

## Editorial

# Infertility Associated to Endometriosis: Clarifying Some Important Controversies

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Endometriosis is an estrogen-dependent gynecological disease characterized by the presence and growth of endometrial tissue (glands and/or stroma) outside the uterine cavity.<sup>1</sup> The disease affects ~ 10% of women of reproductive age<sup>2</sup> and is strongly associated with infertility.<sup>3</sup> It is estimated that more than 30% of infertile women have endometriosis<sup>2</sup> and that 30 to 50% of these women report difficulties in getting pregnant.<sup>4</sup>

Opinion remains divided as to whether minor endometriosis (minimal and mild endometriosis—stages I and II, respectively) has an adverse effect on the likelihood of conception.<sup>5–9</sup> In 1998, a study demonstrated that the fecundity of infertile women with minimal or mild endometriosis is not significantly lower than that of women with unexplained infertility, suggesting that the initial stage of the disease is just a finding and not the cause of infertility.<sup>6</sup> Otherwise, the findings of a randomized controlled trial showing improved natural conception rates following surgical treatment of visible endometriotic lesions suggest that the presence of visible minor lesions alone may have an adverse effect on natural conception.<sup>7</sup> Additionally, a retrospective study of 192 fully investigated infertile couples (117 women with unexplained infertility and 75 with minimal/mild endometriosis without adhesive disease, both managed conservatively after diagnostic laparoscopy) evaluated cumulative pregnancy rates in both groups followed up for up to 3 years following laparoscopy.<sup>8</sup> This study demonstrated that women with endometriosis had a lower probability of pregnancy compared with women with unexplained infertility (36% versus 55%, respectively), which confirmed the presence of lower cumulative pregnancy rates in women in the early stages of endometriosis compared with women with infertility of unknown cause,<sup>9</sup> thus supporting the association between infertility and endometriosis in the early stages.


Infertility presented by women with early endometriosis, in whom pelvic anatomical distortions are not present, raises

questions about the mechanisms involved in the impairment of fertility in patients with the disease. The research group under my supervision has extensively performed studies in this subject and published recent review articles approaching this topic.<sup>10–12</sup> Although the mechanisms involved in endometriosis-related infertility are still not completely understood, in summary, there are studies suggesting the peritoneal, follicular, systemic, and endometrial microenvironments may be altered in these women, with consequent damages to folliculogenesis, oocyte quality, endometrial receptivity, and, even, sperm function.<sup>10–12</sup>

Another very controversial point is whether the indication of in-vitro fertilization (IVF) in infertile women with endometriosis is associated with a worse gestational prognosis after the procedure, and if the progression in disease staging further worsens the results of the IVF.

A systematic review published in 2002<sup>13</sup> showed that patients with endometriosis who underwent ovarian stimulation for IVF had lower pregnancy rates when compared with infertile patients with tubal factor (relative risk (RR) 0.56, 95% confidence interval [95% CI] 0.44–0.70). However, when dividing endometriosis patients according to the staging of the disease (minimal/mild endometriosis—stages I/II and moderate/severe endometriosis—stages III/IV), it was observed that patients with endometriosis I/II presented pregnancy rates similar to those with tubal factor (RR 0.79, 95% CI 0.6–1.03), and patients with endometriosis III/IV had significantly lower rates than those without the disease (RR 0.46, 95% CI 0.28–0.74). Despite being a relevant review, its main limitation is that most of the included studies were published between 1980 and 1999, a period in which ovarian stimulation and technical conditions were quite different from the current ones.

However, more recent studies contradict the results of this meta-analysis published in 2002. Data from the latest published meta-analysis,<sup>14</sup> which analyzed 36 cohort studies and randomized controlled trials, show that compared with women without endometriosis, women with endometriosis undergoing IVF and intracytoplasmic sperm injection (ICSI) had a

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similar live birth rate per woman (RR = 0.94, 95% CI 0.84–1.06, 13 studies, 12,682 patients, I<sup>2</sup> = 35%), lower clinical pregnancy rate per woman (RR = 0.78, 95% CI 0.65–0.94) (mean difference of -1.98, 95% CI, 22.87–21.09, 17 studies, 17,593 cycles, I<sup>2</sup> = 97%), a lower mean number of oocyte retrieved per cycle (mean difference - 1.98, 95% CI - 2.87 to - 1.09, 17 studies, 17,593 cycles, I<sup>2</sup> = 97%). When compared with women without endometriosis, women with more advanced disease (stages III-IV) have lower rates of live births, clinical pregnancy rates, and mean number of retrieved oocytes. Briefly, data from this meta-analysis show a lower number of oocytes captured in women with endometriosis compared with women without endometriosis, and lower live birth rates only in women with stage III/IV endometriosis when compared with women without endometriosis.

It is important to state that women with advanced endometriosis have higher risk of presenting lower ovarian reserve than women without endometriosis, which may be related to the worse live birth rates demonstrated by this meta-analysis. Corroborating this hypothesis, a study published by our group evaluated 787 women who underwent IVF/ICSI (241 with endometriosis and 546 without) and demonstrated that although the mean age was similar between women with and without the diagnosis of endometriosis ( $33.8 \pm 4$  versus  $33.7 \pm 4.4$  years, respectively), poor ovarian reserve, defined as an antral follicle count  $\leq 6$  before the beginning of ovarian stimulation, was more common in women with endometriosis (39.8% versus 22.7%).<sup>15</sup> The chance of achieving live birth was similar between women with the diagnosis of endometriosis and those without it (19.1% versus 22.5%), and also when considering only women with a poor ovarian reserve (9.4% versus 8.9%) and only those with a normal ovarian reserve (25.5 versus 26.5%). Thus, we concluded that women diagnosed with endometriosis are more likely to have a poor ovarian reserve; however, their chance of conceiving by IVF/ICSI is similar to the one observed in patients without endometriosis and with a comparable ovarian reserve.

In conclusion, although still a controversial theme, it seems even minor endometriosis has an adverse effect on the likelihood of natural conception. The treatment of infertility associated with endometriosis has to be individualized, taking into consideration some important aspects, such as the age of the patient, her ovarian reserve, the stage of the disease, the presence of pelvic pain, endometrioma and previous surgical intervention, the presence or absence of tubal abnormality, and the seminal quality of the partner. When IVF is indicated, recent data show that the chance of conceiving is similar to the one observed in patients without endometriosis and with a comparable ovarian reserve.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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