Nulliparity, fertility treatments and twins: a time for rethinking

Arie Berkovitz, M.D., Anat Hershko-Klement, M.D., and Moshe Fejgin, M.D.
Department of Obstetrics and Gynecology, Meir Medical Center, Kfar-Saba, Israel

Objective: To evaluate the risk that nulliparity poses to the outcome of twin pregnancies, an issue that gained importance due to the rise of twin gestations following assisted reproduction interventions.

Design: A prospective cohort study.

Setting and Patient(s): Between January 1, 2004, and January 7, 2008, we prospectively enrolled all pregnancies achieved by assisted reproduction techniques and including ovulation induction, which successfully completed the first trimester. Pregnancies achieved by egg donation were excluded.

Main Outcome Measure(s): Second trimester abortion and severe prematurity (delivery before 32 weeks) rates and the number of live births.

Result(s): Two-hundred-forty-three twin pregnancies were available for evaluation. Second trimester miscarriage rate was 9.3% in nulliparas and 2.4% in multiparas ($P = 0.061$). Severe prematurity rate was 15.1% in nulliparas compared with 2.5% in multiparas ($P = 0.003$). Better outcome of multiparas was also demonstrated by the calculated chance of taking home at least one baby: 97.6% for multiparas compared with 89.2% in nulliparas ($P = 0.024$).

Conclusion(s): Nulliparity is a risk factor for a poor outcome in twin pregnancies achieved by fertility treatments and is associated with an increased risk for severe prematurity and possibly late abortions. This information should be relayed to the patients undergoing fertility treatments and is a consideration regarding the number of fetuses in relation to parity. (Fertil Steril 2010;93:1957–60. ©2010 by American Society for Reproductive Medicine.)

Key Words: Twins, assisted reproductive technique, parity, premature birth, spontaneous abortion

During the last two decades, Western world trends demonstrate a clear rise in twin pregnancy frequency (1). More than half of these pregnancies are the result of assisted reproductive technologies (ARTs) (2). The reported increase in the rate of twin pregnancies was 50%–60% in England, Wales, France, and the United States between the mid-1970s and 1998. The increase in rates of both twins and triplets in each country reflects, to some extent, the rising maternal age at childbirth observed in most developed countries and to a greater extent, the effects of ovarian stimulation and ARTs (3).

Twin pregnancies are considered to be high-risk pregnancies, complicated by higher morbidity and mortality rates as compared to singleton pregnancies (4). Prenatal complications such as gestational hypertension, placental abruption, and anemia are significantly higher in twin pregnancies.

Labor-related excess morbidity and mortality are due to malpresentation, post partum hemorrhage, and cesarean delivery rates, which are all more common for multiple gestations. Clearly, the most substantial factor to influence the lower outcome of these pregnancies is prematurity and the low birth weight related to it (5). The excess of complications in twin gestations also carries an economic burden, largely because of the need for increased perinatal care followed by prolonged care of disabled children (6).

These aforementioned data led the European Society of Human Reproduction and Embryology to state that the preferred outcome of ART should be the birth of one healthy child and that a twin pregnancy should be considered a complication (7).

Not all agree with the policy (8), arguing that the number of embryos should be tailored by considering specific characteristics of patients to be treated by any of the reproductive interventions. Thus, demographic and obstetric factors influencing specifically the outcome of multiple gestations can aid in the treatment plan of reproductive medicine.

Low parity and previous preterm delivery were both suggested as risk factors for preterm twin delivery and low birth weight (5). Very low birth weights were found to be significantly higher in nulliparas as compared to multiparas in...
both twin and triplet gestations (9–12). The general performance of nulliparas, as related to gestational week at delivery, was demonstrated to be analogue to that of women with a history of preterm delivery, and significantly lower than that of multiparas (5). Age was ruled out as a possible explanation for these disparities between the two groups (13, 14). The effect of maternal age on very preterm birth was reported to differ according to parity. The risk of delivering very preterm twins varied little by maternal age among multiparous women, but decreased with increasing maternal age among primiparous women (11).

The purpose of this study was to evaluate the attributable risk of nulliparity to the outcome of twin pregnancies in terms of both second trimester abortion rate and severe prematurity (deliveries at gestational age younger than 32 weeks). In order to clarify this risk and minimize confounding factors, we chose a selected population of twin pregnancies after use of ART and ovarian stimulation and analyzed their performance after completion of the first trimester.

MATERIALS AND METHODS
The study group included a cohort of 247 twin pregnancies, including multiple order pregnancies reduced to twins, in a single outpatient fertility center: we prospectively enrolled all ART and ovulation induction pregnancies after successful completion of the first trimester, excluding the ones achieved by egg donation. After a failure to follow-up four patients, 243 pregnancies were available for analysis. The study period was defined to start at January 1, 2004, and to end at January 7, 2008, including all pregnancies ending by either second trimester abortion or by a spontaneous delivery to that point. Data were collected to a single database with no identifying details. Second trimester abortion was defined as a spontaneous termination of pregnancy after completion of 14 weeks and before 24 weeks since the last menstrual period. Delivery was defined as a pregnancy ending after completing the 24th week of gestation.

For each pregnancy included, the following data were retrieved from the medical record: maternal age, mode of fertility treatment, maternal gravity and parity status, cerclage procedure, fetal reduction procedure, the number of hospitalization days during the pregnancy, gestational age (in weeks) at the day of abortion/delivery, birth weights, and number of live births. We tested these variables by grouping the cohort into two levels: [1] primiparous (no prior births) and [2] multiparous (at least one prior birth). Analysis of data was performed using the SPSS 15.0 computer package (SPSS Inc., Chicago, IL). Normally distributed data were analyzed by unpaired t-test. \( \chi^2 \) or Fisher’s exact test were used for comparisons of rates and proportions. Stepwise logistic regression analysis was used to test prediction of severe prematurity in a multivariate model. Survival curves were produced by using the Kaplan-Meier method (15) and analyzed using the log-rank test (16). All \( P \) values were tested as two-sided and considered significant at less than 0.05.

This study was approved by the local Institutional Review Board.

RESULTS
A total number of 243 pregnancies were included: two thirds nullipara and one third multipara (161 and 82 women, respectively). Distribution of fertility treatment mode was not significantly different between the two parity groups with a similar frequency of each treatment modality: 40.6% ovulation inductions, 16.3% IVF treatments and 43.1% IVF–intracytoplasmic sperm injection (IVF-ICSI) for nullipara women. For multipara women, distribution was 42.7%,

<p>| TABLE 1 |
| Maternal age (mean ± SD), total hospitalization periods (mean ± SD), and related procedures (%) distributed by parity. |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Multiparas</th>
<th>Nulliparas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29.1 ± 4.5</td>
<td>31.9 ± 3.4</td>
</tr>
<tr>
<td>Cerclage</td>
<td>4 (2.5)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Fetal reductiona</td>
<td>17 (11.3)</td>
<td>18 (23.1)</td>
</tr>
<tr>
<td>Hospitalization, d</td>
<td>17.3 ± 8.9</td>
<td>6.4 ± 2.3</td>
</tr>
</tbody>
</table>

a Information existing for 229 women.

| TABLE 2 |
| Pregnancy outcome distributed by parity, including delivery-week and birth weights (mean ± SD), severe prematurity rate (%), and at least one live-born rate (%). |
| --- | --- | --- | --- |
| Nulliparas | Multiparas | \( P \) value |
| Pregnancy week at delivery | 35.2 ± 3.3 | 36.5 ± 1.8 | <0.001 |
| Birth weight 1st twin (g) | 2147.4 ± 545.4 | 2393 ± 467.5 | 0.001 |
| Birth weight 2nd twin (g) | 2166.1 ± 500 | 2404 ± 421.4 | <0.001 |
| Severe prematurity rate | 15.1 | 2.5 | 0.003 |
| At least one liveborn rate | 89.2 | 97.6 | 0.024 |

18.3%, and 39% respectively. Maternal characteristics and hospitalization data, including related procedures, are presented in Table 1. As expected, the multiparous group is older than the nulliparous group, with a mean age of 31.9 years in the multiparous group and 29.1 years in the nulliparous group. The risk-prone character of the nullipara group is expressed by a significantly longer hospitalization periods. Cerclage rates were low and did not differ between the parity subgroups. As for fetal reduction rates, the procedure was used twice as often in multiparas compared with nulliparas (P = 0.03), probably affected by patients’ choice.

The obstetric outcome is displayed in Table 2. The second trimester miscarriage rate was 9.3% in nulliparas and only 2.4% in multiparas, a difference close to a statistical significance (P = 0.061). The proportion of deliveries occurring before 32 weeks (severe prematurity) was 15.1% in nulliparas as compared to only 2.5% in multiparas (P = 0.003). To better define this difference, we tested it in a logistic regression model that included age, mode of treatment, and fetal reduction procedure; parity was still the only significant contributing variable (P = 0.01). The obstetrical behavior of the two groups can be visually demonstrated by using a survival curve (Fig. 1).

Better outcome of multiparas was also expressed in the calculated chance of taking home at least one surviving neonate in a twin pregnancy that completed 14 weeks: 97.6% for multiparas as compared to 89.2% in nulliparas (P = 0.024).

DISCUSSION

The findings of this study enforce the impression that nulliparity is a risk factor for a poor outcome in twin pregnancies. In a recently published paper, surveying the pregnancy complications of primiparous patients in twin pregnancies, nulliparity was also reported as a risk factor for prematurity (17). We deliberately selected a study population of pregnancies conceived by ART, knowing that the literature is not consistent regarding the effect of ART as a risk factor for adverse outcome in these pregnancies (18–19). We chose to address only twin pregnancies reaching the second trimester; this decision is based on the assumption that different mechanisms exist for early and late pregnancy losses in nulliparous and parous women. Our findings suggest that not only is nulliparity associated with earlier gestational age of twin deliveries, but it also poses a risk for second trimester abortions. Late abortions were fourfold more common in nulliparas, although this difference did not reach a statistical significance. We assume that a larger study group would have reached such significance.

One of the impressive findings of this study, reflecting the different obstetrical performance of the two parity groups, is severe prematurity rate (less than 32 weeks) of 15.1% in nulliparas as opposed to only 2.5% in the multiparas. We also calculated the probability of having at least one surviving neonate, after excluding the late abortion cases. Pregnant multiparas will deliver at least one live born infant 97.6% of the time, compared with an 89.2% rate in nulliparas. In other words, among women giving birth in this cohort, 2.4% of multiparas ended with no liveborn, whereas as many as 10.8% of nulliparas experienced such loss. Phrasing the risk in this way seriously obliges us to reconsider the choice of multiple fetus pregnancy in nulliparas.

The obstetrical outcomes discussed here are probably not uniform: the significantly higher variance in nulliparas seems to reflect the existence of subpopulations in this group. Because of our current sample size, we could not delineate the character of these subpopulations nor characterize the patients drafting the whole group toward lower performance. Although limited in this aspect, most of our findings were clearly significant and coherent with the relevant literature. We hope to further define these populations in future studies.

Our data suggest that parity plays a major role in pregnancy outcome of twin pregnancies achieved following fertility treatments. We should consider discussing this information with our patients as a part of the decision process during fertility treatments. Although twin pregnancy in a nullipara can pose risks, our data may justify a more permissive policy regarding conceptions of multiparas in assisted reproduction, accounting for their better “twin performance.”

REFERENCES

3. Blondel B, Kogan MD, Alexander GR, Dattani N, Kramer MS, Macfarlane A, et al. The impact of the increasing number of multiple...
8. Dickey RP, Sartor BM, Pyrzak R. What is the most relevant standard of success in assisted reproduction? No single outcome measure is satisfactory when evaluating success in assisted reproduction; both twin births and singleton births should be counted as successes. Hum Reprod 2004;19:783–7.