Is the endometrium or oocyte/embryo affected in endometriosis?

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One of the most puzzling problems of endometriosis is determining which mechanisms link this spectrum of conditions to infertility. There is conflicting evidence about the effect of endometriosis on the endometrium and on oocyte/embryo quality. Clinical studies reveal that implantation rates seem to be lower in women with endometriosis, while spontaneous abortion rates show variable results which are difficult to interpret due to the design of the studies. Biochemical markers (integrins and other cell adhesion molecules), morphological markers (pinopodes), apoptosis and ultrasound studies confirm that not only does the endometrium from women with endometriosis behave differently from the endometrium of women without endometriosis, but ectopic endometrium also behaves differently from eutopic endometrium. Data from oocyte donation programmes suggest that oocyte quality may be hampered in women with endometriosis. Recent reports have focused on the molecular mechanisms that may be altered, such as ovarian steroid production, or inadequate luteal function. In this review, we analyse the most recent literature dealing with the different mechanisms which affect the endometrium and oocyte/embryo quality and which thereby might cause infertility.

Key words: biochemical markers/endometriosis/endometrium/infertility/oocyte quality

Introduction

More than 70 years have gone by since the most accepted theory on the pathogenesis of endometriosis was first described (Sampson, 1927), and we are still trying to understand how this spectrum of conditions is linked to infertility. It is one of the most frequently investigated disorders of gynaecology, with over 7000 studies published on this subject. Until very recently, most reports on endometriosis suffered from major design flaws, often being retrospective or merely descriptive, with a lack of strong support for the mechanisms proposed, and with inappropriate selection of a control group. In addition, the classification of endometriosis (American Fertility Society, 1985) is based on an arbitrary scoring system designed to promote uniformity of reporting. When this revised classification was evaluated by recent studies (Guzick et al., 1997), no clinical usefulness was found with respect to the prognosis in fertility rates after treatment.

All of the previous confounding variables make it almost impossible to draw any valid conclusion from the published evidence. It is only recently, with the application of scientific rigor to basic and clinical investigations (tissue cultures, molecular biology, advanced genetic studies, randomized clinical trials with proper design and statistical analysis), that we have been able to start to understand some of the mechanisms involved in the development and maintenance of endometriosis. One of the most perplexing issues is the link between endometriosis and infertility, and researchers still have not established a clear-cut cause–effect relationship. Even though many theories have been proposed, the association between endometriosis and infertility, especially in the early stages of the disease, remains speculative. This review covers
Table I. Pregnancy rate in women with endometriosis compared to controls (women with tubal factor infertility). Numbers in parentheses are numbers of cycles studied

<table>
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<th>No impact</th>
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<th>Tubal factor</th>
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<td>Dmowski et al. (1995)</td>
<td>29 (119)</td>
<td>25 (118)</td>
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<td>Tanbo et al. (1995)</td>
<td>23.8 (265)</td>
<td>23.2 (331)</td>
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<tr>
<td>Geber et al. (1995)</td>
<td>40 (249)</td>
<td>45 (1136)</td>
</tr>
<tr>
<td>Inoue et al. (1992)</td>
<td>30.9 (309)</td>
<td>27 (372)</td>
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<tr>
<td>Poor outcome</td>
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<tr>
<td>Arici et al. (1996)</td>
<td>14.8 (89)</td>
<td>25.7 (147)</td>
</tr>
<tr>
<td>Simón et al. (1994)</td>
<td>15.1 (79)</td>
<td>37.3 (91)*</td>
</tr>
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</table>

*Statistically significant difference.

Table II. Implantation rate in women with endometriosis compared to controls (women with tubal factor infertility). Numbers in parentheses are numbers of cycles studied

<table>
<thead>
<tr>
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<th>Tubal factor</th>
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<td>Geber et al. (1995)</td>
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<td>23.4 (1136)</td>
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<tr>
<td>Mills et al. (1992)</td>
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<td>14 (122)</td>
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<td>Poor outcome</td>
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<tr>
<td>Arici et al. (1996)</td>
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<td>8.1 (147)*</td>
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<td>Simón et al. (1995)</td>
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<td>Yovich et al. (1988)</td>
<td>0.9 (57)</td>
<td>8.2 (40)*</td>
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*Statistically significant difference.

the evidence on the effect of endometriosis on endometrium and oocyte/embryo quality.

Implantation and abortion in endometriosis

Implantation

Human embryonic implantation is dependent upon both a good quality embryo and a receptive endometrium. The development of assisted reproductive techniques (ART) during the past decade has provided a very useful tool for studying these two components separately, thus allowing researchers/physicians to discern any effect of endometriosis on implantation. Oocyte donation programmes have allowed us to compare the reproductive outcomes of women with endometriosis who received good quality oocytes from disease-free egg donors with women who received oocytes from women with endometriosis.

Most reported in-vitro fertilization (IVF) outcome results have been controversial. Some authors (Jones et al., 1984; Oehninger et al., 1988; Inoue et al., 1992; Alsalili et al., 1995; Dmowski et al., 1995; Geber et al., 1995; Tanbo et al., 1995) did not find that the presence of endometriosis affected the implantation and pregnancy rates. However, poor results have been reported by other groups (Madahevan et al., 1983; O'Shea et al., 1985; Yovich et al., 1985; Matson and Yovitch, 1986; Wardle et al., 1986; Yovitch and Matson, 1990; Simón et al., 1994; Arici et al., 1996). Tables I and II summarize the discordant data. Retrospective analyses of data, improper control group selection, as well as poor design or small sample size may be responsible for these discrepancies. Among those groups that did find that endometriosis affected implantation and pregnancy rates, a hazardous endometrial environment and/or poor quality embryos have been proposed as explanatory mechanisms.

A hostile endometrial environment has been postulated as a cause of infertility in women with endometriosis (Arici et al., 1996). The tubal and uterine cavity secretions contain part of the serum filtrates. It is well known that serum from infertile women with endometriosis is toxic for murine embryo development (Damewood et al., 1990). This toxicity is correlated with the stage of the endometriosis (Miller et al., 1995), and it decreases after medical (Simón et al., 1992) or surgical treatment (Miller et al., 1995). However, it has been recently reported that this embryotoxicity is not related to the endometriosis itself, but to the infertility associated with the disease (Abu-Musa et al., 1996).

In an effort to elucidate whether the endometrium or the oocyte, or both, are affected in endometriosis, data from oocyte donation programmes were used to separate the endometrial from the ovarian components. An analysis of women with endometriosis who received fresh donor oocytes due to low response in a previous IVF cycle demonstrated a pregnancy rate similar to those of patients in other diagnostic groups, such as other...
low responders, premature ovarian failure, menopause patients, or those who had experienced repeated IVF implantation failure (Remohi et al., 1997b). This evidence alone suggests that endometriosis may affect the oocyte/embryo and not the endometrium, since the implantation rate is similar to that of women without endometriosis when the oocytes are replaced by healthy ones. In a retrospective analysis (Simón et al., 1994), lower implantation and pregnancy rates were observed in women with endometriosis compared to patients with premature ovarian failure or in patients who were low responders to conventional IVF. Interestingly, a significantly lower implantation rate was found in disease-free women who received oocytes from women with endometriosis (Simón et al., 1994). In addition, Sung and co-workers (Sung et al., 1997), in a retrospective analysis of oocyte recipients with and without endometriosis, could not find any detrimental effect of this condition on pregnancy rates or implantation rates, suggesting that an effect on the oocyte or embryo quality is more likely.

If the oocyte quality is affected, obviously the embryo quality will be diminished. It was shown in a retrospective study in 36 patients (Pellicer et al., 1995) that an increased percentage of embryos derived from women with endometriosis had arrested development, as well as a significant decrease in the number of blastomeres after 72 h in culture, compared with those obtained from patients with tubal infertility. Similarly, an increased incidence of aberrant phenotypes in embryos from women with endometriosis in their first 2 days of embryogenesis has been described (Brizek et al., 1995), which may partially account for the suspected altered reproductive outcome in these women.

However, a role for altered endometrium in these women cannot be ruled out. A beneficial effect on implantation in women with severe endometriosis was reported after down-regulation for 2–7 months prior to ovarian stimulation (Marcus and Edwards, 1994). The long-term amenorrhoea was claimed to be beneficial for implantation. There are no published prospective randomized studies in which women with endometriosis who donated oocytes to recipients (diseased and disease-free) and an appropriate control were compared with donors who were not affected by endometriosis. Such a study would provide clear evidence of oocyte quality in women with endometriosis and their ability to implant.

**Abortion**

As a consequence of either poor oocyte quality and/or diminished endometrial receptivity, we may speculate that a higher spontaneous abortion (SA) rate can be found in women with endometriosis than in healthy women. It is well known that different conditions, such as uterine anomalies, uterine fibroids, endometrial cavity synechiae, autoimmune disorders and aneuploidy may cause SA (Kutteh, 1998). Thus, in order to find a specific association between endometriosis and SA, all the factors that account for an increased risk of SA must be corrected in the analysis.

Taking into consideration the available clinical data (Naples et al., 1981; Rock et al., 1981; Olive et al., 1982; Wheeler et al., 1983a; Groll, 1984; Metzger et al., 1986; FitzSimmons et al., 1987), a tendency toward a causal link is suggested. The high rate of SA in these women, and the risk reduction described after treatment for endometriosis lead us to give credence to a causal relationship. However, we should consider that all of these studies were retrospective, which may have biased the results, so their conclusions should be cautiously interpreted. More recent reports did not find any evidence of an increased incidence of miscarriage in women with endometriosis (Geber et al., 1995; Matorras et al., 1998). Also, with the recent evidence of the Canadian study on endometriosis (Marcoux et al., 1997), we know that surgical removal of small endometriotic lesions does make a difference in the follow-up of these patients. Most of the retrospective studies linking SA with endometriosis did not mention if, in the untreated group, they intervened surgically at the time of diagnosis, which may have confounded the follow up results.

An inverse relationship between the stage of endometriosis and the risk of SA has been reported, both in natural pregnancies (Wheeler et al., 1983b) and in IVF patients (Olivennes et al., 1995), with the highest rate of SA in mild endometriosis. This
may reflect an altered function in the endometrium and/or oocyte/embryo rather than an anatomical mechanical distortion that accompanies the advanced stages of the disease (Gleicher and Pratt, 1993).

It seems that there may be a causal link between SA and endometriosis, even though we are lacking prospective randomized trials with properly selected controls to provide a more valid answer.

**Is the endometrium affected in endometriosis?**

There is enough evidence today to admit that eutopic endometrium (EEE) and ectopic endometrium (EEC) from women with endometriosis behave differently to eutopic endometrium from women without endometriosis (EN). This is primarily based on three basic points: (i) EEC does not follow the cyclic changes of the endometrium, probably due to different amounts of steroid receptors in EEE and EEC (Jänne et al., 1981; Vasquez et al., 1984); (ii) the capacity of EEE and EEC to produce oestrogens locally, as they express aromatase enzyme as opposed to EN, may enable EEC to implant in the peritoneal surface and grow, acting in an autocrine or paracrine fashion (Noble et al., 1996); (iii) these three types of cells (EEE, EEC and EN) respond in a different manner to cytokine production and regulation, indicating intrinsic differences (Tseng et al., 1996; Hornung et al., 1997; Iwabe et al., 1998).

To understand why the endometrium may be affected in endometriosis, endometrial receptivity markers (biochemical and morphological), apoptosis events, contractility and clinical data on ultrasound studies are reviewed below.

**Biochemical markers**

Since the initial studies of integrins in the endometrium (Lessey et al., 1992; Tabibzadeh, 1992), it has been apparent that determining the presence or absence of specific integrins may provide useful information regarding uterine receptivity. Although there are some constitutive integrins, the more relevant ones are those integrins that show cyclic changes through the menstrual cycle. Lessey et al. showed in a large number of endometria that the co-expression of α1, α4 and β3 integrin chains framed the implantation window (Lessey et al., 1994a). Since abnormal expression of β3 integrin was found in women with luteal phase defects (Lessey et al., 1992) and in women with unexplained infertility (Lessey et al., 1995), these investigators proposed a role for α4β3 integrin as a marker of endometrial receptivity. This molecule recognizes the RGD sequence (Arg-Gly-Asp) within vitronectin and osteopontin, which is also present in the endometrium (Somigliana et al., 1996). Hence, osteopontin could act as a bridge between the human embryo and the endometrium, since both express α4β3 (Campbell et al., 1995).

Interestingly, when endometrial biopsies from women with endometriosis were stained for α4β3 integrin, a defective expression was found (Lessey et al., 1994b). First, in a retrospective analysis of 268 endometrial biopsies considered ‘in-phase’ by traditional histological criteria (Noyes et al., 1950), the absence of expression of α4β3 integrin was closely correlated with the presence of endometriosis. Likewise, in a prospective, double-blind assessment of 89 endometrial samples taken before laparoscopy, most women who showed defective integrin expression had mild or minimal endometriosis. Thus, α4β3 integrin may act as an effective marker for minimal or mild endometriosis with a high specificity and positive predictive value. At the same time, this integrin may identify some women with decreased cycle fecundity due to defects in uterine receptivity. Other authors have not confirmed these results (Bridges et al., 1994; Hii and Rogers, 1998). These discrepancies among the results may be due to limited numbers of samples, different antibodies used, or lack of a proper control group. The validity of integrins as markers of uterine receptivity was demonstrated recently in a preliminary study in which improvement in fertility and a return of α4β3 was documented after treating women with endometriosis with gonadotrophin-releasing hormone analogues and laser ablation of implants (Lessey and Young, 1997). Larger, prospective, randomized, controlled trials will be necessary to provide supporting evidence.

On the other hand, when researchers have attempted to identify differences in integrin expression between EEE and EEC, they have obtained
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disappointing results. A loss of cyclicity in the expression of epithelial $\alpha_v\beta_3$ in EEC has been reported (Rai et al., 1996), and this loss of hormonally-mediated events was presumably due to the loss of normal regulatory mechanisms found in EEC.

Why is the expression of some integrins altered in women with endometriosis? We still do not know if this alteration in integrin expression occurs prior to the development of endometriosis or as a result of the endometriosis. It is possible that such changes are the result of differences in the extracellular matrix in ectopic sites, or of the loss of neighbouring cells with their paracrine effects, as previously suggested (Lessey and Young, 1997). The regulation of integrin expression is currently being studied, as cytokines and growth factors, as well as sex steroids, may modulate their expression. The expression of $\alpha_v\beta_3$ integrin is normally linked to the down-regulation of the epithelial progesterone receptor (Lessey et al., 1996), although in patients with endometriosis this may not be true. Other factors present at high concentrations in endometriosis, e.g. cytokines and growth factors, may interfere (Oral and Arici, 1996). Interestingly, a decrease in intracellular structural proteins (cytokeratin and vimentin) has been noted in women with endometriosis (Nisolle et al., 1995). This decrease may have implications for gene regulation and signal transduction, both of which are linked to the internal cytoskeleton.

Intercellular adhesion molecule-1 (ICAM-1), a ligand for the leukocyte integrin family, has recently been studied in women with endometriosis. A significantly higher amount of soluble ICAM-1 was released from the endometrial stromal cell cultures of women with endometriosis compared to the cell cultures of women without endometriosis (Somigliana et al., 1996). Whether increased ICAM-1 release is characteristic of these cells of advanced stages of endometriosis or is merely the result of the inflammatory process that accompanies the disease is not clear. Nevertheless, it may influence the ability of these cells to implant outside the uterus.

Other adhesive glycoproteins, such as cadherins (van der Linden et al., 1995) and carbohydrate-rich membrane-bound glycoproteins (Linderberg et al., 1988; Kliman and Keffe, 1995), CD44 (hyaluronate receptor) (Yaegashi et al., 1995) and trophinin (Fukuda et al., 1995) have been identified in the endometrium, but their role in implantation and their possible altered expression in endometriosis, if any, await further investigation. A role for insulin-like growth factor binding protein-1 (IGFBP-1) was suggested in implantation and endometriosis because it binds to the $\alpha_v\beta_3$ integrin, a stromal integrin (Jones et al., 1993), and it is elevated in the peritoneal fluid of women with endometriosis (Taskin et al., 1996). This binding protein could act through an autocrine mechanism that modifies the behaviour of endometrial implants in vivo.

Morphological markers

The most important morphological markers of uterine receptivity are pinopodes, sacular formations at the apical part of the epithelial cells. The endometrial epithelial cells lose their microvilli and develop these structures, which appear on day 20 of the menstrual cycle and last for 24-48 h, after which they regress (Psychoyos and Nikas, 1994). Their role seems to be related to the internalization of the liquid inside the uterine cavity. The endometrial walls are forced to collapse and the apposition of the embryo is favoured.

In a recent prospective study, pinopode formation was evaluated in women with and without endometriosis who underwent oocyte donation due to low response to conventional IVF (Garcia-Velasco et al., 1998). No difference was found between these two groups, a result that suggests that the endometrium of women with endometriosis develops an adequate response to hormone replacement therapy in terms of uterine receptivity as assessed by the formation of pinopodes.

Apoptosis

Apoptosis is a physiological process used by the body to delete unwanted cells without inducing an immune response or inflammatory reaction (Lincz, 1998). The cyclical growth and remodelling that occur in the endometrium throughout the fertile years are closely related to programmed cell death. If pregnancy does not occur, a programmed regression of the functional layer of the endometrial cells

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ends a menstrual cycle (Kokawa et al., 1996). We may postulate that ectopic endometrial cells from women with endometriosis are immunoprivileged, and the immune system will not detect them; thus these ectopic cells will be allowed to implant and grow. Two markers of apoptosis have been recently studied in human EEE and EEC: the bcl-2 (B cell lymphoma/leukaemia-2) gene family and the Fas/FasL system.

* bcl-2 is a proto-oncogene encoding an intracellular protein that may protect specific cell types from apoptosis (Vaux et al., 1988). It is expressed in the human endometrium, and its levels change during the menstrual cycle (Otsuki et al., 1994), an observation that suggests hormonal regulation. Immunohistochemistry and DNA nick-end labelling (TUNEL) studies showed a strong bcl-2 expression during the proliferative phase in the endometrial glandular cells (Harada et al., 1996; Tao et al., 1997; Watanabe et al., 1997), while there was a dramatic increase in the concentrations of bax protein, the pro-apoptosis protein, in the secretory phase (Tao et al., 1997). Other groups found no change in bax concentrations during the entire menstrual cycle (McLaren et al., 1997).

Expression of bcl-2 in endometrial stromal cells has also been recently described. There was a rise in stromal bcl-2 expression from the proliferative to the premenstrual phase, a result that is mainly attributed to an increase in stromal CD56-positive lymphocytes (Koh et al., 1995) or an up-regulation by endometrial granulated lymphocytes (Jones et al., 1998).

No cyclic changes were observed in EEC cells (Harada et al., 1996; Watanabe et al., 1997). However, pitfalls in applying the TUNEL technique to study apoptosis in the human endometrium have been described (Yasuda et al., 1995). It is noteworthy that no differences were found between the endometrial bcl-2/bax expression of women with endometriosis and healthy women (McLaren et al., 1997).

Fas, a cell surface antigen, belongs to the tumour necrosis factor receptor superfamily. Its ligand (FasL), when cross-linked to Fas, induces apoptosis in lymphocytes and epithelial and malignant cells (Trauth et al., 1989; Yonehara et al., 1989). When EEE and EEC cells were stained for Fas, it was only found in the glandular cells, and no cyclic changes in expression were observed (Watanabe et al., 1997).

Immunohistochemical staining of EEE and EEC cells for FasL shows a strong expression in the glandular cells, and no staining was observed in the stromal cells. No cyclic changes during the menstrual cycle were found. These findings were confirmed by reverse transcriptase–polymerase chain reaction (unpublished observations).

Taken together, these findings allow us to speculate that apoptosis in the endometrium may be related to the loss of the protective effect of bcl-2 protein, as well as the acquisition of the pro-apoptosis protein bax. The lack of cyclic changes of bcl-2, Fas and FasL expression brings out two points: first, in-vivo regulation of the expression of these genes in endometrial implants is not hormonally driven; and second, the continuous expression of bcl-2 and FasL in the implants protects them from apoptosis and, possibly, from immune system recognition and deletion.

**Contractility**

Among the differences between uteri from women with and without endometriosis is the subendometrial activity during the menstrual cycle. Since this activity can be detected sonographically (Birnholz, 1984), intracavitary uterine transducers are no longer needed. It is well established that during the different phases of the cycle, contractions are present in a retrograde fashion, except during menstruation, when they are antegrade (de Vries et al., 1990). Recently, several reports have been published using transvaginal ultrasound (Salamanca and Beltrán, 1995; Leyendecker et al., 1996). In these studies, the subendometrial activity of women with and without endometriosis was compared. Dysestaltic movements appeared in women with endometriosis during the late follicular phase and these may compromise sperm transport and thereby contribute to the subfertility found in these women (Leyendecker et al., 1996). Uterine hyperperistalsis was also described in these women. When menstruation approached, the fundus-to-cervix myometrial activity in the control group showed a retrograde pattern in women with endometriosis which may increase...
both the amount of endometrial debris transported into the peritoneal cavity and the chances of its heterotopic implantation (Salamanca and Beltrán, 1995). Recently, in a larger study of 88 patients, a significantly higher uterine contraction frequency was found in women with endometriosis than in women without endometriosis. Women with endometriosis also displayed an increased presence of viable ectopic glands in the pelvis (Bulled et al., 1998).

Although the altered subendometrial activity, dyskinesia, may contribute to the development of endometriosis as well as to the reduced fertility described in women with endometriosis, larger, randomized studies need to be performed before we can draw any solid conclusion.

**Ultrasound markers**

Ultrasonographic studies of the endometrium prior to embryo transfer have been used to predict pregnancy outcome, with variable results. The measurement of endometrial thickness is an easy technique to perform, but this measurement cannot be used to predict whether an embryo transfer will be successful (Remohi et al., 1997a). Only one study has addressed the effect of endometriosis on the thickness and echo pattern of the endometrium on the day of human chorionic gonadotrophin administration for IVF and embryo transfer (Check et al., 1995). Regardless of the stage of the cycle, no effect of endometriosis on endometrial thickness or echo pattern could be found. This result may indicate that endometrial echo pattern and/or thickness is a parameter that is not sensitive enough to detect any differences that may exist in endometrium quality among women with endometriosis.

Although much progress has been made, a true predictive test of endometrial receptivity does not exist, and comparison between women with endometriosis and disease-free women is not yet possible.

**Is the oocyte/embryo affected in endometriosis?**

Ovulatory dysfunction is one of the mechanisms blamed for the reduced fertility associated with endometriosis. Patients with minimal endometriosis were described as having an increased number of follicles and follicles of smaller size at the time of the luteinizing hormone (LH) surge. In addition, these patients had lower oestradiol concentrations both at the preovulatory stage and at the LH surge (Tummon et al., 1988). This observation suggested that ovulatory dysfunction may decrease fertility in women with endometriosis. The same group reported in a previous retrospective, non-randomized study that not only did ovulatory dysfunction affect fertility in these patients but also that medical treatment with danazol could change the outcome of ovulation induction (Dmowski et al., 1986). These findings were confirmed in some later studies (Cahill et al., 1995), which suggests an altered regulation of the pituitary–ovarian axis.

Recently, basic research has focused on the molecular mechanisms that may be altered in the ovulatory process of women with endometriosis. Disturbed ovulatory function may produce perturbed ovarian steroid secretion or inadequate luteal function. A defect in granulosa cell steroidogenesis associated with endometriosis was noted by one group of authors (Harlow et al., 1996). They reported lower aromatase activity and progesterone production in granulosa–lutein cells that were obtained from women with endometriosis. This reduced steroidogenesis may produce subtle impairment of corpus luteum formation and function.

Apoptosis research has attempted to establish differences between the ovaries of women with and without endometriosis. This form of controlled cell death is found in the ovary during natural cycles, as well as during gonadotrophin-stimulated cycles (Palumbo and Yeh, 1994). Apoptotic bodies are cytoplasmic fragments containing condensed chromatin. A positive correlation was found between the lower incidence of apoptotic bodies in pooled follicular aspirates and reproductive outcome (Nakahara et al., 1997). The incidence of apoptotic bodies in granulosa cells from women with endometriosis has recently been reported (Nakahara et al., 1998). As the stage of the endometriosis advanced, the incidence of apoptotic bodies increased, suggesting an altered oocyte quality in these patients. However, two other para-
meters which are known to influence pregnancy outcome, the number of oocytes retrieved and the number of mature oocytes, were significantly higher in the control group, and these two factors may have contributed to the differences found. Nevertheless, these observations are a promising finding with major future clinical applications in the reproductive medicine field.

The bcl-2 gene family and the Fas/Fas L gene system play a role in folliculogenesis and follicular atresia (Gosden and Spears, 1997). Recently, it has been reported that apoptosis occurs throughout the menstrual cycle in ovarian endometriotic tissue, with suppression of bcl-2 expression (Harada et al., 1996). It is possible that monthly changes in steroid hormone concentrations are not involved in apoptosis regulation in this tissue.

**LUF syndrome**

Luteinized unruptured follicle (LUF) syndrome is the failure of ovulation despite secondary ovulatory changes such as a LH peak, a rise in progesterone, and the secretory transformation of the endometrium (Coetsier and Dhont, 1996). Since its first description in humans in 1975 (Jewelewicz, 1975), it is still not clear whether we should consider LUF as a biological variable rather than as a syndrome. Several authors noted an increased association between LUF and endometriosis (Donnez and Thomas, 1982; Dhont et al., 1984; Mio et al., 1992) and have connected LUF with infertility in these patients. However, others reported a low frequency (Thomas et al., 1986), with similar rates of LUF in infertile patients with endometriosis and in normal fertile women (Dmowski et al., 1980; Vanrell et al., 1982).

Earlier reports were mainly based on the absence of ovulation stigma diagnosed by laparoscopy, on abdominal ultrasound follicle monitoring, or on biochemical parameters. Since the luteinized unruptured follicle produces progesterone and behaves steroidogenically as a corpus luteum (Kerin et al., 1983; Plas-Roser et al., 1984), it may be misleading to diagnose LUF based on a single serum determination of progesterone. Since the introduction of transvaginal ultrasound, especially with Doppler monitoring (Kupesic and Kurjak, 1997), more accurate diagnosis of LUF is possible.

Mahmood and Templeton (1991) used transvaginal ultrasound to monitor women with mild endometriosis and found that LUF occurred in only one out of 27 cycles (4%). This result supports the hypothesis (Kerin et al., 1983) that LUF is a sporadic and infrequent event that even occurs in normal fertile women. They studied 183 cycles in 66 regularly cycling women and found LUF in 4.9% of the cycles. More interestingly, they found only one recurrence in 35 subsequent cycles.

Many subfertile women with endometriosis undergo controlled ovarian hyperstimulation. In this set up, LUF is not an ‘all or nothing’ event. Coetsier and Dhont (1996) found that one or more of the follicles stimulated with clomiphene citrate/human menopausal gonadotrophin/human chorionic gonadotrophin did not rupture. Overall, half of the follicles did rupture, and a complete LUF syndrome occurred in 20% of the cycles. This indicates that intrinsic follicle defects and/or an altered follicular phase rather than a weak ovulatory signal may be responsible for LUF syndrome (Mattheij and Swarts, 1995).

Prostaglandin synthetase inhibitors such as indomethacin are known to produce LUF. The high prevalence of dysmenorrhoea among women with endometriosis may lead to a higher consumption of these drugs. Thus, we may speculate that inhibition of prostaglandin synthesis may increase the percentage of LUF. More common use of these drugs by women with dysmenorrhoea may partially explain the higher reported LUF rate among endometriosis patients.

Luteal phase disturbances in women with endometriosis is a very controversial issue, and these two circumstances do not always appear to be linked (Kusuha, 1992; Matorras et al., 1996). Larger, prospective, carefully-monitored trials are needed before we can provide a valid answer to the question of whether LUF is associated with endometriosis.

**Oocyte fertilization**

Impaired fertilization has been suggested as a possible mechanism of infertility associated with endometriosis (Wardle et al., 1986). However, when only normozoospermic partners are considered, the most recent evidence suggests
otherwise. No significant differences could be found in the fertilization rate of the oocytes from women with endometriosis when compared with the rates of women with tubal factor or unexplained infertility (Mahmood and Templeton, 1991; Simón et al., 1994; Dmowski et al., 1995; Geber et al., 1995; Arici et al., 1996). On the other hand, a recent retrospective analysis (Hull et al., 1998) showed a small but significant reduction in the fertilization rate in couples with endometriosis compared with tubal infertility couples (60 versus 56%), with similar rates with spermatoza from either the husband or a donor. Clinically speaking, this 4% reduction in an IVF setting may reflect a subtle dysfunction which can be easily overcome by the superabundance of oocytes obtained by stimulation. Furthermore, the presence of endometriosis does not affect fertilization in couples undergoing intracytoplasmic sperm injection because of severe male infertility (Minguez et al., 1997).

Some other factors, such as increased phagocytosis of spermatozoa by peritoneal macrophages, which may reduce the fertilization potential of oocytes in women with endometriosis, or the regulation of this phagocytosis by cell membrane stabilizing agents such as lignocaine (Edeltam et al., 1998), might further explain the intricate mechanisms of sperm–oocyte interactions by which such women with endometriosis may have a diminished reproductive potential.

**Conclusion**

We believe that oocyte growth and maturation are altered in women with endometriosis, resulting in lower quality embryos that have a decreased ability to implant in an already partially altered endometrium. Low oocyte quality in women with endometriosis is reflected in ovulation defects, lower response to IVF, poor quality embryos, and lower implantation rates. When good quality oocytes are fertilized or when a higher number of embryos are transferred, implantation rates return to control values. Thus, a good quality embryo may overcome the slight decrease observed in endometrial receptivity.

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**References**


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Endometrium/oocyte quality in endometriosis


