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Running title: Endometriosis and miscarriage

Risk of miscarriage in women with endometriosis: insights from *in vitro* fertilization cycles.

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Capsule

Women with endometriosis achieving singleton pregnancies with *in vitro* fertilization do not face an increased risk of miscarriage.

Abstract

Objective: To evaluate whether women with endometriosis achieving singleton pregnancies with *in vitro* fertilization (IVF) face an increased risk of miscarriage.

Design: Matched case-control study

Setting: Two Italian infertility Units.

Patients: Women achieving singleton pregnancies with the use of IVF were considered. Cases were women with a history of surgery for endometriosis and those who were documented the presence of ovarian endometriomas at the time of the IVF cycle (n=313). Controls were matched to cases by age (± 6 months), type of cycle (fresh or frozen cycle) and study period (n=313).

Interventions: Retrospective review of women undergoing IVF.

Main outcome measures: Rate of miscarriage before 12 weeks' gestation

Results: The number of miscarriages in women with and without endometriosis was similar, being 48 (15%) and 60 (19%), respectively. The Odds Ratio (OR) of miscarriage in affected women was 0.76 (95%CI: 0.50-1.16). The OR adjusted for body mass index, parity, duration of infertility and male factor was 0.81 (95%CI: 0.53-1.25). Subgroup analyses according to the type of cycle, the number of embryos transferred, the presence of endometriomas and the history of surgery for endometriosis did not document any subgroup at significant increased risk of miscarriage.

Conclusions: The risk of miscarriage is not increased in women with endometriosis achieving pregnancy with the use of IVF.

Key words: endometriosis / miscarriage / IVF

Introduction

The endometrium of women with endometriosis has been extensively studied and several differences with the endometrium of healthy women have emerged. Differences have been found in stem cells content, hormone sensitivity, cellular proliferation, adhesion, invasiveness, angiogenesis and immune-modulation (1-3). To date, however, it is still difficult to discern whether these differences have pathogenic implications or, conversely, whether they are consequent to the presence of the disease.

Regardless of the significance of the detected differences, the observation that the endometrium of women with endometriosis has peculiar characteristics inevitably raises the question of the possible impact on pregnancy outcome and, in particular, on the risk of miscarriage. This aspect has received initial attention in the eighties but studies had significant flaws and evidence was inconclusive (4-7). Recently, interest on this argument has re-flourished (8,9) but, to date, definite conclusions cannot be drawn because the designs of the available studies are generally weak and results inevitably exposed to confounders (Table 1) (10-16).

In vitro fertilization (IVF) may be a good model to provide evidence on the risk of miscarriage in women with endometriosis because, in contrast to natural pregnancies, women are actively followed-up in the early stage of pregnancy. Moreover, this setting allows for the recruitment of unaffected controls undergoing the same ascertainments. According to two recent independent meta-analyses on the impact of endometriosis on IVF rate of success, the Relative Risk (RR) of miscarriage in affected women was 1.31 (95%CI: 1.07-1.59) (17) and 1.26 (95%CI: 0.92-1.70) (18), respectively. However, the use of aggregate data rather than individual patient data and the inclusion of studies not specifically designed to evaluate the rate of miscarriage in women with endometriosis impedes firm conclusions.

In the present study, we aimed at drawing some more robust evidence on the relation between endometriosis and miscarriage. Specifically, we evaluated the rate of miscarriage in a large sample of singleton in IVF pregnancies obtained in women with endometriosis. To limit the impact of confounders, controls were singleton IVF pregnancies matched for age, type of cycle and study period.

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, Milan (between January 2011 and June 2014) were retrospectively reviewed. Inclusion criteria were as follows: 1) age 18-42 years, 2) classical IVF or intracytoplasmatic sperm injection (ICSI) cycle (fresh or frozen), 3) clinical singleton pregnancy as documented by a transvaginal ultrasound performed four weeks after embryo transfer, 4) follow-up available up to 12 weeks' gestation. Exclusion criteria included: 1) abnormal uterine cavity (presence of submucosal fibroids or endometrial polyps, 2) uterine malformations (such as in particular uterine septum), 3) abnormal karyotype of the woman or her partner, 4) Antiphospholipid syndrome, 4) diabetes or overt distyroidism, 5) multiple pregnancies (including those with an early vanishing twin), 5) suspected but not surgically or sonographically documented endometriosis. Women could be included only for one cycle (the first cycle ending into a clinical pregnancy). Cases were women with a history of surgery for endometriosis and those who were documented the presence of ovarian endometriomas at the time of the IVF cycle. Controls were matched to cases in a 1:1 ratio by age (± 6 months), type of cycle (fresh or frozen cycle) and study period (the following woman fulfilling the criteria for

selection and matching). The study was approved by the local institutional review board. An informed consent was not required since this is a retrospective study. However, all women referring to the involved units signed an informed consent for their data to be used for scientific purposes and agreed to be contacted after the procedure for follow-up. Women who denied this consent were excluded.

Women undergoing IVF in the two Units involved followed standardized protocols. They are reported in details elsewhere (19,20). Of interest here is that no adjuvant treatments (acetylsalicylic acid, cortisone or low weight molecular heparin) were given with the exception of folic acid that was conversely systematically prescribed. Pre-implantation genetic screening (PGS) was never performed. Vaginal luteal phase support modalities varied during the recruitment period and between Centers but was systematically given in fresh cycles until at least human Chorionic Gonadotropin (hCG) identification in the maternal serum. Women receiving hormone replacement therapy (HRT) for frozen cycles continued the therapy for the whole first trimester of pregnancy (treatment was discontinued only in case of miscarriage). Women undergoing frozen embryo transfer replacement on a natural cycle did not receive any luteal phase support. Pregnancy assessment was performed testing serum hCG at +14 days after oocytes retrieval (adapted for frozen cycle). Women found to be pregnant were scheduled a second serum assessment 48 hours later and, if appropriate, they underwent transvaginal sonography two weeks later (thus four weeks after embryo transfer). The ultrasound scan could be done earlier in case of abnormalities in serum hCG growth or in the presence of suspicious symptoms (pain or blood loss). According to the Italian legislation, all IVF pregnancies were subsequently actively followed-up by repeated phone calls and, if required, by clinical and sonographic assessments. Miscarriage was defined as the interruption of pregnancy within 12 weeks' gestation (based on the crump-row length). Data was obtained from outpatient and inpatients charts. Discrepancies or missing data were solved by directly contacting the women.

The diagnosis of endometrioma was performed by transvaginal ultrasound and had to be documented on at least two occasions and at least two menstrual cycles apart. More specifically, 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 vascularized proliferations (21).

Data was analyzed using the SPSS software 18.0 (Chicago, IL). Fisher Exact test, Student *t*-test and Wilcoxon non parametric test were used as appropriate. P values below 0.05 were considered statistically significant. Association between endometriosis and miscarriage was provided using Odds Ratios (OR) and relative 95%Confidence Interval (95%CI). A logistic regression model including baseline characteristics found to differ and univariate analyses ($p<0.10$) was used to calculate the adjusted ORs. The sample size was calculated setting type I and II errors at 0.05 and 0.20, respectively, expecting a miscarriage rate among controls of 20% and claiming as clinically relevant a relative increase of the risk of 50% (from 20% to 30%). On these bases, the number of women to be recruited was 300 per group. Based on the characteristics of the Units involved, we estimated that data from a 6-year period was necessary.

Results

Three hundred thirteen women with endometriosis and 313 controls without the disease were selected. Main baseline characteristics of the two study groups are shown in Table 2. As expected, indications to the procedure differed. Moreover, a statistically significant difference was found for the body mass index (BMI) and for the duration of infertility. Specific characteristics of women with endometriosis are shown in Supplementary Table 1. Two

hundred thirty-five cases and 235 controls (75% of the studied women) achieved pregnancy during a fresh cycle. Characteristics of these cycles are illustrated in Supplementary Table 2. Women with endometriosis required a higher dose of gonadotropins and retrieved less oocytes. Supplementary Table 3 illustrates the characteristics of the frozen cycles (78 per group). A higher proportion of control women underwent ICSI.

Overall, the number of pregnancies ending into miscarriage in women with and without endometriosis was 48 (15%) and 60 (19%), respectively (p=0.25). The OR of miscarriage in affected women was 0.76 (95%CI: 0.50-1.16). The OR adjusted for BMI, parity, duration of infertility and male factor was 0.81 (95%CI: 0.53-1.25). We did subgroup analyses according to the type of cycle (fresh and frozen), the number of embryos transferred, the presence of endometriomas and the history of surgery for endometriosis (Table 3). None of these analyses documented any subgroup at significant increase risk of miscarriage. Further, the exclusion of women with adenomyosis (n=29) did not modify the general results. The adjusted OR for miscarriage in affected women was 0.86 (95%CI: 0.55-1.36). Finally, data was analyzed separately for the two involved Institutions but no main differences emerged (data not shown)

Discussion

Women with endometriosis do not appear to face an increased risk of miscarriage. Our results did not show an association between endometriosis and spontaneous abortion in women achieving singleton pregnancies with the use of IVF. Subgroup analyses indirectly confirmed our findings since we failed to observe any condition at increased risk.

Albeit our results are based on a large sample size and appear robust in sensitivity analyses, inference of data obtained in IVF pregnancies to natural pregnancies should be made with

caution for at least two reasons. Firstly, natural and IVF-mediated conceptions differ in some aspects. In particular, natural conception occurs in the distal part of the tube, in a milieu that may actually be adversely affected by the peritoneal inflammation milieu (22). Moreover, the oocyte that is picked-up by the tubes has already been in direct contact with the inflammatory peritoneal fluid prior to be fertilized (23). More in general, even if the detrimental effects of inflammation on folliculogenesis are expected to be similar for both IVF and natural pregnancies, IVF has the advantage to prevent the direct contact of the oocyte with the peritoneal fluid. It may be speculated that the harmful milieu consequent to the presence of the disease may in some cases cause sublethal harm to the oocyte or to the early embryo, allowing conception and early embryo development but impeding progress of pregnancy over the first trimester of pregnancy. If this pathogenic possibility plays a role, the risk of abortion would be more relevant for natural pregnancy. Secondly, we cannot exclude that the hyper-stimulation may obscure the detrimental effects of endometriosis on the endometrium. Endometrium is markedly influenced by the hyper-stimulation (24) and one may speculate that, in these circumstances, potential differences between women with and without the disease may become unremarkable. Moreover, endometrial alterations encountered in endometriosis may be normalized by surgery. However, these two possibilities are not supported by our subgroup analyses. Indeed, we failed to document a statistically significant impairment on the chances of pregnancy when focusing on frozen cycles. Moreover, when restricting the analysis to women with ovarian endometriomas, we also failed to detect reduced chances of pregnancy when focusing on all cycles or only on fresh cycles. The statistical power of these three subgroup analyses was however modest (30%, 57% and 46%, respectively).

Our observation may be at prima face surprising since it contrasts with the common view that endometriosis may enhance the risk of abortion (25) and with some available epidemiological and biological evidence. In the recent literature, we indeed identified seven studies reporting on

the risk of abortion in women with endometriosis (10-16), of whom three showed a statistically significant positive association (11,14,16) (Table 1). Moreover, two recent meta-analyses investigating the rate of miscarriage in women with endometriosis achieving pregnancy through IVF reported an about 30% increased risk (17,18). On the other hand, it is crucial to emphasize that the study designs of these epidemiological studies are generally weak and the results inevitably exposed to significant biases. The most important limitations include the lack of an appropriate control group, inaccuracies in the diagnosis of abortion and the confounding effect of age. This latter point is of utmost relevance. Multivariate analysis to adjust for age may not completely overcome this confounder because the relationship between age and risk of abortion is not linear (26). For this reason, matching rather than adjusting for age is in our opinion more appropriate. Noteworthy, the above-mentioned meta-analyses on the risk of abortion in women with endometriosis undergoing IVF do not adjust for age since the authors aggregated crude data (17,18).

In our opinion, the observation that endometriosis is not associated to an increased risk of abortion in an IVF context does not radically contrast with the available biological evidence of the disease. There is undoubtedly several experimental data suggesting that the endometrium and the uterus of women with endometriosis may be altered and thus more prone to cause abortion (3). They include: 1) the endometrial resistance to selective actions of progesterone that affects the downstream progesterone target genes and thus, ultimately, decidualization (27), 2) the inflammatory process whose consequences can be manifested also at endometrial level with in particular an increased release of reactive oxygen species (2), 3) the inadequate uterine contractility (28), 4) the well-known association with adenomyosis (29,30) that was suggested to increase the risk of abortion on its own (31). On the other hand, it is intriguing to note that several characteristics of the endometrium that are deemed essential to allow the implantation of the embryo are also concomitantly involved in the pathogenesis of endometriosis. For

instance, proliferation, immune-modulation, angiogenesis, adhesion are all involved in both the endometrial capacity to receive the embryo and the development of the disease (32-34). In other words, endometriosis may develop only if the endometrium is particularly healthy and receptive, if not even more receptive than normal. Noteworthy, a recent study investigating the molecular pattern involved in embryo implantation failed to document any difference between women with and without endometriosis (35). The endometrium of affected women might be paradoxically more adapted to receive the embryo and the local modifications consequent to the presence of the disease may only marginally affect this situation (resulting in a global absence of effect). This possibility is however difficult to demonstrate and remains speculative. More evidence is warranted.

Some limitations of our study should be acknowledged. Firstly, we exclusively included women with a sonographic demonstration of a gestational sac. Since sonography was routinely scheduled four weeks after embryo transfer, we may have missed some very early abortions. The active follow-up that is routinely performed in our Units (allowing us to include also some very early abortions provided that a gestational sac was documented) may not fully protect our results from this inaccuracy. One may even claim that studying biochemical rather than sonographic pregnancies would have been more informative. However, we decided to exclude biochemical pregnancies because these pregnancies have to be considered of unknown location and tubal abortions cannot be excluded. Secondly, basal characteristics of the two groups differ. Even if we matched for the most important variables, i.e. age, type of cycle and study period, some differences emerged. In particular, the total dose of gonadotropins given and the number of oocytes retrieved differed in fresh cycles. Again, we do not estimate this limitation of main relevance considering that estrogens did not differ: the reduced number of oocytes retrieved may presumably be secondary to the well-known technical difficulties during oocytes retrieval in women with endometriosis (36) and, to a less extent, a lower responsiveness. Noteworthy,

considering the reported negative association between the number of oocytes retrieved and miscarriage rate following IVF treatment (37), this bias could be expected to overestimate the difference rather than diluting it. Finally, regardless of the direction of the interferences, we adjusted for all the variables who were found to differ for a p value < 0.10 (total dose of FSH administered and number of oocytes retrieved, BMI, previous deliveries and duration of infertility) Thirdly, we included among cases also women without a surgical diagnosis of endometriosis. In this regard, it has to be emphasized that the sonographic diagnosis of ovarian endometrioma is very reliable (38) and that we excluded women with a suspected diagnosis of endometriosis from both cases and controls. Moreover, when excluding women without a surgical diagnosis in the subgroup analysis, the figure did not change. Further, we could not evaluate the impact of the presence of deep endometriosis or adenomyosis. Their sonographic diagnosis is more challenging and has improved only in recent years (39). Albeit sometimes recorded, we deem the collection of these variables insufficiently reliable for robust analyses. We only performed a secondary analysis excluding women with adenomyosis because of the recent (and debated) view that this condition may increase *per sè* the risk of abortion (31). Fourthly, we cannot exclude that some women with endometriosis were erroneously classified in the control group. This is a common limitation of case-control studies on the disease and it is due to the lack of non-invasive tools for the diagnosis of early cases. However, the impact of this limitation is presumably modest considering that misclassification could occur in less than 10% of cases and that that only mild forms of the disease can be missed (39,40). Finally, the karyotypes of the aborted fetuses were not available. This information would have been interesting since the potential detrimental effects of endometriosis are expected to exclusively occur in pregnancies with normal karyotypes.

In conclusion, endometriosis does not expose women to an increased risk of miscarriage in IVF cycles. Inference of this conclusion to women with endometriosis who conceive naturally is plausible but requires confirmation with properly designed epidemiological studies.

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