Pregnancy outcome in women with endometriosis achieving pregnancy with IVF

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Abstract

Study question: Are women with endometriosis who conceive with IVF at increased risk of preterm birth?

Summary answer: Women with endometriosis who conceive with IVF do not face an increased risk of preterm birth.

What is known already: The eutopic endometrium of women with endometriosis has been repeatedly shown to present molecular and cellular alterations. On this basis, it has been hypothesized that pregnancy outcome may be altered in affected women. However, to date, available evidence from epidemiological studies is scanty and conflicting. Data tended to be partly consistent only for an increased risk of preterm birth and placenta previa.

Study design, size, duration: Retrospective matched case-control study of women achieving an IVF singleton pregnancy progressing beyond 12 weeks' gestation.

Participants/materials, setting, methods: Women achieving IVF singleton pregnancies that progressed beyond 12 weeks' gestation at two infertility units were reviewed. Cases were women with a history of surgery for endometriosis and/or with a sonographic diagnosis of the disease at the time of the IVF cycle. Controls were women without current or past evidence of endometriosis who were matched to cases by age (± 6 months), type of cycle (fresh or frozen cycle) and study period. Male factor and unexplained infertility were the most common diagnoses in the control group. Two hundred and thirty-nine women with endometriosis and 239 controls were selected. The main outcome of the study was the rate of preterm birth (birth < 37 weeks' gestation) regardless of the cause. Secondary analyses were performed for the most common obstetrical complications.

Main results and the role of chance: The rate of preterm birth was similar in the two study groups (14% and 14%, respectively, p=0.89). The rate of live birth and the incidence of hypertensive disorders, gestational diabetes, small and large for gestational age newborns and neonatal problems also did not differ. In contrast, placenta previa was more common in women with endometriosis

than controls (6% versus 1%, respectively; p=0.006): The adjusted odds ratio was 4.8 (95% confidence interval: 1.4-17.2).

Limitations, reasons for caution: As for all observational studies, confounders cannot be totally excluded. Moreover, the retrospective study design exposes the findings to some inaccuracies. For example, the independent role of adenomyosis could not be reliably assessed because this diagnosis is complex and would necessitate a prospective recruitment. Second, the selection of controls may also be a matter of concern because some affected women may have been erroneously included in this group. Third, even if the sample size is significant, it is insufficient for robust subgroup analyses. Finally, it is mandatory to point out that our conclusions are valid for IVF pregnancies only, andspecific data from properly designed studies are required to support any inference for natural pregnancies.

Wider implications of the findings: The results of our study suggest that women with endometriosis conceiving with IVF can be reassured regarding the risk of preterm birth. The observed association with placenta previa requires further investigation and may open a new avenue of research.

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Key words: endometriosis / pregnancy / IVF / placenta previa / preterm birth

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Introduction

There is robust biological evidence showing that the endometrium of women with endometriosis differs from the endometrium of healthy unaffected women. Differences have been found in stem cell content, hormone sensitivity, cellular proliferation, adhesion, invasiveness, angiogenesis and immune modulation (May *et al*., 2011; Benagiano *et al*., 2014; Vercellini *et al*., 2014). Moreover, the endometrium of women with endometriosis was shown to be resistant to selective actions of progesterone, a hormone that affects decidualization and modulates the local inflammatory process during implantation (Burney *et al*., 2007, Benagiano *et al*., 2014). Noteworthy, there is also accumulating evidence suggesting that complications occurring during the second and third trimester of pregnancy, such as pregnancy-related hypertensive disorders or reduced fetal growth, may actually originate from local disturbances occurring at the time of implantation (Sharkey *et al.* 2013; Chaiworapongsa *et al.* 2014; Hsu *et al.* 2014).

On this basis, it has been hypothesized that pregnancy outcome may be altered in women with endometriosis. However, to date, available evidence is scanty and conflicting (Brosens *et al.* 2007; Stephansson *et al.* 2009; Fernando *et al.* 2009; Hadfield *et al.* 2009; Benaglia *et al.* 2012; Vercellini *et al.* 2012; Conti *et al.* 2015; Mekaru *et al.* 2014; Stern *et al*., 2015). The validity of most of these studies is actually hampered by methodological limitations, insufficient sample size or diagnostic inaccuracies (Viganò *et al*., 2015; Leone Roberti Maggiore *et al*., 2016). Two recent systematic reviews of the literature failed to draw definite conclusions on the relation between endometriosis and obstetrical complications. The data tended to be consistent only for an increased risk of preterm birth and placenta previa (Viganò *et al*., 2015; Leone Roberti Maggiore *et al*., 2016).

In order to shed more light on this debated and intriguing issue, we set up a two-center study to evaluate pregnancy outcomes in IVF singleton pregnancies. In order to overcome the limitations of previous studies, controls were singleton IVF pregnancies matched to cases by age, type of cycle (fresh or frozen) and study period. The recruitment of cases and controls from the same population,

the matching design and the use of an active individualized follow-up rather than data from national registries were expected to overcome most of the limitations of previous studies.

Materials and Methods

Women undergoing IVF at the infertility unit of the Fondazione Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy (between January 2008 and June 2014) and at the infertility unit of the San Raffaele Scientific Institute of Milan, Italy (between January 2009 and June 2014) were retrospectively reviewed. Inclusion criteria were as follows: age 18-42 years; classical IVF or ICSI cycles (fresh or frozen); clinical singleton pregnancy progressing beyond 12 weeks' gestation; follow-up available up to the end of pregnancy (by law, infertility units in Italy are requested to actively investigate pregnancy outcome of IVF pregnancies). A questionnaire aimed at collecting pregnancy and neonatal outcome and complications was systematically used in both centres. Exclusion criteria included: uterine malformations (such as, in particular, septate uterus); intramural fibroids; multiple pregnancy at first ultrasound assessment performed at 7 weeks' gestation (women with a vanishing twin were thus excluded); 4) major pathological conditions with possible impact on pregnancy course such as pre-pregnancy diabetes, previous organ transplantation, antiphospholipid syndrome, chronic renal diseases, systemic lupus erythematosus, and pre-pregnancy hypertension. Thyroid disorders were not an exclusion criteria but, in the two centres all women were requested to have a serum thyroid-stimulating hormone test and, if thyroid disorders emerged, they had to normalize thyroid function before starting the cycle. Women could be included only for the first IVF cycle ending in a clinical pregnancy progressing beyond 12 weeks' gestation. Conversely, there was no restriction on the number of previous failed cycles.

Cases were women with a history of surgery for endometriosis and those in whom ovarian endometriomas were identified at the time of the IVF cycle. Controls were matched to cases on a

1:1 ratio by age (± 6 months), type of cycle (fresh or frozen cycle) and study period (the next woman fulfilling the criteria for selection and matching). Women without a history of surgery for endometriosis but who were diagnosed with soft markers of the disease or suspected deep nodules (Guerriero *et al*., 2016) were excluded from both cases and controls.

The institutional review boards of the two participating hospitals approved the study. An informed consent was not required as this is a retrospective study. However, all women aattending the two centres are requested to sign an informed consent for their data to be used for scientific purposes and agree to be contacted after the procedure for follow-up. Women who denied this consent were excluded.

The diagnosis of endometrioma was by transvaginal ultrasound according to established criteria (Savelli, 2009) and had to be documented on at least two occasions and at least two menstrual cycles apart. Women with a history of surgery for endometriosis were routinely requested to provide documentation of the intervention in order to obtain a surgical description and histological confirmation.

Women undergoing IVF followed standardized protocols that are reported in detail elsewhere (Benaglia *et al*., 2014; Papaleo *et al*., 2014). Embryo transfer was performed 48-72 hours after oocyte collection or, in selected subjects, at the blastocyst stage. In fresh cycles, vaginal progesterone was given for 2 weeks after the oocytes retrieval. In frozen cycles, women receiving hormone replacement therapy (HRT) continued the therapy for the whole first trimester of pregnancy. HRT consisted of oral estradiol valerate 4-6 mg daily and subsequently vaginal progesterone 600 mg daily. Women undergoing frozen embryo transfer in a natural cycle did not receive any therapeutic support.

Clinical data were recovered from clinical charts, including pregnancy follow-up information. If inconsistencies emerged or if data were incomplete, the obstetrical charts were consulted and, if doubts persisted, women were contacted for clarifications.

Information that was actively sought at the time of follow-up included gestational age at the end of pregnancy, hypertensive disorders developing during pregnancy or during puerperium, diagnosis of gestational diabetes, diagnosis of placental disorders, mode of delivery and, if applicable, indication for labour induction or caesarean delivery, neonatal sex and weight, viability and health conditions of the newborn including malformations and neonatal intensive care unit admission. Small for gestational age (SGA) and large for gestational age (LGA) were defined as a newborn weight < 10 centile and > 90 centile, respectively. Centiles were determined using the local referral values (Parazzini *et al*., 1991). Pre-eclampsia was defined as the concomitant presence of hypertension and significant amounts of protein in the urine (Mol *et al*., 2015). Hypertension in the absence of proteinuria was defined as pregnancy-induced hypertension.

The main outcome used to calculate the sample size was the rate of preterm birth (birth < 37 weeks' gestation) regardless of the cause. More specifically, we calculated the sample size setting type I and II errors at 0.05 and 0.20, respectively, postulating a rate of preterm birth in unexposed women of 10% and claiming as clinically relevant a two-fold increased risk of preterm birth (from 10% to 20%). On this basis, the number of women to be recruited was at least 200 per group. Data were analyzed using the Statistical Package for the Social Sciences software 18.0 (Chicago, IL, USA). The Fisher's Exact test, Student's *t*-test and Wilcoxon nonparametric test were used, as appropriate. P values below 0.05 were considered statistically significant. A logistic regression model including baseline variables found to significantly differ between the two groups was used to calculate the adjusted odds ratio (OR) of variables found to significantly differ at univariate analysis.

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Results

We ultimately selected 239 women with endometriosis and 239 unexposed controls. Among cases, a previous history of surgery for endometriosis was reported by 186 women (78%). The remaining

53 (22%) had an ultrasound diagnosis of endometriomas and did not undergo previous surgery for the disease. Specific characteristics of the affected women are shown in Table 1. Baseline characteristics of the two study groups are summarized in Table 2. A statistically significant difference was found for BMI, duration of infertility and indication to treatment. Male factor infertility and unexplained infertility were the two most common diagnoses in the control group. One-hundred and eighty-seven cases and 187 controls achieved pregnancy during a fresh cycle. Characteristics of these fresh cycles are illustrated in Table 3. Women with endometriosis had slightly fewer oocytes retrieved. Table 4 shows the characteristics of the frozen cycles (52 per group), none of which differed between groups.

Pregnancy outcomes in the two groups are illustrated in Table 5. The rate of preterm birth was similar: The crude OR was 1.15 (95% confidence interval (CI): 0.60-2.17), while the OR adjusted for BMI and duration of infertility was 1.14 (95%CI: 0.58-2.22). Moreover, the incidence of live birth, hypertensive disorders, gestational diabetes, SGA, LGA and neonatal problems did not also differ. In contrast, we observed a statistically significant increase in the frequency of placenta previa in women with endometriosis (6% versus 1% in controls; p=0.006). The crude OR of placenta previa in women with endometriosis was 5.1 (95%CI: 1.4-17.8) and the OR adjusted for BMI and duration of infertility was 4.8 (95%CI: 1.4-17.2, p=0.015).

Analyses for the primary outcome (preterm birth) in different subgroups of women with endometriosis are presented in Supplementary Table 1. No significant differences among groups emerged. Finally, all the analyses were repeated excluding unexposed women with a diagnosis of unexplained infertility, and including only women with a histologically confirmed diagnosis of endometriosis: The results were largely similar (detailed analyses not shown).

Discussion

Results from this observational study of IVF singleton pregnancies did not confirm an increased risk of preterm birth in women with endometriosis. We also failed to observe an increased risk of the other major obstetrical complications with the exception of placenta previa. Indeed, women with endometriosis have an increased risk of this complication, the adjusted OR being 4.8 (95%CI: 1.4-17.2).

The lack of any association between endometriosis and preterm birth (the primary aim of the study) is only partly surprising. Even if the available evidence generally tends to support a possible link (Vigano *et al*., 2015: Leone Roberti Maggiore *et al*., 2016), results were not univocal and the magnitude of the detected associations was in general too modest to support causality (Grimes and Schultz, 2012). Two main studies using national registries from Australia and Sweden initially supported a relation between endometriosis and preterm birth (Stephenson *et al*., 2009; Fernando *et al*., 2009). However, in the Australian study, this association was statistically significant only in the subgroup analysis that compared the group of ART-pregnancies obtained in women with endometriomas to the group of natural pregnancies in fertile women (Fernando *et al*., 2009). The Swedish study showed a statistically significant association for the whole group of affected women but the magnitude was modest (OR=1.3, 95%CI: 1.2-1.4) (Stephenson *et al*., 2009). Subsequent studies showed either an increased (Kuivassari-Pirinen *et al.,* 2012; Conti *et al*., 2015; Stern *et al.,* 2015; Lin *et al.,* 2015) or unchanged risk (Benaglia *et al.,* 2012; Mekaru *et al.,* 2014). Noteworthy is that the OR exceeded 3 in only one study (Kuivassari-Pirinen *et al.,* 2012). As recently emphasized by Grimes and Schulz (2012), ORs below 3 should not be considered credible. The presence of confounders, rather than causality, is the main explanation of such findings. Based also on the negative findings emerging from our study, a causal association between endometriosis and preterm birth appears unlikely.

The observation of an association between endometriosis and placenta previa is intriguing but not novel. Some recent epidemiological studies actually supported this possibility (Vigano *et al*., 2015: Leone Roberti Maggiore *et al*., 2016). However, the study designs were in some cases debatable, the estimated magnitude varied widely and the 95%CI are in most cases very large. In the large Swedish study using national registers, Stephensson *et al.* observed that women with endometriosis had a higher risk of placental complications in general. However, the magnitude of the association (OR=1.8, 95%CI: 1.6-2.0) was less remarkable than the one observed in our study, probably because of a diluting effect (Stephenson *et al*., 2009). Two retrospective cohort studies comparing pregnancy outcomes of ART singleton pregnancies with those of natural pregnancies found higher rates of placenta previa in the ART groups, and showed by subgroup analyses that this risk was particularly evident for women requiring ART for endometriosis (Kuivassari-Pirinen *et al.*, 2012; Healy *et al*. 2010). The adjusted OR was 1.7 (95%CI: 1.2-2.3) (Healy *et al*. 2010). A Japanese retrospective analysis aimed at identifying risk factors for placental abnormalities showed a strong positive association with endometriosis (OR=15.1, 95%CI: 7.6-500) (Takemura *et al*., 2013). Finally, a recent retrospective cohort study comparing the outcome of singleton natural pregnancies between women with and without endometriosis confirmed the higher risk of placenta previa in the affected women (adjusted OR=4.5, 95%CI: 1.2-16.5) (Lin *et al.*, 2015).

In the past, significant associations between endometriosis and obstetrical complications were seldom suggested in the literature. A striking protective effect of endometriosis towards pre-eclampsia was claimed by Brosens *et al*. (2007). Unaffected women had an OR of pre-eclampsia of 7.5 (95%CI: 1.7-33.3). Subsequent studies (Hadfield *et al*., 2009; Vercellini *et al*., 2012; Conti *et al*., 2015; Mekaru *et al*., 2014; Stern *et al*., 2015; Kuivassari-Pirinen *et al*., 2012; Lin *et al*., 2015; Aris, 2014) failed to confirm these findings. Stephenson et al. (2009) even detected an increased risk of pre-eclampsia in women with endometriosis (OR=1.1, 95%CI:1.0-1.3). On the basis of these findings, the two available systematic reviews tended to conclude that no association between endometriosis and pre-eclampsia actually exists (Vigano *et al*., 2015: Leone Roberti Maggiore *et*

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al., 2016). Our data are in line with this statement. Similar conclusions can be drawn for all the other obstetrical and neonatal complications investigated in our study (Vigano *et al*., 2015: Leone Roberti Maggiore *et al*., 2016).

Some main limitations and strengths of this study deserve to be mentioned. First, our study is retrospective. This study design exposes our findings to some inaccuracies. For instance, we could not perform subgroup analyses according to the presence/absence of deep peritoneal lesions or adenomyosis. These types of lesion can be reliably identified with transvaginal ultrasound (Exacoustos *et al*., 2014; Guerriero *et al*., 2016), but this requires an active approach and utmost expertise. These lesions were seldom reported in the charts but, given our retrospective study design, we estimated that performing analyses based on these findings could lead to unreliable results. Further studies are thus required to disentangle this aspect. On the other hand, inaccuracies in the selection of cases is unlikely. The diagnosis of operated cases is unquestionable. For non-operated cases, the exclusive inclusion of those with ovarian endometriomas (an easy and reliable sonographic diagnosis) protects our findings from relevant confounders. Of note, non-operated women with this form of the disease represented a minority of the included cases and a secondary analyses excluding these women led to similar results. Selection of the controls may, however, be a matter of concern. Controls did not undergo laparoscopy prior to IVF and, despite a suspected diagnosis of endometriosis being an exclusion criterion in our study, we cannot totally exclude the possibility that we erroneously selected some affected women. The inclusion of a relevant proportion of women with unexplained infertility (36%) among the controls supports this concern. However, the impact of this inaccuracy may be of limited relevance. First, the frequency of undetected endometriosis in women with an evident cause of infertility, such as pelvic inflammatory disease or male infertility (64% of our cohort of unexposed controls), can be postulated to be low (<10%), thus similar to the one observed in the general population (<10%) (Holt and Weiss, 2000; Zondervan *et al*., 2002). Conversely, in the remaining group of women with unexplained infertility, one has to expect that the condition has not been detected clinically in one-

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third to one-half of the women (Vercellini *et al*., 2009). Even if this proportion is more troublesome, it has to be pointed out that the severity of the disease in these undetected cases is expected to be minimal-mild in most of them. Finally, it is noteworthy that the exclusion (from both cases and controls) of women who were exclusively found with soft markers of the disease) and/or suspected nodules may have limited the risk of misclassification.

Second, some basal characteristics of the two groups differed (BMI, duration of infertility and number of oocytes retrieved were lower among cases) and we cannot fully exclude an influence of confounders. BMI in particular may be of relevance because it may affect independently pregnancy outcome. However, detected differences were modest and of doubtful clinical relevance. Of note, is that the mean BMI was 21-22 Kg/m^2, thus within the normal range for both study groups. The differences in duration of infertility and the number of oocytes retrieved are unlikely to bias our results considering that they were small and that there is no biological rationale to postulate a significant impact on pregnancy outcome. Moreover, the use of a logistic regression analysis may have further lessened the impact of the confounders. Noteworthy, the decision to select both cases and controls from IVF singleton pregnancies and the matching for age, type of cycle and study period will help to protect our data from other main confounders. This study design was not previously used and, in our opinion, it represents a main strength of our contribution.

Third, even if the sample size is considerable, it is insufficient for robust subgroup analyses. In this regard, it has to be recognized that, even if based on national register analyses and thus exposed to inaccuracies, some of the previous studies presented data from larger sample sizes (Fernando *et al*., 2009; Hadfield *et al*., 2009). This limitation should also be kept in mind when considering the detected association with placenta previa. Albeit the OR was considerable (4.8), the 95%CI was extremely large (from 1.4 to 17.2) and the statistical power for placenta previa calculated *a posteriori* was 78%. As a matter of fact, the lower limit falls into the previously discussed area of associations (<3) that could be explained by confounders (Grimes and Schulz, 2012). Disentangling

the possible causal relation between endometriosis and placenta previa thus requires further evidence from specifically designed and properly powered studies.

Finally, it is mandatory to point out that our conclusions are valid for IVF pregnancies only. Even if one may be tempted to speculate that our results may be valid for natural pregnancies, specific data from properly designed studies are warranted to support this inference.

In conclusion, women with endometriosis do not face an increased risk of preterm birth. However, they may be exposed to an increased risk of placenta previa. Further evidence is warranted to explore this latter intriguing association.

Authors' roles

L.B., E.P., P.Vi., M.C., P.Ve. and E.S. participated to two investigational meetings aimed at designing the study. G.C., L.P., M.L., M.R., L.Q. and M.M retrieved the data from the two participating units. Analyses were performed by G.C. and M.R.. L.B. wrote the first draft of the manuscript. All the authors participated to the discussion of the results and critically revised the manuscript.

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Conflict of interest

None of the authors have any conflict of interest related to the topic to declare.

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