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ARTICLE

Asymptomatic adenomyosis and embryo implantation in IVF cycles

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Abstract Research on the effect of adenomyosis on the rate of success of IVF is controversial. Differences in study design, study power, criteria and instrument used to diagnose adenomyosis and choice of controls may explain these discrepancies. To establish whether embryo implantation is impaired in women with adenomyosis, women scheduled for IVF were prospectively evaluated for the presence of adenomyosis and whether this condition affected embryo implantation. Forty-nine women with adenomyosis diagnosed at transvaginal ultrasound with no abnormal uterine bleeding were recruited. They were matched for study period, age, day of embryo transfer and number of transferred embryos to 49 controls without the disease. In women with adenomyosis, 24 out of 76 embryos transferred implanted (32%); this occurred in 16 out of 76 (21%) in unaffected controls. The crude odds ratio of implantation in affected women was 1.73 (95% CI 0.83 to 3.60). The odds ratio adjusted for body mass index (the unique variable found to differ at univariate analysis) was 1.78 (95% CI 0.85 to 3.77). In conclusion, implantation rate is not impaired in asymptomatic women who are diagnosed with adenomyosis at transvaginal sonography. Affected women can be reassured about the effect of this condition on their chances of success.

KEYWORDS: adenomyosis, IVF, implantation, live birth, pregnancy, prospective

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Introduction

Adenomyosis results from the invasion of basal endometrial glands and basal endometrial stroma into the underlying myometrium (Brosens et al., 1998; Leyendecker et al., 2002). This process disrupts the architecture of the myometrium and causes local inflammation, thus potentially interfering with fertility. Available data on the relationship between adenomyosis and infertility, however, is still scant and controversial (Campo et al., 2012; Maheshwari et al., 2012; Tomassetti et al., 2013).

To establish whether adenomyosis negatively affects fertility, several investigators have focused on affected women undergoing IVF, as this model offers the unique opportunity to obtain precise data on the influence of adenomyosis on embryo implantation (Vercellini et al., 2014). To the best of our knowledge, nine original studies have been published using this study design, most of them during the past 3 years (Ballester et al., 2012; Chiang et al., 1999; Costello et al., 2011; Martínez-Conejero et al., 2011; Maubon et al., 2010; Mijatovic et al., 2010; Salim et al., 2012; Thalluri and Tremellen, 2012; Youm et al., 2011). Results from these contributions, however, are conflicting, with four of them suggesting an association (Ballester et al., 2012; Maubon et al., 2010; Thalluri and Tremellen, 2012; Youm et al., 2011) and five failing to document any statistically significant effect (Chiang et al., 1999; Costello et al., 2011; Martínez-Conejero et al., 2011; Mijatovic et al., 2010; Salim et al., 2012). Differences in study design, study power, criteria and instrument used to diagnose adenomyosis and choice of controls may explain these discrepancies (Vercellini et al., 2014). Of particular relevance here is that only four studies were prospective (Ballester et al., 2012; Chiang et al., 1999; Maubon et al., 2010; Salim et al., 2012), and that reported data were seldom adjusted for age, ovarian responsiveness and embryo quality (Ballester et al., 2012; Costello et al., 2011; Thalluri and Tremellen, 2012), three pivotal confounders when focusing on embryo implantation.

In this study, the aim was to elucidate whether embryo implantation is impaired in women with adenomyosis undergoing IVF. To this aim, women scheduled for the procedure were prospectively evaluated for the presence of adenomyosis and subsequently evaluated whether this condition affected embryo implantation.

Materials and methods

Patients undergoing IVF–intracytoplasmic sperm injection (ICSI) cycles between November 2012 and April 2013 at the Infertility Unit of the Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy, were prospectively and consecutively considered for study entry. Specifically, inclusion criteria were as follows: indication to IVF–ICSI; age 42 years or younger; no previous IVF–ICSI cycles; no previous surgery for adenomyosis; no uterine malformations; no abnormal uterine bleeding; and no endometrial abnormalities as assessed by transvaginal sonography. Women whose uterine ultrasounds were doubtful, and those with fibroids or endometrial polyps, were excluded. Moreover, women who did not achieve fresh embryo transfer because of cancelled cycle or unavailability of viable embryos were also excluded. Exposed cases were women who were diagnosed adenomyosis at baseline transvaginal ultrasound during the diagnostic phase. Unexposed controls were women whose sonographic evaluation of the uterus was unremarkable at prospective evaluation. They were retrospectively matched by study period, age (±1 year), day of embryo transfer and number of transferred embryos to cases in a 1:1 ratio. Women in both study groups were included only for their first IVF–ICSI attempt. The local Institutional Review Board approved the study (Number 2413, 16 October 2012), and all recruited patients signed an informed consent.

Eligible women underwent a baseline transvaginal ultrasound scan the month before their treatment cycle aimed at identifying the presence of adenomyosis. The uterus was scanned in three anatomical planes (sagittal, coronal and tranverse). Adenomyosis was diagnosed when asymmetrical thickening of the anterior and posterior walls of myometrium was identified or irregular cystic areas were found within the myometrium or linear striations radiating out from the myometrium or irregular endometrial-myometrial junction was observed (Naftalin et al., 2012). Adenomyosis was considered focal when singular foci with adenomyotic characteristics were identified. Otherwise, the disease was classified as diffuse. All ultrasound scans were conducted by three physicians experienced in gynaecological ultrasonography. Two preliminary meetings on the sonographic appearance of adenomyosis using iconographic material were performed among the physicians to standardize diagnosis. Doubtful cases were concomitantly evaluated by at least two of the physicians. If agreement was not reached, cases were judged as doubtful and, as previously mentioned, they were excluded to prevent confounders.

Selected women were then monitored and managed according to a standardized clinical protocol as reported elsewhere (Benaglia et al., 2013; Busnelli et al., 2013). Briefly, the dose of gonadotropins was determined on an individual basis according to the characteristics of the patients as age, serum hormonal levels and antral follicles count. Patients underwent serial transvaginal ultrasound and hormonal monitoring during hyperstimulation. When three or more leading follicles with a mean diameter greater than 18 mm were visualized, 10000 IU of human chorionic gonadotrophin (HCG) was administered subcutaneously. Oocyte retrieval was carried out transvaginally 36 h after the HCG injection (day 0). Embryo transfer was carried out on day 2, day 3 or day 5. Transfer was carried out on day 2 if the number of viable embryos on day 2 was two or less and at blastocyst stage (day 5) if the number of good-quality embryos on day 3 was four or more. In the remaining situations, embryo transfer was carried out on day 3. The numbers of embryos to be transferred was chosen on an individual basis, taking into consideration prognostic factors and quality of the available embryos. Cycles were cancelled because of poor or hyper-response of the ovaries. Cycles could be also cancelled after oocyte retrieval if the number of retrieved oocytes exceeded 15 or in the presence of symptoms and signs suggestive for ovarian hyperstimulation syndrome or if serum progesterone exceeded 1500 pg/ml at the time of HCG administration. In all these situations, oocytes, embryos, or both, were frozen and used in subsequent cycles. These women, however, were excluded from the present analysis. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer.

Biochemical and extrauterine pregnancies were not considered clinical pregnancies. Selected women were actively monitored until the end of the first trimester. Subsequent pregnancy outcome was assessed by phone contact 8–10 months after embryo transfer.

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS 15.0, Chicago, IL). Data are reported as number (%), mean ± SD or median (interquartile range), as appropriate. Data were compared using chi-squared test, Fisher's exact test, Student *t*-test and unpaired Wilcoxon test as appropriate. $P < 0.05$ were considered statistically significant. The main outcome of the study was the implantation rate, defined as the number of gestational sacs detected at transvaginal ultrasound per the number of embryos transferred. Secondary outcomes were clinical pregnancy rate, spontaneous abortion rate and the live birth rate. A logistic regression model, including variables found to significantly differ at univariate analysis, was used to calculate the adjusted odds ratio of pregnancy, implantation and live birth. The sample size was calculated based on the following assumptions: type 1 and 2 errors: 0.05 and 0.20, respectively; expected implantation rate in the control group: 20%; expected frequency of adenomyosis: 15% (Chiang et al., 1999; Costello et al., 2011; Maubon et al., 2010; Youm et al., 2011); mean number of embryos transferred per woman: 1.5; and difference to be regarded as clinically relevant: 15% (from 20% in the unexposed group to 5% in the exposed group). On this basis, at least 75 embryos needed to be transferred in the group of affected women, corresponding to about 50 women.

Results

Forty-nine women with adenomyosis and 49 controls were ultimately selected. The median (interquartile range) volume of the uterus in affected cases was 61 (52–85) ml. The disease was focal in 24 (49%) women and diffuse in the remaining 25 (51%). Baseline characteristics of women with and without adenomyosis are shown in **Table 1**. No statistically significant differences emerged, with the exception of the body mass index (BMI) ($P = 0.04$). Considering IVF–ICSI outcome, variables reflecting ovarian responsiveness to hyperstimulation were similar (**Table 2**).

The chances of success in the two study groups are shown in **Figure 1**. The clinical pregnancy rate in women with and without adenomyosis was 43% ($n = 21$) and 29% ($n = 14$), respectively. The crude and BMI-adjusted odds ratios of clinical pregnancy in affected women were 1.88 (95% CI 0.81 to 4.34) and 2.05 (95% CI 0.86 to 4.90), respectively. The number of twin pregnancies in women with and without adenomyosis was three (14%) and two (14%), respectively. Overall, in women with adenomyosis, 24 out of 76 embryos implanted (32%), whereas this occurred in 16 out of 76 (21%) in unaffected controls ($P = 0.14$). The crude and BMI-adjusted odds ratios of implantation in affected women were 1.73 (95% CI 0.83 to 3.60) and 1.78 (95% CI 0.85 to 3.77), respectively. Spontaneous abortion occurred in four affected women (19%) and five unaffected controls (36%). The number of live births in women with and without adenomyosis was 17 (35%) and nine (18%), respectively. The crude and BMI-adjusted odds ratios of live birth in affected women were 2.36 (95% CI 0.93 to 6.00) and 2.62 (95% CI 0.98 to 6.96), respectively.

The type and severity of adenomyosis did not markedly affect the outcome. The clinical pregnancy rate in women with focal ($n = 24$) and diffuse ($n = 25$) adenomyosis was 46% ($n = 11$) and 40% ($n = 10$), respectively. The live birth rate was 33% ($n = 8$) and 36% ($n = 9$), respectively. The implantation rate was 32% (12 out of 38) and 32% (12 out of 38), respectively. The clinical pregnancy rate in women whose uterine volume was above ($n = 24$) or equal/below ($n = 25$) the median (61 ml) was 42% ($n = 10$) and 44% ($n = 11$). The implantation rate was 31% (11 out of 36) and 33% (13 out of 40), respectively. The live birth rate was 33% ($n = 8$) and 36% ($n = 9$), respectively.

Table 1 Baseline characteristics of women with and without adenomyosis.

Characteristics	*Adenomyosis (n = 49)*	*Controls (n = 49)*
Age (years)	35 ± 4	35 ± 4
BMI (kg/m^2)[a]	22.6 ± 3.8	21.3 ± 2.3
Duration of infertility (months)	48 ± 27	59 ± 34
Day 3 serum FSH (IU/ml)	7.1 ± 2.1	8.2 ± 4.6
Serum AMH (ng/mL)	1.7 ± 2.2	2.4 ± 3.0
Previous pregnancies *n* (%)	14 (29)	18 (37)
Previous deliveries *n* (%)	3 (6)	4 (8)
Previous cesarean section *n* (%)	2 (4)	3 (6)
Previous dilataion and curretage *n* (%)	9 (18)	8 (16)
Previous operative hysteroscopy *n* (%)	5 (10)	4 (8)
Previous myomectomy *n* (%)	3 (6)	1 (2)
Main indication to IVF-ICSI		
Male Factor *n* (%)	12 (24)	23 (47)
Endometriosis *n* (%)	21 (43)	13 (27)
Tubal factor *n* (%)	8 (16)	6 (12)
Unexplained / Reduced ovarian reserve *n* (%)	8 (16)	7 (14)

AMH, anti-Mullerian hormone; BMI, body mass index; ICSI, intracytoplasmic sperm injection.
[a]$P = 0.04$.

Table 2 Characteristics of IVF–ICSI cycles in women with and without adenomyosis.

Characteristics	*Adenomyosis (n = 49)*	*Controls (n = 49)*
Stimulation protocol		
Long protocol *n* (%)	26 (53)	26 (53)
GnRH antagonist *n* (%)	11 (22)	14 (29)
Short protocol *n* (%)	11 (22)	8 (16)
Others *n* (%)	1 (2)	1 (2)
Total dose of administered FSH (IU)	2998 ± 1288	2706 ± 1318
Duration of stimulation (day)	10.5 ± 2.5	10.3 ± 2.8
Number of oocytes retrieved	7.3 ± 4.1	7.3 ± 4.5
Number of suitable oocytes	4.8 ± 2.4	5.0 ± 3.0
Technique used		
IVF *n* (%)	15 (31)	15 (31)
ICSI *n* (%	34 (69)	34 (69)
Fertilization rate n (%)	83 (75–100)	86 (67–100)
Day of embryo transfer[a]		
Day 2 *n* (%)	20 (41)	20 (41)
Day 3 *n* (%)	18 (37)	18 (37)
Day 5 *n* (%)	11 (22)	11 (22)
Number of embryos transferred[a]		
1 *n* (%)	24 (49)	24 (49)
2 *n* (%)	23 (47)	23 (47)
3 *n* (%)	2 (4)	2 (4)
Top quality embryos at 48–72 h		
None *n* (%)	13 (27)	7 (14)
≥1 *n* (%)	36 (73)	42 (86)

GnRH, gonadotrophin-releasing hormone; ICSI, intracytoplasmic sperm injection.
[a]Matching variables. No statistically significant differences were found between the two groups.

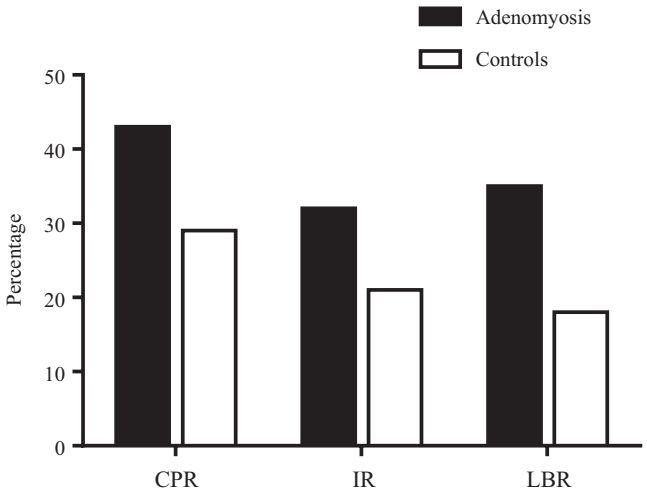

Figure 1 Outcome of IVF in women with (black bars) and without (white bars) adenomyosis. CPR, Clinical pregnancy rate; IR, implantation rate; LBR, live birth rate. No statistically significant differences emerged.

Discussion

In this study, a detrimental effect of adenomyosis on embryo implantation was not identified. Our observation is in line with five previous studies on this subject (Chiang et al., 1999; Costello et al., 2011; Martínez-Conejero et al., 2011; Mijatovic et al., 2010; Salim et al., 2012) and, in contrast with the remaining four (Ballester et al., 2012; Maubon et al., 2010; Thalluri and Tremellen, 2012; Youm et al., 2011). Our study has some important strengths compared with the previous available contributions. First, it is prospective. This recruitment strategy should have limited inaccuracies in group allocation. Misdiagnoses are more likely in retrospective studies given that adenomyosis requires active and careful investigation to be detected or ruled out. Retrospective studies are exposed to either over-estimation of the effects (if only more advanced adenomyosis is reported) or under-estimation (if subtle forms are missed and affected women are erroneously allocated among controls). Second, cases and controls were matched for study period, age, day of embryo transfer and number of embryos transferred. We deem this study design of utmost relevance to protect the results from confounders. Indeed, women with and without adenomyosis may actually differ in some important baseline characteristics. We speculate that this point may have played a critical role in explaining discrepancies among the available studies on the effect of adenomyosis on IVF. We also advocate that future studies on this issue should take into utmost consideration this aspect. Matching or at least adjustment for known confounders is crucial. Moreover, for the same reason, future studies aimed at grouping data from different studies should consider individualized patient data analyses rather than classical meta-analyses.

The absence of any effect of adenomyosis on embryo implantation in the context of IVF should, however, not lead to the conclusion that this condition does not afect fertility for

at least three reasons. First, women with abnormal uterine bleeding were generally excluded from the studies. This was an exclusion criterion also in the present study. These women may have more advanced and detrimental forms of the disease. We cannot exclude that embryo implantation may be actually impaired in women with this form of adenomyosis. Inferences of our conclusions should therefore, be limited to the population studied (i.e. women with sonographically detected adenomyosis and without abnormal uterine bleeding). Second, the protocol of ovarian stimulation used for IVF may have a therapeutic effect on adenomyosis. For instance, gonadotrophin-releasing hormone (GnRH) analogues have actually been suggested to improve pregnancy rate in women with this condition (Mijatovic et al., 2010; Niu et al., 2013). A short period of sex steroid deprivation may transiently annul the detrimental effects of adenomyosis on the receptivity of the endometrium. In other words, it cannot be ruled out that the harmful effects of adenomyosis may be overcome in the context of IVF. Of note, most of the women in our study received a long protocol regimen. Third, the lack of any effect of adenomyosis on pregnancy rate in an IVF setting cannot be used to draw general conclusions on the relationship between adenomyosis and infertility in general. Some investigators have also suggested that the possible harmful effects of adenomyosis may not be limited to the implantation of the embryo, and claim a role also for an abnormal utero–tubal sperm transport (Leyendecker et al., 2002).

Two main limitations of our study should be acknowledged. First, we lack a histological confirmation of adenomyosis as women were not operated on. Moreover, the studied women did not undergo magnetic resonance imaging or hysteroscopy, two evaluations that may improve the reliability of the diagnosis and may help to exclude other concomitant potentially detrimental conditions. The accuracy of transvaginal ultrasound in identifying adenomyosis and ruling out other uterine abnormalities, however, is well-established and deemed similar to magnetic resonance imaging (Bazot et al., 2001; Campo et al., 2012; Champaneria et al., 2010; Levy et al., 2013; Shwayder and Sakhel, 2014). The sonographic diagnosis of adenomyosis is commonly used in clinical practice and was used in most of the previous studies on adenomyosis and IVF (Chiang et al., 1999; Costello et al., 2011; Martínez-Conejero et al., 2011; Mijatovic et al., 2010; Salim et al., 2012; Youm et al., 2011). Moreover, in our study, all scans were carried out by few expert gynaecologists, criteria for diagnosis were univocal and specifically clarified before starting the study and doubtful cases were excluded. Second, the study was underpowered for secondary but relevant outcomes. In particular, even if subgroup analyses according to localization and severity of the disease failed to document any effect, these results are exposed to a significant risk of type 2 error and should not be viewed as conclusive. For the same reason, we could not draw robust conclusions on the risk of spontaneous abortion, and that is an important concern in the context of adenomyosis (Martínez-Conejero et al., 2011). Further larger evidence is required to definitively address these points. To the best of our knowledge, however, the present study represents the largest prospective study on the relationship between adenomyosis and IVF.

In conclusion, asymptomatic women with a sonographic diagnosis of adenomyosis who are scheduled for IVF can be reassured about the effect of this condition on their chances of success. The lack of any detrimental effect on the success of the procedure, however, does not exclude a possible detrimental effect on spontaneous fertility. Moreover, we cannot exclude a beneficial effect of the use of GnRH analogues, a drug that is part of the most common regimens of ovarian stimulation aimed at IVF. Further studies using different study designs are, therefore, warranted to establish whether adenomyosis does or does not affect fertility.

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