

What is the evidence that endometriosis is a cause of subfertility?

Endometriosis is a common disease found in women and is usually characterised as a chronic and painful disease. It occurs in 1-2% of reproductive aged women, but is 20 times greater in infertile women. Tissues that are normally found in the uterus are also found in other parts of the body such as ovaries, the lining of abdominal cavity, fallopian tubes or spaces between the uterus and rectum. These specialised tissues are responsive to hormonal changes for example during menstrual cycle. The lining builds up and breaks down according to the hormonal cycle, leading to internal bleeding, inflammation, blood-filled cysts formation and chronic pelvic pain. (Carlson K. et al, 1996, p227-228)

The exact cause of endometriosis is unknown, but a combination of genetic, immune system and hormonal factors may be involved. There are a number of proposed theories trying to explain the cause.

- Retrograde menstruation – Process of the endometrium flowing backwards through the fallopian tubes, instead of leaving the body by menstruation. These tissues embed onto the membranes of the organs of the pelvis.
- Genetic factor – It is believed that there is a link between endometriosis and genetics. Some women may be more susceptible to endometriosis. Studies show that patients having close family members suffering from endometriosis will have a risk of developing this disease 7 times greater than normal individuals do.
- Lymphatic or circulatory spread – The process is unknown but this helps to explain why these cells are found in other parts of the body which are far away from the endometrium.
- Immune dysfunction – Many women with this condition have a lower immunity than normal women.
- Environmental causes – It may be caused by exposure of certain toxins in the environment such as dioxins.

The symptoms include painful and heavy periods, pain around pelvis area, pain when passing out urine and pain during sexual intercourse. (Hicks R., 2008). Clinical diagnosis of endometriosis is characterised by thickened pelvic ligaments, uterine and ovarian enlargement and a fixed retroverted uterus. Laparoscopy is a procedure using a slender and bendable microscope, capable of providing a view of internal organs by passing through small incisions made on the external surface of abdomen, and this is used to make the diagnosis. (Carlson, Eisenstat & Ziporyn 1996, p. 227-228; NHS direct, 2007)

Subfertility is a condition describing a reduced ability to reproduce. A couple is described as subfertile if they are unsuccessful to have a child for a year or more. Subfertility can be caused by different reasons such as alcohol abuse and endometriosis. (Willacy H., 2008).

Endometriosis and subfertility

"According to medical statistics around 35% to 40% of women who suffer from endometriosis also suffer from subfertility" (Endo Resolved, 2010). These women not only have to deal with this painful disease but also fear the incapability of having children.

The causal relationship between the presence of endometriosis and subfertility can be supported by the finding that there is an increased prevalence of endometriosis in subfertile women compared with women of proven fertility. The term fecundity refers to a woman's ability to become pregnant. Evidence suggests that there is a reduced monthly fecundity rate (MFR) in baboons with endometriosis compared with those with a normal pelvis and that there is a trend towards a reduced MFR in infertile women with endometriosis compared with unexplained infertility. These findings further support the hypothesis that endometriosis is a

cause of subfertility. Furthermore, it has been found that there is a reduced MFR and cumulative pregnancy rate after donor sperm or husband sperm insemination, and a reduced implantation rate per embryo after in-vitro fertilisation in women with endometriosis compared with women with a normal pelvis. Additionally, evidence also shows an increased MFR and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis. These findings all further support the hypothesis that endometriosis is a cause of subfertility. (Thomas M., 2003).

The exact mechanism by which endometriosis reduces fertility is uncertain, however, the impairment of coital, sperm, tubal and ovarian functions have been suggested. (Drife J. et al, 2004, p223).

1) Endometriosis often causes painful intercourse (dyspareunia) resulting in a reduced frequency of coitus. So couples may fail to have intercourse during the woman's most fertile time, and this therefore reduces the possibility of conception.

2) For a successful pregnancy to take place, sperm has to enter the body. Sperm is detected as a 'foreign particle'. However, the immune system of a woman who does not have endometriosis adapts to this foreign particle thus allowing the sperm and therefore embryo to survive. Endometriosis may interfere with the immune system, causing the sperm to be attacked by antibodies or phagocytosed by macrophages. This modification of the immune system inactivates the sperm that enters the body resulting in unsuccessful pregnancy.

3) Endometriosis may lead to scarring of the fallopian tubes, damage to the fimbriae, adhesions, and blockage of the tubes. Damage to the fimbriae may reduce their ability to pick up the egg and direct it into the fallopian tube, and adhesions around the tube may reduce their mobility, thus also affecting their ability to pick up the egg. Damage to the cells lining the tube can prevent the sperm from actually reaching the egg thus reducing fertilisation. Blockage of the tubes can also prevent sperm from reaching the egg, or could increase the incidence of ectopic pregnancy by disrupting the movement of the fertilized egg to the uterus. (Dr Marcus, 2010). Additionally, it has been theoretically suggested that high prostaglandin release from endometriotic tissue could impede tubal motility thus reducing fertility. (Drife J. et al, 2004, p223).

4) Endometriosis can cause anovulation, i.e. the lack of ovulation. It may be associated with luteinized unruptured follicle syndrome (LUFS) in which follicular development occurs along what appears to be normal lines, but the oocyte release does not occur. It may additionally affect luteolysis caused by prostaglandin $F_{2\alpha}$. Luteolysis is the structural and functional degradation of the corpus luteum that occurs at the end of the luteal phase of the menstrual cycles in the absence of pregnancy. Endometriosis may also alter the release of gonadotrophins. All of which could reduce fertility. (Drife J. et al, 2004, p223).

Medical Treatments

Medical treatments, such as surgical procedure and drug therapy, for endometriosis are useful for relieving symptoms, including pelvic pains and cramps. Due to almost all drugs' influences on menstrual cycle and the surgical risk of preventing women from conception, women should carefully consider their decisions in receiving surgical or drug treatment if they wish to conceive in the future. (Carlson, Eisenstat & Ziporyn 1996, p.227-228).

In comparison of the two types of treatments, the surgical treatment of removing endometriotic deposits to relieve pain usually lasts longer than that of drug treatments. If the patient wishes to conceive in the future, the surgery needs to be done carefully to avoid creating scar tissues that could prevent patients from conception. As mentioned in “The Harvard Guide to Women’s Health”, the surgical treatment includes laser surgery, electrocautery, knife excision, or curettage (scraping) with the assistance of a laparoscope.

If patients do not wish to bear child in the future, hysterectomy, which removes the uterus, or bilateral oophorectomy, which removes the ovaries, can be performed. However, post-operative care, such as hormone replacement, is required. Normally, a combination hormone therapy rather than oestrogen-only hormone therapy is preferred to reduce the recurrence of endometriotic symptoms. If surgical treatment fails or the patient chooses non-surgical treatment, prescribed drugs can be given. Progestogen, such as medroxyprogesterone acetate, is a first-line drug to treat endometriosis. Progestogens bind to the progestogen receptors on the endometrial tissues, which then decidualize and eventually undergo necrosis, thus giving its clinical effectiveness of reducing endometriosis. (Carlson, Eisenstat & Ziporyn 1996, p.228; Drife & Magowan 2004, p.224-225)

Second-line drugs, such as gonadotrophin-releasing hormone (GnRH) analogue, work by lowering the secretion of luteinizing hormone (LH), follicle stimulating hormone (FSH), and eventually the level of oestrogen, thus inducing a state of false menopause and affecting the endometrial tissue. The GnRH agonists include leuprolide acetate, nafarelin acetate, and goserellin acetate. The duration of this therapy is 3-6 months. Danazol, which is a synthetic male hormone, is also used; however, it has more undesired side effects than the previous two drugs. Common side effects of using Danazol include weight gain, acne, and fatigue. The recommended duration of use is also 3-6 months. (Carlson, Eisenstat & Ziporyn 1996, p.228; Drife & Magowan 2004, p.224-225).

References

1. Carlson, Karen J, Eisenstat, Stephanie A & Ziporyn, Terra 1996, *The Harvard Guide to Women’s Health*, Cambridge, Massachusetts.
2. CKS-NHS Direct 2007, National Institute for Health and Clinical Excellence, UK, viewed 1st March 2010, <http://www.cks.nhs.uk/patient_information_leaflet/Laparoscopy#>
3. Dr Hayley Willacy (Jan 2008) Subfertility- Investigation and Management. Available at:<http://www.patient.co.uk/doctor/Subfertility-Investigations-and-Management.htm>
4. Dr Rob Hicks (Feb 2008) Endometriosis. Available at:
<http://www.bbc.co.uk/health/conditions/endometriosis1.shtml>
5. Dr Marcus. (2010) ivf-infertility.com | Causes of infertility | Tubal problems. Available at:
<http://www.ivf-infertility.com/infertility/causes/tubal.php>. Date accessed: 02/03/2010.
6. Drife, J. and Magowan, B. (2004) Clinical Obstetrics and Gynaecology. *Saunders*. Pp. 223.

7. Endo Resolved. (2010) Endometriosis and Infertility. Available at: <http://www.endo-resolved.com/infertility.html>. Date assessed: 01/03/2010.
8. Pubmed J Reprod Med.1998 Dec;43(12):1034 -42; Subfertility associated with minimal to mild endometriosis. Main mechanism by Panidis DK, Matalliotakis IM
9. Thomas, M. (2003) Endometriosis and Subfertility: Is the Relationship Resolved? *Thieme Medical Publishers*. Available at: <http://www.medscape.com/viewarticle/460131>. Date assessed: 27/02/2010.