decreases further after two or more previous term deliveries. This finding should be considered when deciding on the number of embryos to be transferred in IVF.

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Rates of twins and higher order multiples have risen over the last few decades [1] owing largely to the use of fertility treatments [2]. Twin pregnancies are associated with high risk for many obstetric complications such as preterm delivery (PTD), complications of prematurity [3], preeclampsia [4], neonatal death [5], and low birth weight [1]. To reduce the multiple pregnancy rates in assisted reproductive technologies (ART), fertil-

ity organizations worldwide currently recommend transferring fewer embryos, with emphasis on transferring a single embryo [6,7]. Consequently, there is a growing trend in many countries for elective single-embryo transfer [8-13]. A number of publications have shown that this policy with subsequent transfer of frozen embryos does not always result in an overall decreased cumulative pregnancy rate, as compared to double-embryo transfer [10-16]. However, considering the absolute low implantation rate of each single embryo, single-embryo transfer may reduce pregnancy rates per transfer and consequently increase time to delivery, personal costs, and possibly overall satisfaction. Nevertheless, some authors claim that the small increased risk of pregnancy complication for twin pregnancies does not justify the effort and cost of a second pregnancy, particularly for women/couples wishing for more than one child [17]. At present, single-embryo transfer is still rare in ART cycles in the United States, reported to be as low as 5.6% [18].

Policies and guidelines are, by definition, created for the average patient, possibly overlooking relevant individual factors. When a specific IVF patient has known risk factors for PTD, such as previous history of PTD or a malformed uterus, every effort should be made to prevent a multiple pregnancy. On the other hand, for some infertile patients, twin deliveries may represent a favorable and cost-effective treatment outcome [19]. Treating a woman assessed to have low risk for PTD may afford greater leeway with regard to the number of embryos transferred back to the uterus. Therefore, maternal risk factors for PTD may assist in determining the number of embryos for transfer on an individual basis.

In the general obstetric population, primiparity is reported to be an independent risk factor for preterm twin delivery [20-22]. The purpose of this study was to assess the outcome of twin pregnancies in relation to previous obstetric history and parity in a large cohort of twin pregnancies following IVF or spontaneous conception.

PATIENTS AND METHODS

This was a retrospective study in which we assessed all women with a twin delivery, using data collected between August

Table 1. Gestational age groups at delivery and rates of preeclampsia in nulliparous, second delivery, and multiparous women (> 1 previous delivery)

Variable/Parity	Primiparous (N=499)	Second delivery (N=401)	Multiparous (N=751)	Pvalue*
Term (> 37 weeks)	262 (52.5%)	222 (55.4%)	475 (63.2%)	
Late preterm (34–37 weeks)	152 (30.6%)	130 (32.4%)	214 (28.5%)	< 0.001
Moderate preterm (32–34 weeks)	22 (4.4%)	15 (3.7%)	20 (2.7%)	
Early preterm (< 32 weeks)	63 (12.6%)	34 (8.5%)	42 (5.6%)	
Deliveries complicated by preeclampsia	47 (9.4%)	24 (2.6%)	2 (1.1%)	< 0.001

Values are numbers (percentages) of women

*Chi-square test

Table 2. Neonatal outcomes according to parity

Variable/Parity	Primiparous (N=499)	Second delivery (N=401)	Multiparous (N=751)	Pvalue*
Newborn cumulative birth weight (g) (mean ± SD)	4579 ± 1093	4836 ± 954	5066 ± 962	< 0.0001
Weight discordance > 20% between twins (%)	91 (18.4%)	54 (13.7%)	102 (13.7%)	< 0.05
NICU admission (%)	336 (33.7%)	226 (28.2%)	314 (20.9%)	< 0.0001
5 minute Apgar score < 7 (%)	58 (5.8%)	42 (5.2%)	62 (4.1%)	NS

*Chi-square test

SD = standard deviation, NICU = neonatal intensive care unit

2005 and March 2012 from the Shaare Zedek Medical Center (Jerusalem, Israel) computerized data recording system. For the purpose of data collection women with a twin delivery were classified into three groups: primiparous, second delivery, and multiparous (more than two previous deliveries). Any deliveries before fetal viability (24 weeks) were excluded. All twin deliveries were divided into four gestational age groups: term delivery (defined as those occurring after completing 37 weeks of gestation), late preterm delivery (34–37 weeks gestation), moderate preterm delivery (32–34 weeks gestation), and early preterm delivery (before completing 32 gestational weeks). We analyzed the relation of the three parity groups and the four gestational age groups at delivery to the occurrence of preeclampsia.

Based on available data from previous deliveries, we compared parous women with at least one previous preterm delivery before 34 weeks to those without. In addition, we compared women who had undergone a previous cesarean delivery to women who had not. Newborn outcomes, including cumulative weight, weight discordance (defined as > 20% difference between twins), admission to the neonatal intensive care unit (NICU) and 5 minute Apgar scores < 7, were also compared among parity groups. In addition, similar indicators in singleton deliveries were analyzed. The study was approved by the hospital institutional review board in accordance with national regulations and received exemption from informed consent.

STATISTICAL ANALYSIS

All statistical analyses were done using SPSS® (IBM, Armonk, NY, USA) statistical package version 20.0. All tests were two sided; *P* values < 0.05 were considered statistically significant. Univariate analyses included chi-square test, Student's *t*-test and one-way ANOVA. Chi-square tests were used to compare the rates of term, late preterm, preterm, and early preterm deliveries among the three parity groups and to assess the correlation between previous PTD and prior cesarean section with current PTD. Student's *t*-test and one-way ANOVA were used to compare continuous variables among the study groups. A multivariate logistic model was created to identify independent risk factors for PTD. This model included preterm (< 34 weeks) delivery as the dependent variable, and the covariates: namely maternal age, preeclampsia pregnancy achieved with IVF treatment, prior cesarean delivery, prior PTD, and parity group (using nulliparous as the reference group). Odds ratios (OR) with 95% confidence intervals (95%CI) were calculated.

RESULTS

During the study period, August 2005 to March 2012, there were 85,100 deliveries at Shaare Zedek Medical Center. Of these, 1651 (1.94%) were twin deliveries. Eight pre-viable deliveries (< 24 weeks) were excluded from analysis. Of all twin deliveries, 499 (30.2%) parturients were primiparous, 401 (24.3%) were second deliveries, and 751 (45.5%) were multiparous (third or more). Altogether, 674 pregnancies and deliveries (40.8%) were the result of IVF treatment.

The mean gestational age at nulliparous, second, and multiparous delivery was 35.80 ± 3.00, 36.20 ± 2.57, and 36.57 ± 2.51 weeks, respectively (*P* < 0.001). Table 1 shows significantly higher rates of early preterm and preterm delivery, as well as preeclampsia in nulliparous compared to second and multiparous delivery (*P* < 0.001 for both).

Neonatal outcomes according to parity are presented in Table 2. Newborns of primiparous women had a lower mean cumulative weight, a higher rate of weight discordance of more than 20% between the twins, and an increased rate of admittance to the NICU compared to second and multiparous deliveries. However, the percentage of newborns with 5 minute Apgar scores < 7 did not differ significantly among the parity groups.

Associations between maternal and obstetric characteristics and PTD are presented in Table 3. Univariate analysis shows higher rates of PTD (< 34 weeks) in primiparous women than in women at their second deliveries and in multiparous women (17.0%, 12.2%, and 8.3% respectively, *P* < 0.001), in women with preeclampsia (24.3% vs. 11.3%, *P* = 0.001), in pregnancies following IVF treatment (14.7% vs. 9.9%, *P* = 0.003), and in women with a history of PTD (16.1% vs. 6.9%, *P* = 0.013). A multiple logistic regression analysis, adjusting for maternal age, preeclampsia, IVF, prior cesarean section, prior PTD, and parity,

identified only two independent risk factors for PTD: primiparity (adjusted OR for multiparity compared to primiparity 0.48, 95%CI 0.31–0.75, $P = 0.001$) and preeclampsia (adjusted OR 1.99, 95%CI 1.12–3.54, $P = 0.019$). Other characteristics, including IVF treatment, were not significant in the model. In a separate analysis of all primiparous deliveries ($n=499$) compared to women with one or more deliveries in the past ($n=1152$), we found no statistically significant association between IVF treatment and PTD.

The results for singleton deliveries were similar [Table 4]. Higher rates of preterm deliveries and preeclampsia were found in nulliparous compared to second and multiparous deliveries ($P < 0.001$ for both). Higher rates of PTD (< 34 weeks) were found in women with a prior preterm delivery (5.1% vs. 0.8%, $P < 0.0001$). Multivariate analysis shows higher rates of preterm delivery (< 34 weeks) in primiparous women, in women with preeclampsia, in pregnancies following IVF treatment, and in women with a history of PTD ($P < 0.001$ for all). Primiparity was an independent risk factor for PTD (OR 9.4, 95%CI 3.0–29.8, $P < 0.001$).

DISCUSSION

With the aim of preventing multiple pregnancies and their associated complications, guidelines recommending limiting the number of embryos transferred to the uterus have been published [6,23]. However, these recommendations may not be optimal for all women undergoing ART and individualized parameters should be considered. The identification of women at reduced risk for PTD may help to establish management strategies that will increase IVF success rates while decreasing PTD rates and its complications. Our results show that obstetric history is strongly associated with the risk of PTD in future twin pregnancies. Women carrying twins who delivered at term in their previous pregnancies are at significantly lower risk for PTD < 34 weeks compared to women in their first pregnancy (6.9 vs. 16.1%, $P = 0.013$). Thus, we recommend single-embryo transfer for primiparous women and for women with previous obstetric history of PTD. Double-embryo transfer can be considered in cases of previous term deliveries, in line with patients’ requirements and other risk factors.

Our findings show that primiparity is an independent risk factor for PTD in twin pregnancies. Furthermore, it is a risk factor for neonatal complications such as low birth weight, weight discordance

Table 3. Associations between maternal and obstetric characteristics and preterm delivery: univariate and multivariate analyses

Variable/Delivery time	All N=1651	> 34 weeks N=1455 (88%)	< 34 weeks N=196 (12%)	Pvalue unadjusted	OR (95%CI)	Pvalue adjusted
Maternal age, years (mean \pm SD)	30.28 \pm 5.8	30.3 \pm 5.6	29.7 \pm 7.0	NS	0.99 (0.96–1.02)	NS
Parity						
Primiparous	499 (30.2%)	414 (83.0)	85 (17%)	< 0.0001	1	–
Second delivery	401 (24.3%)	352 (87.8%)	49 (12.2%)		0.70 (0.46–1.05)	NS
Multiparous (third delivery or more)	751 (45.5%)	689 (91.7%)	62 (8.3%)		0.48 (0.31–0.75)	0.001
Preeclampsia						
Preeclampsia	74 (4.5%)	56 (75.7%)	18 (24.3%)	0.001	1.99 (1.12–3.54)	0.019
Non-preeclampsia	1577 (95.5%)	1399 (88.7%)	178 (11.3%)		1	
IVF treatment						
► All deliveries						
IVF	674 (40.8%)	575 (85.3%)	99 (14.7%)	0.003	1.22 (0.87–1.72)	NS
Non-IVF	977 (59.2%)	880 (90.1%)	97 (9.9%)		1	
► Primiparous (499)						
IVF	325/499 (65.1%)	265 (81.5%)	60 (18.5%)	NS	–	–
Non-IVF	174/499 (34.9%)	149 (85.6%)	25 (14.4%)		–	
► 2 or more deliveries (1152)						
IVF	349/1152 (30.3%)	310 (88.8%)	39 (11.2%)	NS	–	–
Non-IVF	803/1152 (69.7%)	731 (91.0%)	72 (9.0%)		–	
► Prior cesarean section						
Prior CS	208/1152 (18.1%)	184 (88.5%)	24 (11.5%)	NS	1.16 (0.70–1.91)	NS
No prior CS	944/1152 (81.9%)	857 (90.2%)	184 (9.2%)		1	
► Prior preterm delivery						
Yes	56/762 (7.3%)	47 (83.9%)	9 (16.1%)	0.01	1.67 (0.77–3.62)	NS
No	706/762 (92.7%)	657 (93.1%)	49 (6.9%)		1	

Table 4. Gestational age groups at delivery and rates of preeclampsia for singleton in nulliparous, second delivery, and multiparous women (> 1 previous delivery)

Variable/Parity	Primiparous (N=30,518)	Second delivery (N=26,606)	Multiparous (N=67,067)	Pvalue*
Term (> 37 weeks)	28,880 (94.6%)	25,372 (95.4%)	64,435 (96.1%)	< 0.001
Late preterm (34–37 weeks)	1167 (3.8%)	913 (3.4%)	2003 (3%)	
Moderate preterm (32–34 weeks)	186 (0.6%)	140 (0.5%)	257 (0.4%)	
Early preterm (< 32 weeks)	285 (0.9%)	181 (0.7%)	372 (0.6%)	
Deliveries complicated by preeclampsia	1104 (3.6%)	429 (1.6%)	1228 (1.8%)	< 0.001
Preterm delivery (< 34 weeks)	471 (1.5%)	321 (1.2%)	629 (0.9%)	< 0.001

Values are numbers (percentages) of women

between twins, and NICU admission. Our findings concur with those of Erez et al. [21], who investigated a large cohort of 2601 women pregnant with twins and found higher rates of preeclampsia, PTD, and other pregnancy and neonatal complications among primiparous compared to multiparous women. Evaluating 243 second and third-trimester IVF twin pregnancies, Berkovitz and co-authors [24] demonstrated that primiparity is a risk factor for pregnancy loss and for preterm delivery in IVF twin pregnancies, concurring with our results. We not only demonstrated that primiparity is an independent risk factor for PTD but also that multiparity is a protective factor for PTD. These data are relevant for multiparous women who require fertility treatments. In our experience, in Israel, there is a large population of multiparous women who seek fertility treatment. More than half the women treated by ART in the current study were multiparous.

Nulliparous infertile women are common among those seeking ART treatments, and since the desire to succeed is strong the option to transfer more than one embryo is appealing to both the patient and the physician. In light of our findings and those from the medical literature cited here, we endorse the policy of single-embryo transfer in nulliparous women.

In the univariate analysis that we conducted, IVF treatments were found to be a significant risk factor for preterm labor. However, almost 50% of IVF patients were primiparous, which was found to be an independent risk factor for PTD. After adjustment for parity, IVF was no longer a significant risk factor for preterm labor, even in primiparous women. IVF was an independent risk factor for PTD in our population only in singleton pregnancies.

This connection between ART and PTD has been the subject of debate in the current medical literature. While Erez and colleagues [21] reported contrasting results, Szymusik et al. [3] and Koudstall et al. [25] reached similar conclusions – namely, that the risk for PTD in ART is attributed to primiparity rather than to ART itself. In a review of current medical guidelines [6,23] for embryo transfer, we did not find any mention of primiparity as a risk factor for preterm labor in twin pregnancy. Although Erez et al. [21] published this significant observation in 2008 (mentioned above) it did not become part of the medical guidelines concerning embryo transfer. Most guidelines pertaining to the number of embryos transferred emphasize embryo quality and maternal age with minimal, if any, significance to obstetric history. A history of preterm delivery is considered a contraindication for double-embryo transfer in SOGC-CFAS* clinical practice guidelines [23], as are other medical conditions such as diabetes mellitus, cardiovascular disease, morbid obesity, uterine malformation, and previous hysterectomy. Consistent with the principles of ‘personalized medicine’, individual factors, such as history of preterm delivery and malformed uterus,

should be considered in the decision as to how many embryos should be transferred in IVF. The data presented here, combined with previous reports, suggest parity as an additional factor to be considered.

One of the limitations of this study is the lack of information on late abortions/very preterm deliveries < 24 gestational weeks. As previously mentioned, the data for the study were retrieved from a computerized database that excludes peri-viable deliveries.

To summarize, due to both neonatal and maternal risks, twin pregnancies should not be encouraged. By considering the two independent risk factors – primiparity and previous preterm delivery – while recognizing those who are at reduced risk for preterm delivery, we can minimize iatrogenic preterm deliveries and maintain IVF success rates. In light of the above results and previous research, our recommendation for embryo transfer guidelines is that both multiparity and previous term delivery be considered significant protective factors for preterm delivery.

Correspondence

Dr. N. Srebnik

Dept. of Obstetrics and Gynecology, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 904342, Israel

Fax: (972-2) 666-6053

email: srebnikn@szmc.org.il

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