Endometrial receptivity in eutopic endometrium in patients with endometriosis: it is not affected, and let me show you why

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Many women with endometriosis experience compromised fertility. This disease clearly exerts quantitative damage on the ovaries, and perhaps, also qualitative damage. However, it remains controversial whether endometrial receptivity is compromised. Here we review the evidence from basic transcriptomic signature data to clinical data from an oocyte donation model and find support for the concept that endometrial receptivity is not impaired in women with endometriosis when healthy embryos reach the endometrial cavity. (Fertil Steril® 2017;108:28–31. ©2017 by American Society for Reproductive Medicine.)

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Endometriosis is an estrogen-dependent disorder that typically affects women of reproductive age, impacting their physical, mental, and social well-being. An estimated 10% of women suffer from endometriosis (1), with symptoms ranging from practically nonexistent to severe chronic pelvic pain, dysmenorrhea, and cyclic urinary or bowel complaints. Endometriosis is historically related to infertility, although the association remains unclear. Therapeutic approaches are far from curative, and focus on clinical symptom management rather than curing the disease. The increasingly widespread use of in vitro fertilization (IVF), especially oocyte donation techniques, has provided insights into possible mechanisms of endometriosis-related infertility.

CLINICAL EVIDENCE THAT ENDOMETRIOSIS DOES NOT AFFECT ENDOMETRIAL RECEPTIVITY

The influence of endometriosis in the clinical outcome of IVF remains controversial. Simon et al. (2) published a comparison of IVF outcomes from 96 cycles in 78 patients with tubal infertility, and from 96 cycles in 96 women with endometriosis, showing that endometriosis patients seemed to have poorer IVF outcomes in terms of reduced pregnancy rate per cycle, pregnancy rate per transfer, and implantation rate. However, when the data were analyzed separately for patients undergoing oocyte donation for different causes, including endometriosis, IVF outcome (based on the same measures as in the previous study) did not differ among the groups. Interestingly, implantation rates were significantly lower in patients who received oocytes from women with endometriosis compared to the remaining groups (Table 1, data extracted from Simon et al., 1994) (2). This finding suggests that the apparent infertility in endometriosis patients may be caused by certain oocyte alterations that result in embryos that are less likely to implant.

Jones (3) has also reported favorable results of IVF in patients with endometriosis. During a 3-year period, follicular stimulation was initiated for 600 cycles in 319 patients, with endometriosis being the primary diagnosis in 20 cycles. The results show good IVF outcomes among patients with endometriosis who did not become pregnant after surgical and/or endocrine therapy. Furthermore, the findings highlight the fact that endometriosis does not influence the sperm/egg interface or the implantation mechanism.

A study published in 1988 compared IVF outcomes in 136 patients (4). The patients were divided into three groups: patients with a previous history

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TABLE 1

Reproductive outcome according to donors' cause of infertility.

Donors' cause of infertility	Cycles, n	Pregnancy rate/ transfer (%)	Implantation rate (%)
Fertile	34	44	16.2
Polycystic ovaries	58	60.3	23.6
Idiopathic infertility	20	45	11.2
Tubal infertility	27	55.5	18.7
Male infertility	28	60.7	19.1
Endometriosis	11	27.3	7.0[a]

Note: Adapted from Simon et al. (2).
[a] $P<.05$.

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of endometriosis but a normal pelvis at the time of oocyte retrieval, those with stage I–II endometriosis, and those with stage III–IV endometriosis. The results demonstrated that the global fertilization rates, per cycle/per transfer pregnancy rates, and miscarriage rates in the patients with endometriosis were similar to those of tubal factor patients. This suggested that patients with moderate or severe endometriosis have a compromised reproductive potential, likely due to a reduced oocyte recovery rate and poor embryo quality.

To exclude all factors that can affect embryo implantation except endometrial receptivity, a study was performed in which healthy oocyte donors were shared between 25 women with stage III–IV endometriosis and 33 healthy control women (5). Each healthy donor gave half of their oocytes to a recipient with severe endometriosis and the other half to a control recipient without endometriosis. All women underwent a hormone replacement therapy (HRT) cycle at luteal phase (checked with endometrial biopsy), with only one cycle performed per woman. The groups did not significantly differ in age intervals, mean numbers of donated oocytes, or numbers of embryos transferred. As shown in Table 2 (data extracted from Díaz et al., 2000) (5), the stage III–IV endometriosis and control groups did not significantly differ in pregnancy, implantation, or miscarriage rates. These results suggest that severe endometriosis does not affect implantation of donated oocytes in HRT cycles, although the power of the study was limited (0.57), reducing the ability to draw final conclusions.

Similarly, a slightly earlier study (6) retrospectively analyzed 239 oocyte recipients who were divided into two groups: patients with and without endometriosis. The group with endometriosis was further subdivided into mild and severe stages of the disease. Patients with and without endometriosis did not differ with regards to pregnancy rates (28% versus 29%) or implantation rate (12% and 13%), nor did these rates differ according to endometriosis stage. These results support the same conclusion drawn in Sung et al. (6) study—namely, that the adverse effect of endometriosis on reproductive outcomes is not related to implantation.

TABLE 2

Impact of endometriosis in the egg recipient.

Variable	Control group	Stage III/IV endometriosis
Implantation rate (%)	16	14.8
Pregnancy rate (%)	45.5	40
Miscarriage rate (%)	26	30

Note: All values are percentages. Differences are not significant. Adapted from Díaz et al. (5).

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A 2007 study by Budak et al. (7) compared outcome parameters and cumulative pregnancy rates in oocyte donation cycles over a period of 10 years. They concluded that this IVF technique provides similar success rates among women with a variety of reproductive disorders, including endometriosis. Their findings support the idea that oocyte and embryo quality are the main determinants of IVF success, and cast doubt on whether implantation is affected by the uterine environment of women with endometriosis.

More recent population-based retrospective cohort studies have been performed by analyzing data from the Society for Assisted Reproductive Technology. The results confirm that an endometriosis diagnosis itself is associated with lower numbers of oocytes, but with a live birth rate similar to with other diagnosis. The lower number of oocytes retrieved could potentially impact the cumulative live birth rate among patients with endometriosis, but not the live birth rate per cycle. Notably, success rates were compromised when a diagnosis of endometriosis was accompanied by other infertility factors (8).

BASIC EVIDENCE THAT ENDOMETRIOSIS DOES NOT AFFECT ENDOMETRIAL RECEPTIVITY

Many studies suggest that patients with endometriosis have lower implantation rates in either natural or IVF cycles (9–11). Such impaired embryo implantation has been associated with altered gene expression in the eutopic endometrium of patients with endometriosis compared to healthy women (12–17). These findings have led to the proposal of several candidate endometrial markers, including integrins, glycodelin A, osteopontin, lysophosphatidic acid receptor, hepatocyte growth factor, 17-β-hydroxysteroid dehydrogenase, leukemia inhibitory factor, matrix metalloproteinases, endometrial bleeding factor, and Indian hedgehog (13–17). Moreover, findings indicate altered steroid hormone pathways in women with endometriosis compared to healthy women, including upregulation of estrogen receptors and progesterone resistance status due to the absence of the β isoform of its receptor (18, 19).

Although the results of several studies support this concept, the single-molecule approach has not reached clinical applicability in the field of endometrial receptivity (20). The implantation process is complex and the receptive phenotype implies the coordination of many biological processes; therefore, it seems prudent to approach endometrial receptivity from a holistic point of view. Transcriptomic analyses could help us to better understand the behavior of the endometrium and the consequences of any pathology affecting it. Along this line, several researchers have used microarray

technology to detect differential gene expression in the eutopic endometrium of women with endometriosis compared to controls (21–24). However, none of these arrays have shown clinical applicability for detecting fertility.

A molecular tool termed endometrial receptivity analysis (ERA) can identify a personalized window of implantation (pWOI) for every woman. This tool evaluates the expressions of 238 genes related to the endometrial receptivity process, enabling determination of whether a specific patient requires a longer or shorter duration of progesterone administration to reach a receptive status. This represents the first application of the concept of "personalization" to the endometrial factor, allowing synchronization between the blastocyst and a receptive endometrium—a key factor in promoting implantation. The ERA is a clinically validated assay that has helped thousands of women with recurrent implantation failure achieve pregnancy. Moreover, its accuracy and consistency is superior to endometrial histology, and its results are completely reproducible for 29–40 months after the first ERA test (25).

To establish whether endometrial receptivity might be affected by endometriosis, ERA was used to determine whether different endometriosis stages were associated with higher rates of non-receptive results compared to women without endometriosis (26). This study included 17 patients with different stages of endometriosis (stages I–IV) based on the revised staging system of the American Society for Reproductive Medicine (27), and 5 healthy women. Endometrial biopsies were taken from each woman at day 18–20 of a natural cycle according to Noyes criteria (28), and all samples were subjected to ERA, obtaining a diagnosis as receptive (R) or non-receptive (NR). For NR cases, the endometrial status was further assessed to be pre-receptive (showing a delayed WOI) or post-receptive (advanced WOI). Interestingly, the results showed clustering of samples that was not based on endometriosis stage, but rather on the day of the cycle on which the samples were taken (day 18 versus days 19–20). Specifically, the NR samples grouped together and were all taken on day 18, while all of the R samples were taken on days 19–20. This correlation was expected, since an earlier day of the menstrual cycle would logically be associated with a higher probability of needing more time with progesterone administration (pre-receptive profile) to reach a receptive status. In this study, a total of nine clinical variables were analyzed, but none provided a better explanation for the clustering of the samples than the menstrual cycle day.

Proceeding to deeper gene expression analysis, comparisons between the four endometriosis stages and controls revealed that none of the 238 genes present in the ERA array were significantly overexpressed or under expressed between any of these groups. Comparisons between samples taken on different days of the menstrual cycle (adjusted P value of $<.05$) revealed that only 13 genes were differentially regulated: *ARG2*, *CLDN4*, *HRASLS3*, *MAOA*, *EFNA1*, *RPRM*, *DEFB1*, *S100P*, *KRT7*, *BCL6*, *RARRES3*, *GDF15*, and *GABARAPL1*. Three of these genes (*ARG2*, *CLDN4*, and *S100P*) were previously investigated in terms of endometriosis and receptivity (29–32), but the reports do not identify the specific mechanisms in which they are involved. Analysis using a gene ontology approach suggests that if these genes have a clinical effect, it may be minimal. Notably, endometrial receptivity is a process influenced by multiple factors, and this analysis approach is based exclusively on the expression profiles of 238 genes. It is also important to consider the known inter-individual variations (33) among endometriosis-affected patients as well as among healthy patients.

In conclusion, data from clinical IVF and egg donation programs, and basic data regarding the transcriptomic signature of the endometrium, seem to indicate that endometrial receptivity is similar between women with and without endometriosis, and across the different stages of endometriosis. Clinical data provide valuable information that helps us understand this process, but may be biased for patient selection. New molecular tools confirm the information previously obtained from clinical models. For example, results of ERA confirm that the endometrial receptivity gene signature during the window of implantation is similar between infertile woman with and without endometriosis, and is independent of endometriosis stage. Moreover, reports in patients undergoing IVF treatment demonstrate that the effect of endometriosis is related to embryo and oocyte quality more than to the endometrial factor itself.

It would be interesting to perform a deeper study, including more factors involved in receptivity, such as epigenetic aberrations and pathologic proteomic profiles. Such investigations could improve our knowledge of the enigmatic disease that is endometriosis. Although the single-molecular approach has not reached clinical applicability in the field, further data must be obtained using ERA and other newly developed assays before a final conclusion can be reached on this subject.

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