Endometriosis and risk of embryonic aneuploidy?

Endometriosis is one of the most challenging diseases for reproductive gynecologists. Many factors have been suggested to cause infertility in women suffering from endometriosis: pelvic adhesions, pelvic inflammation, increased oxidative stress, ovulatory dysfunction, disturbed folliculogenesis, and defective implantation.

Data on the impact of endometriosis on IVF results are controversial. A recent systematic review and meta-analysis by Hamdan et al. (1) concluded that women with more severe endometriosis (stages III and IV) had poorer reproductive outcomes. They also found a similar clinical pregnancy rate, live birth rate, and miscarriage rate in women with and without intact endometriomas.

However, the cancellation rate was 3 times higher in women with endometriomas. Moreover, fewer mature oocytes were retrieved, which could have repercussions by reducing the number of embryos potentially available for frozen embryo transfer.

In their evaluation of the Society for Assisted Reproductive Technology database, Senapati et al. (2) concluded that endometriosis is associated with lower pregnancy rates after IVF in the presence of other alterations to the reproductive tract.

Among the multiple pathologic pathways possibly explaining poorer IVF outcomes in endometriosis patients, alterations to the meiotic spindle, subsequently affecting the rate of aneuploidy, have been suggested. Indeed, alterations to the meiotic spindle apparatus have been described in women with endometriosis undergoing IVF, and in some studies, the peritoneal and follicular environments themselves were found to be hostile to the integrity and intrinsic functions of the oocyte, with consequences on embryo development (3). Some in vitro studies cited by Juneau et al. (3) have also reported that the follicular fluid of women with endometriosis causes higher rates of meiotic anomalies in bovine oocytes matured in this fluid. The real question is: Could it be that oocytes from women with endometriosis undergoing IVF are more susceptible to meiotic errors and chromosomal instability?

In this issue of *Fertility and Sterility*, Juneau et al. (3) have attempted to answer this question. They retrospectively examined rates of aneuploidy in blastocysts obtained from endometriosis patients undergoing IVF compared with the general IVF population by evaluating a large series of blastocysts (1,880 blastocysts from 350 endometriosis patients and 23,054 blastocysts from 3,798 control patients). Their results are interesting because the number of usable blastocysts formed was equivalent in both groups, despite the number of oocytes being smaller in endometriosis patients.

They clearly demonstrated that there was no difference in aneuploidy rates between the two groups after stratifying by age. Of course, as previously shown by others, the rate of aneuploidy increased significantly with patient age to >50% after the age of 39 years. However, it was important to show that the rate of aneuploidy was similar between patients with endometriosis and age-matched control patients in the IVF population.

As stressed by the authors, there are a number of potential limitations:

1) The study was unable to stratify aneuploidy outcomes according to the severity of the disease.
2) The control group may have inadvertently included patients with endometriosis, because the absence of endometriosis was not confirmed by laparoscopy.
3) The analysis considers usable blastocysts and so cannot evaluate aberrations in the spindle apparatus, resulting in developmental arrest before the blastocyst stage.

Despite these limitations, the study is strong enough to conclude that women with endometriosis undergoing IVF are not at any increased risk of aneuploidy. Other pathologic mechanisms must therefore be involved to explain the poorer reproductive outcomes observed in women with severe disease.

In the literature, one of the most commonly cited mechanisms is the smaller number of oocytes retrieved and reduced antimüllerian hormone levels in women with severe endometriosis or endometriomas, even in the absence of previous surgical intervention. There is no doubt that ovarian endometriotic disease per se has a detrimental effect on the ovarian reserve. Indeed, Kitajima et al. (4) clearly demonstrated the "burn-out" effect on the ovarian reserve induced by the "toxic" intraovarian environment and inflammation due to the presence of ovarian endometriomas, leading to increased fibrosis, loss of cortex-specific stroma, vascularization defects, and ultimately, impaired follicular maturation and greater follicular atresia. Moreover, the role of oxidative stress should not be overlooked (5), because excessive release of reactive oxygen species alters cellular function by dysregulating protein activity and gene expression, resulting in harmful effects (5).

Clearly, many other factors may be involved, but we can conclude from Juneau et al. (3) that poor outcomes obtained in women with endometriosis undergoing IVF are not linked to a higher risk of aneuploidy in this population.

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http://dx.doi.org/10.1016/j.fertnstert.2017.06.019

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