Endometrium or embryo quality in minimal or mild endometriosis - related infertility

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Abstract

Background: There is controversy related to pathogenesis and mechanism by which minimal or mild endometriosis affects fertility in women. It is accepted that moderate-severe endometriosis disrupt the anatomical relationships between fallopian tube and ovary. Some researchers found impaired implantation in patients with endometriosis, but such defects in implantation may be caused by either embryos or altered endometrium. Further investigations on follicular fluids have also found differences between women with endometriosis and women without the disease. In addition, recent advances on implantation research, show features in the eutopic endometrium of women with endometriosis that are not found in endometrium of women without the disease, although it is controversial. The review aims at describing the available information from the eutopic endometrium or embryo standpoint infertility related to endometriosis.

Objective: To explore the interrelation of the eutopic endometrium or embryo in women with infertility and the endometriosis.

Methods: Retrospective review of literature using all the available English databases, Cochrane register and articles which addressed the question “Whether the endometrium or embryo quality is different in women with endometriosis associated infertility?”

Conclusion: Although contradictory results have been reported, different clinical studies have demonstrated worse success rates for pregnancy in women with endometriosis compared with healthy women or with tubal factor among those that found lower pregnancy rates in women with endometriosis compared with controls without the disease, some found alterations in implantation rates in women with endometriosis when they were compared with controls. The debate continues, and other approaches should be developed before we can determine the authentic origin of the defects that make conception more difficult in these patients. These new studies must include an adequate design and controls, in order to avoid misleading data that can complicate the interpretation of the pathophysiology of this enigmatic disease.

Keywords: Minimal or mild endometriosis, Pathogenesis, Infertility, Assisted reproduction, Endometrium, Embryo quality

Introduction

Endometriosis is a benign estrogen-dependent and progestin-resistance gynecological disease. It is characterized by the attachment of endometrial cells, both stroma and epithelium outside the uterine cavity. The most common sites of endometriosis, in decreasing order, are the ovaries, anterior/posterior cul-de-sac, broad ligaments and uterosacral ligaments, uterus, fallopian tubes, sigmoid colon, and appendix.

Within the spectrum of symptoms that are displayed with the disease, one of the most controversial is the link between minimal or mild endometriosis and infertility, particularly in patients with no mechanical alteration of the reproductive tract. But a large of data supported the concept of low fecundity in patients with endometriosis. The fecundity rate in untreated endometriosis is estimated from 2% to 10% than in women without disease (15-20%). Women with minimal or mild endometriosis have been shown a significantly lower probability of pregnancy over 3 years than women with unexplained infertility (36% VS 55%).

In addition, endometriotic lesions have been shown to have an increased production and decreased inactivation of estradiol (E2). Partly this is due, to abnormal expression of both aromatase and 17beta hydroxysteroid dehydrogenase. In addition, recent research suggests morphological differences between endometriosis and endometrium.

Epidemiology

Endometriosis is very common debilitating disease that in 6 to 10% of the general female population. In women with pain, infertility, or both, the frequency is 35–50%. About 25 to 50% of infertile women have endometriosis and 30 to 50% of women with endometriosis are infertile. More recent data indicate that the incidence of
endometriosis has not increased in the last 30 years and remains at 2.37–2.49/1000/y, which approximate prevalence of 6–8%. To date, it has not been possible to determine whether medical approach is less expensive than a surgical approach in patients with chronic pelvic pain11,12. Also, data is lacking regarding the cost of treating endometriosis in infertile patients. On May 10th, 2007, the Public Health Executive Agency of the European Union announced that a €296,000 grant was awarded to a European coalition of universities and patient support organizations to improve the awareness of endometriosis in Europe.

Pathogenesis

No single theory can explain the pathogenesis of endometriosis9. Endometriosis is sometimes called the disease of theories. The implantation theory was described by Dr. Sampson in 1925. He proposed that retrograde menstruation regurgitates viable endometrial cells through the fallopian tubes. These cells are capable of implantation and development. Dissemination to distant sites is possible by lymphatic and vascular spread. This theory remains the most popular and is supported by experiments that show that endometrial cells are viable in vivo and in vitro9,10.

The coelomic metaplasia theory explains the unusual sites of endometriosis but evidence for it has yet to be established10. Dr. Meyer proposed that coelomic epithelium undergoes metaplasia to become endometriosis. Endometriosis does not show the distribution with older age that is found in other organs that undergo metaplasia, e.g. squamous metaplasia in the lung.

Iatrogenic dissemination can occur during gynecological procedures, but it is not clear whether the rate of transplantation varies with the time if cycle10,11.

Recent studies on pathogenesis showed immunogenetic defects, e.g. aberrant expression of factor. Steroidogenetic Factor-1 activates the expression of the aromatase enzyme and increased expression of cyclooxygenase-2 in the stromal cells10,11.

Results and Discussion

In vitro fertilization (IVF) studies have suggested that women with endometriosis have poor ovarian reserve, low oocyte and embryo quality and poor endometrial receptivity to embryonic implantation10,11,12. Authors who found lower success rates caused by implantation defects in women with endometriosis have described three different alterations: an oocyte/embryo impairment, endometrial defects and defective cross-talk. Altered oocyte/embryo quality due to altered embryo development has been described (Brizek et al. 2009, or high embryo blockage in women with endometriosis compared with controls11,12).

Oocyte donation is an interesting method to investigate the reproductive outcome of endometriosis-affected women, because it is possible to compare women who received fresh oocytes from non-endometriosis women with those receiving oocytes from endometriosis women12.

Authors (Simon et al., 1998) retrospectively analyzed the results of oocyte donation programme (women without endometriosis). Recipient women divided into three groups: (I) premature ovarian failure (n=54), (II) low responders to controlled ovarian stimulation (n=77) and (III) women with endometriosis who underwent oocyte donation because of low response (n=11). A similar number of embryos were replaced in each group. There was no difference among groups in the pregnancy rate per woman, per cycle or implantation11,12,13.

Furthermore, other authors (Diaz et al., 2000) designed a prospective, case-control study in order to evaluate the impacts of severe endometriosis on in vitro fertilization outcome in women receiving oocytes from the same donor, thus ruling out the possibility of assigning oocytes of different quality to the different groups12,13. The results showed no differences in pregnancy (40 versus 45%), implantation (14.8 versus 16.0%), miscarriage (30 versus 26%) and live birth rates (28 versus 27.2%) between the groups (endometriosis stage III-IV and controls).

Implantation is an extremely important process requiring the presence of developing embryos with the ability to induce the correct changes in the endometrial epithelium, together with the presence of an endometrium ready to receive these signals and to act in consequence. Subsequently, any endometrium unable to answer properly, without the correct timing in the endometrial changes, would be adversely effecting the reproductive success.11,12,13.

Studies compared eutopic endometrium of women with endometriosis with healthy controls without endometriosis. Majority of studies regarding endometrium endometriosis are focused on the differences between eutopic and eutopic endometrium in these patients and are hence concerned with molecules presumably implicated in the origin of the disease. They are mainly focused on molecules previously related to implantation and infertility.

Accumulated data suggest that eutopic endometrium of women with endometriosis behaves different from the endometrium of women without the disease, but to establish a cause–effect relationship between endometrial alterations in women with endometriosis and infertility, the key factors concerning endometrium and implantation should first be accurately determined.

Nowadays, there are many molecular and morphological markers of endometrial receptivity that may alter endometrium in women with endometriosis.

Fedele et al. using electron microscopy, have been described defects in the structural morphology of endometrial in women with endometriosis, which could be responsible for infertility13. Recently, pinopods have been suggested as morphological indicators of uterine receptivity. Therefore, their presence in the eutopic endometrium of women with endometriosis must be studied. They recently addressed that pinopod formation in women with and without endometriosis undergoing oocyte donation programme. There were no differences between the two...
groups analyzed, suggesting that the endometrium of women with endometriosis is able to develop an adequate response to hormonal replacement therapy in terms of pinopod formation.

Lessey et al., studied integrins \( (\alpha_1 \alpha_2 \beta_1 \beta_2) \) as an indicators of endometrial receptivity\(^{14}\). The study of this molecules in eutopic endometrium from women with endometriosis, during laparoscopy. Providing evidence that majority of women with abnormal \( \alpha_2 \), \( \beta_3 \) integrin expression had endometriosis stage I or II. It concluded that endometriosis could adversely effect the endometrial environment in natural cycles\(^{14}\).

However, other authors did not confirm these findings (Bridges et al., Creuset al. Hill and Rogers), possible due to a slightly different study design, controls or sample size\(^{6}\). Afterwards, the same group correlated the increase in pregnancy rates with an increase in \( \alpha_2 \), \( \beta_3 \) integrin expression after the treatment of endometriosis, making use of surgical procedures or GnRH analogues (Lessey and Yong)\(^{14}\).

Another factor involved in alterations of the endometrium of women with endometriosis is glutathione peroxidase, an enzyme that eliminates free-radicals. Glutathione peroxidase exhibits a varying expression during menstrual cycle in normal endometria, but no variation in eutopic endometrium of women with endometriosis. This lack of variation leads to defects involving protection against oxidative stress of these endometria, whose relevance in implantation, the endometrium or embryo development is unknown but it appears a promising field for study (Ota et al.,)\(^{11,12}\).

Finally, many factors involved in implantation have not yet been studied comparing the eutopic endometrium of women with endometriosis with the endometrium of healthy controls, as depicted in there: LUMINAL EPITHELIUM: Apoptosis, MUC-1, Ezrin, IL-IRII, Telomerase activity, Interferon-inducible guanylate binding protein, Interferon-regulated gene, Leptin, COX-1 and COX-2.

\[ \text{Conclusion} \]

Although contradictory results have been reported, different clinical studies have demonstrated worse success rates for pregnancy in women with endometriosis compared with healthy women or with tubal factor among those that found lower pregnancy rates in women with endometriosis compared with controls without the disease, some found alterations in implantation rates in women with endometriosis, when they were compared with controls.

Several studies suggest that an altered ovarian problem in women with endometriosis could be responsible for a defective oogenesis, subsequently low quality embryos, with diminished ability to implant.

Endometrial aspects have also been discussed, and molecular studies on factors involved in the receptivity

\[ \text{Table 1. IVF outcome in recipients of sibling oocyte with and without endometriosis} \]

| Study group | P - value |
|-------------|-----------|
| **endometriosis** |    |
| No. of patients | 25 |
| No. cycles | 25 |
| Age (years) | 35.0± 3.4 |
| No. of oocytes donated | 7.8± 1.6 |
| No. of embryos transferred | 4.0± 0.7 |
| No.of good quality embryos transferred | 3.6± 0.2 |
| Implantation (%) | 15/101 (14.8) |
| No. of pregnancies (%) | 10 (40.0) |
| Miscarriage (%) | 3 (30.0) |
| Live birth (%) | 33 |
|  | 33 |
|  | 38.5± 4.9 |
|  | 0.004 |
|  | 7.7 ± 1.9 |
|  | NS |
|  | 4.1± 1.2 |
|  | NS |
|  | 3.7± 0.1 |
|  | NS |
|  | 22/137 (16.0) |
|  | NS |
|  | 15 (45.5) |
|  | NS |
|  | 4(26.0) |
|  | NS |
status of the eutopic endometrium in women with endometriosis resulted again in conflicting data, although some differences with normal controls have been described. Mixed causes—defects both the endometrium and embryo, cannot be ruled out, and in the ovum donation programme, good embryos could by-pass an affected endometrium.

The debate continues, and other approaches should be developed before we can determine the authentic origin of the defects that make conception more difficult in these patients. These new studies must include an adequate design and controls, in order to avoid misleading data that can complicate the interpretation of the pathophysiology of this enigmatic disease.

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