Infertility

Pregnancy outcome in women with endometriomas achieving pregnancy through IVF

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BACKGROUND: There is a growing consensus that ovarian endometriomas should not be systematically removed in women selected for IVF. However, some recent evidence suggested that the presence of these cysts may negatively affect the course of pregnancy.

METHODS: We set up a multicenter retrospective cohort study, including two infertility units. We analyzed data from patients achieving singleton clinical pregnancies through IVF comparing the pregnancy outcome between 78 pregnant women with endometriomas at the time of IVF and 156 patients who achieved pregnancy through IVF without endometriomas.

RESULTS: The number of live births in women with and without endometriomas were 61 (78%) and 130 (83%), respectively ($P=0.39$). The adjusted odds ratio (OR) of live birth in affected cases was 0.79 [95% confidence interval (CI): 0.38–1.68]. No differences were observed in late pregnancy and neonatal outcomes between the two groups. In particular, the rate of preterm birth and small-for-gestational age (SGA) was similar. The adjusted ORs were 0.47 (95% CI: 0.14–1.54) and 0.56 (95% CI: 0.12–2.56), respectively.

CONCLUSIONS: Women with endometriomas achieving pregnancy through IVF do not seem to be exposed to a significant increased risk of obstetrical complications.

Key words: endometriosis / IVF / pregnancy outcome

Introduction

The management of women selected for IVF who are carrying ovarian endometriomas has been a matter of debate (Garcia-Velasco and Somigliana 2009; Benschop et al., 2010). At present, however, there is a growing consensus that these cysts should not be systematically removed. In fact, the few available clinical trials failed to demonstrate that surgical excision enhances pregnancy rate (Benschop et al., 2010). Moreover, there is consistent evidence showing that ovarian reserve is injured following surgical excision of ovarian endometriomas (Garcia-Velasco and Somigliana 2009; Almog et al., 2010; Benaglia et al., 2010; Almog et al., 2011; Benaglia et al., 2011). The question remains however open. Some secondary but clinically relevant points deserve attention. They include the risk of developing ovarian abscess following egg retrieval due to contamination of the cyst content, the risk of rupturing the endometrioma, difficulties in follicular aspiration, growth of the cyst, the risk of mis-diagnosing an ovarian cancer and the detrimental impact of the presence of an endometrioma on the pregnancy outcome. Available literature, albeit preliminary, on some of these aspects is generally reassuring (Somigliana et al., 2006; Benaglia et al., 2008; Benaglia et al., 2009; Garcia-Velasco and Somigliana, 2009).

In the present study, we focused on the latter of these points, i.e. the possibility that the presence of an ovarian endometrioma during IVF may negatively affect the course of pregnancy. Available evidence on this issue is scanty and not reassuring. A recent paper reported an increased risk of preterm birth and small-for-gestational age (SGA) newborns among women carrying ovarian endometriomas at the time of IVF (Fernando et al., 2009). Even if some data regarding the pregnancy outcome in women with endometriosis have been provided (Brosens et al., 2007; Stephansson et al., 2009), we however failed to identify other contributions specifically focusing on ovarian
endometriomas. We thus deemed worthwhile further investigating this issue. To this aim, we set up a multicenter cohort study, recruiting women with ovarian endometriomas who got pregnant through IVF. The unexposed group consisted of women without known endometriosis who also achieved pregnancy through IVF and who were matched to cases for age and study period. The ultimate aim was to compare the pregnancy outcome in the two study groups.

Materials and Methods

This is a multicenter retrospective cohort study performed at the infertility unit of the Department of Obstetrics and Gynecology of the Fondazione Cà Granda, Ospedale Maggiore Policlinico (Milan, Italy) and at the IVI Infertility Unit (Madrid, Spain). Data from patients achieving singleton pregnancies through IVF-ICSI cycles in these two Centers between January 2005 and December 2009 were reviewed. We included women with singleton clinical pregnancies (intrauterine gestational sac 4 weeks after embryo transfer). Biochemical pregnancies (transient increase in serum hCG levels without ultrasonographic demonstration of intrauterine or ectopic pregnancy), ectopic pregnancies and twin pregnancies were conversely excluded. Data were collected using the patients’ chart of the Infertility and Obstetrical Units of the participating centers. An additional phone contact using a standardized questionnaire was done to verify available information and to collect missing data about the obstetrical outcome. Phone follow-up was performed at least 40 weeks after embryo transfer. Women who were managed throughout their pregnancy by independent obstetrical units were not excluded. All women who referred to the participating centers routinely provided informed consent for their clinical data to be used for research purposes and they were informed about the possibility of subsequent phone contacts. Local Institutional Review Board approvals were obtained.

Cases corresponded to women who underwent IVF-ICSI with one or more ovarian endometrioma(s). Ovarian endometrioma was defined as a round-shaped cystic mass with a minimum diameter of 10 mm, with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes, and without papillary projections was observed (Savelli et al., 2009). To rule out functional cysts, the presence of the endometriomas had to also be documented at least on one previous ultrasound scan performed at least 2 months before the IVF-ICSI cycle. The diameter of the endometriomas was calculated as the mean of three perpendicular diameters. Doubtful and atypical cases were excluded. The group of women without endometriomas (unexposed group) consisted of patients who did not have any ultrasonographic sign of endometriotic and/or non-endometriotic ovarian cysts at the time of the cycle and who did not have a previous surgical or clinical diagnosis of endometriosis. Unexposed women underwent the IVF-ICSI attempt at the same time period of the cases and they were matched with cases by age (± 1 year) at the time of the cycle. Two women with no evidence of endometrioma were matched to each woman with endometriomas.

During the IVF-ICSI cycle, the patients selected for IVF were monitored and managed according to a standardized clinical protocol as reported elsewhere (García-Velasco et al., 2004; Benaglia et al., 2008). Briefly, the patients underwent transvaginal ultrasound within Day 8 of the cycle before ovarian stimulation. The presence of ovarian cysts was systematically recorded at this time. The regimen used and the dose of gonadotrophins were determined on an individual basis according to the woman’s age, Day 3 serum FSH value and echographic characteristics of the ovaries. The patients underwent serial transvaginal ultrasound starting on Day 6 of ovarian hyperstimulation. When three or more leading follicles with a mean diameter >18 mm were visualized, human chorionic gonadotrophin (hCG) was administered s.c. Oocyte retrieval was performed transvaginally 36 h after the hCG injection. Embryo transfer was performed 48–72 h after the oocyte collection. Collected information referred to the pregnancy outcomes (ectopic pregnancy, induced abortion, spontaneous abortion, intrauterine fetal demise and delivery), complication of pregnancy (prematurity, pre-eclampsia, placenta previa, placental abruption and others), date and mode of delivery (including indications to Cesarean section) and neonatal outcomes (weight at birth, sex, malformation, difficulties in neonatal adaptation and general health at the time of phone contact).

Analysis of the data was carried out with the Statistics Package for Social Sciences (SPSS 18.0, Chicago, IL, USA). Statistically significant differences were determined using unpaired Student’s t-test or Fisher’s exact test as appropriate. Adjusted associations were assessed by using a binary logistic regression model that included smoking, previous preterm birth and baseline variables found to differ in the study groups (P < 0.10). Results were reported as odds ratio (OR) and 95% confidence interval (CI). A P-value ≤ 0.05 was considered statistically significant. Given the paucity of previous evidence, we decided to consider live birth rate as the primary outcome to calculate the sample size. We assumed a 20% reduction in the chances of live birth in the study group to be clinically relevant. Based on an expected live birth rate per starting cycle in the unexposed group of ~80% (corresponding to the mean rate of our units during the study period) and setting Type I and II errors at 0.05 and 0.20, respectively, we calculated that the total number of women to be included using a matched 1:2 strategy was of ~240 (80 affected women and 160 unexposed women).

Results

A total of 78 pregnant women with endometriomas were included. The indication for IVF-ICSI was mainly endometriosis (52 corresponding to 67%), whereas in the remaining 26 cases (33%), there was also a concomitant male factor. Twenty-nine (37%) did not undergo previous surgery for endometriosis, 43 (55%) were operated once, whereas the remaining 6 (8%) underwent two or more interventions. Surgery consisted in removal of ovarian endometriomas in 40 cases (51%). They were monolateral in 28 cases and bilateral in 12 cases. At the time of IVF, endometriomas were monolateral and bilateral in 67 (86%) and 11 (14%) cases, respectively. Forty-nine women (63%) had one cyst, 27 (34%) carried two cysts and 2 (3%) had three or more cysts. The mean ± SD diameter of the bigger cyst per woman was 22 ± 10 mm. A total of 156 unexposed women without endometrioma were matched to these cases (unexposed group). Indication to IVF-ICSI was as follows: male factor in 65 (42%) cases, tubo-peritoneal factor in 30 (19%) cases and unexplained/reduced ovarian reserve in the remaining 61 (39%) cases.

Baseline clinical characteristics and IVF outcome of the two study groups are shown in Tables I and II, respectively. Levels of Day 3 serum FSH were significantly higher in women with endometriomas (Table I). The proportion of women with secondary infertility was similar in the two groups (Table I). Only two of them (one per group) reported previous preterm birth (P = 1.00). None of the women included in the study reported SGA. Moreover, women with endometriomas received higher doses of gonadotrophins and fewer oocytes were retrieved (Table II). The number of transferred embryos was, conversely, similar.

Follow-up of pregnancy was available in all cases. The number of live births in women with and without endometriomas were 61 (78%) and
The adjusted OR (aOR) of live births in affected cases was 0.79 (95% CI: 0.38–1.68). Causes of pregnancy loss were as follows: 8 induced abortions due to chromosomical abnormalities (5 among women with endometriomas and 3 among unexposed women), 34 first trimester abortions (12 among women with endometriomas and 22 among unexposed group) and 1 intrauterine fetal death in the endometrioma group after a premature rupture of membrane at 22 weeks of gestation.

Late pregnancy and neonatal outcomes were thus available in 61 women with endometriomas and 130 unexposed group. They are shown in Table III. No remarkable differences emerged. In particular, the rate of preterm birth and SGA was similar in both groups. Similarly, severe obstetrical complications did not differ. They include pre-eclampsia (four cases among the study group and four cases in unexposed group), placental abruption (three cases among unexposed group), growth restriction (three cases among unexposed group) and macrosomia (one case and one unexposed woman).

### Table I Baseline clinical characteristics of women with and without endometriomas.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endometriomas (n = 78)</th>
<th>No endometriomas (n = 156)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.6 ± 3.5</td>
<td>36.1 ± 3.1</td>
<td>0.30</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (12%)</td>
<td>18 (12%)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.6 ± 2.7</td>
<td>22.3 ± 3.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Duration of infertility</td>
<td>3.1 ± 1.6</td>
<td>2.9 ± 2.0</td>
<td>0.39</td>
</tr>
<tr>
<td>Previous pregnancies</td>
<td>5 (6%)</td>
<td>15 (10%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Previous IVF cycles</td>
<td>39 (50%)</td>
<td>56 (36%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Day 3 serum FSH (IU/ml)</td>
<td>7.3 ± 2.6</td>
<td>6.4 ± 2.1</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or number (%) as appropriate.

### Table II IVF-ICSI cycle characteristics in women with and without endometriomas.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endometriomas (n = 78)</th>
<th>No endometriomas (n = 156)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperstimulation protocols</td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Long protocol</td>
<td>36 (53%)</td>
<td>57 (37%)</td>
<td></td>
</tr>
<tr>
<td>GnRH antagonists</td>
<td>41 (60%)</td>
<td>92 (59%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1 (1%)</td>
<td>7 (4%)</td>
<td></td>
</tr>
<tr>
<td>Total dose of FSH used (IU)</td>
<td>2267 ± 852</td>
<td>1855 ± 903</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of treatment (days)</td>
<td>10.6 ± 2.4</td>
<td>10.6 ± 1.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>7.2 ± 3.7</td>
<td>9.9 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Number of transferred embryos</td>
<td>2.1 ± 0.5</td>
<td>2.3 ± 0.75</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or number (%) as appropriate.

### Table III Pregnancy and neonatal complications in women with and without endometriomas.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endometriomas (n = 61)</th>
<th>No endometriomas (n = 130)</th>
<th>P-value</th>
<th>Adj. OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>4 (7%)</td>
<td>18 (14%)</td>
<td>0.22</td>
<td>0.47 (0.14–1.54)</td>
</tr>
<tr>
<td>SGA birth (&lt;10th centile)</td>
<td>3 (5%)</td>
<td>8 (6%)</td>
<td>1.00</td>
<td>0.56 (0.12–2.56)</td>
</tr>
<tr>
<td>Fetal weight &lt;2500 g</td>
<td>5 (8%)</td>
<td>17 (13%)</td>
<td>0.47</td>
<td>0.61 (0.20–1.86)</td>
</tr>
<tr>
<td>Severe obstetrical complications&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (12%)</td>
<td>10 (8%)</td>
<td>0.42</td>
<td>1.86 (0.61–5.68)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>23 (38%)</td>
<td>44 (34%)</td>
<td>0.63</td>
<td>1.25 (0.63–2.50)</td>
</tr>
<tr>
<td>Neonatal complications&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (8%)</td>
<td>15 (11%)</td>
<td>0.61</td>
<td>0.62 (0.19–1.94)</td>
</tr>
</tbody>
</table>

<sup>a</sup>P-values refer to univariate analysis. Adjusted (Adj.) OR was calculated using a logistic regression model (see text).

<sup>b</sup>They include pre-eclampsia (three cases and two unexposed women), placenta previa (three cases and one unexposed woman) and abruptio placentae (three unexposed women), growth restriction (three cases) and macrosomia (one case and one unexposed woman).

<sup>c</sup>They included monolateral hydronephrosis (1 case), perinatal asphyxia (10 cases and 4 unexposed women), necrotizing enterocolitis (1 unexposed woman), congenital dislocation of the hip (1 unexposed woman), hypospadia (1 unexposed woman) and intravenous cerebral malformation (1 unexposed woman).
and placenta previa (three cases among the study group and two cases in an unexposed group).

The median interquartile range (IQR) of the follow-up of children in women with and without endometriomas was 11 (5–15) and 12 (5–17) months, respectively (*P* = 0.41). One neonatal death occurred in unexposed women on Day 3 of age because of severe prematurity (the mother delivered a 420 g newborn at 25 weeks of gestation). Other neonatal complications included intraventricular hemorrhage (1 woman with endometriosis), intracerebral hemorrhage (1 unaffected woman), necrotizing enterocolitis (1 unaffected woman), congenital dislocation of the hip (1 un-affected woman), hypospadias (1 unaffected women) and intravenous cerebral malformation (1 unaffected woman). All of them recovered after proper treatment and they were reported to be in good conditions at the time of follow-up.

**Discussion**

Eutopic endometrium of women with endometriosis was reported to be abnormal (Braun and Dmowski, 1998; Pritts and Taylor, 2003) and these abnormalities may impair decidualization and placentation in women affected (Fujimoto et al., 1996). Since these latest processes are crucial for pregnancy implantation and development, it has been hypothesized that several complications of pregnancy may be more frequent in women with endometriosis (Fernando et al., 2009). Available clinical data are not fully consistent with this hypothesis. The literature on the relationship between endometriosis and abortion rate is conflicting, with some studies reporting increased risk (Fitzsimmons et al., 1987; Matorras et al., 1998; Omland et al., 2005) and others failing to document any association (Pittaway et al., 1988; Candiani et al., 1991). Stephansson et al. recently evaluated the risk for obstetric complications in a large cohort of women with a previous diagnosis of endometriosis. They showed an increased risk of preterm birth, pre-eclampsia, antepartum bleeding/placental complications and Cesarean section. There was conversely no association with small-for-gestational-age (SGA) birth or stillbirth (Stephansson et al., 2009). In contrast, Brosens et al. (2007) reported that the rate of pre-eclampsia is reduced in women with endometriosis. Moreover, Fernando et al. (2009) failed to document an association between endometriosis in general and SGA and preterm birth. This latter study is particularly illuminating in regard of the topic of the present study. Indeed, it is the first report presenting data separately for the group of women with ovarian endometriomas. Of relevance here is that the study suggested an increased risk of preterm birth and SGA in this specific group. The adjusted OR for preterm birth was 1.98 (95% CI: 1.09–3.62) when women with endometriomas were compared with fertile subjects. The authors however failed to confirm this risk when using women with other forms of endometriosis or causes of infertility as controls. Similarly, they documented and adjusted OR for SGA of 1.95 (95% CI: 1.06–3.60) when comparing women with endometriomas to those who underwent ART for non-endometriosis causes of infertility. Again, however, this enhanced risk was not confirmed when using women with other forms of endometriosis or subfertile subjects as controls (Fernando et al., 2009).

Results of our study do not support the notion that women with ovarian endometriomas achieving pregnancy through IVF are at increased risk of preterm birth or SGA. There is even a trend to a lower risk. The adjusted ORs were 0.47 (0.14–1.54) and 0.56 (0.12–2.56), respectively. We also failed to observe any association with other obstetrical complications. Moreover, the live birth rate was not reduced in women with ovarian endometriomas. The adjusted OR of live birth in affected cases was 0.79 (95% CI: 0.38–1.68). The differing data in these studies may be explained by the differences in study designs, Fernando et al used national IVF and perinatal databases to identify 95 women with ovarian endometriomas who got pregnant through IVF. The study power was thus similar to the one of our study but the accuracy of collected information was inevitably lower since we retrieved data with an active follow-up and by consulting patients’ charts whereas they relied on databases. For instance, Fernando et al. could not provide information on the risk of pregnancy loss since this outcome was not included in the perinatal database that they used for their analysis. Moreover, the choice of the group for comparison may influence the results. In our study, we used women without endometriosis achieving pregnancy through IVF as comparators. This choice is, in our view, more appropriate to investigate the impact of ovarian endometriomas since infertile women may be per se at higher risk of obstetrical complications (Wisborg et al., 2010; Kalra and Barnhart, 2011). Conversely, Fernando et al. used several control groups. In fact, when specifically focusing on the comparison with the ART non-endometriosis group, they detected a statistical significant difference only for the risk of preterm birth. On the other hand, it has to be recognized that our study design may have lead to underestimation of some associations because some women in the unexposed group may be affected by some undiagnosed forms of the disease (adhesions or peritoneal implants). It has however to be pointed out that the present study is mainly aimed at giving a clinical response. In particular, we wanted to disentangle whether endometrioma had to be removed because of obstetrics concerns. Moreover, the magnitude of this inaccuracy is presumably mild since only a minority of women belonging to the unexposed group is expected to hide endometriosis.

Some further limitations of this study have to be recognized. Firstly, the sample size was relatively small impeding definite conclusions. Even if the estimate of ORs for preterm birth and SGA is <1, the 95% CI is large. This limit is of even more relevant for other major obstetrical complications such as pre-eclampsia, placenta previa, abruptio placenta and fetal growth abnormalities. Further evidence is therefore required. Nevertheless, given that our aim was to provide information for clinical practice we were mainly interested on the association of relevant magnitude. Considering the risk and costs associated with surgery for ovarian endometriomas, only relevant concerns regarding the obstetric outcome would tip the balance in favor of the intervention.

Secondly, the dimension of ovarian endometriomas was relatively small (the mean diameter was 22 mm). We therefore cannot rule out that larger cysts may be detrimental. Further evidence is also required to address this point. Nonetheless, we believe that our results are of clinical relevance since they reflect what physicians face daily in clinical practice.

In conclusion, women with endometriomas achieving pregnancy through IVF do not seem to be exposed to a significant increased risk of obstetrical complications. Fear about this possibility is not substantiated and thus removal of the endometriomas to reduce pregnancy complications is not justified. However, considering that
previous publication on this topic reports opposing results, our data must be considered preliminary, and further larger evidence is required to definitively answer the research question and rule out any detrimental effects in women with endometriomas achieving pregnancy through IVF.

Authors’ roles
L.B. and E.S. designed the study. A.B., C.S. and G.R. collected and analyzed the data. L.B. and E.S. wrote manuscript. L.F., J.GV. supervised the study. All authors critically revised the manuscript and approved the final version.

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Conflict of interest
None declared.

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Kalra SK, Barnhart KT. In vitro fertilization and adverse childhood outcomes: what we know, where we are going, and how we will get there. A glimpse into what lies behind and beckons ahead. Fertil Steril 2011;95:1887–1899.