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Why Endometriosis Causes Infertility?

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Endometriosis is a common disorder of reproductive age group, defined as the presence of endometrial glands and stroma outside the lining of the uterus. The disease carries enormous medical and economic burden on the society mainly due to the its symptoms and prolonged course. There is no promising non-invasive test to diagnose it and can only be diagnosed invasively by laparoscopy. The symptoms include chronic pelvic pain and infertility. The estimated prevalence of the disease is 10% which rises to 35 to 50% in women with infertility. Here we give a brief overview about the factors leading to infertility in patients with endometriosis.

Keywords: Endometriosis; infertility; endometrioma; laparoscopy.

1. BACKGROUND

Endometriosis is a common gynaecological disorder of women in reproductive age group characterised by the presence of endometrial glands and stroma outside the uterine cavity. It has been estimated that 10% women in the reproductive age group are affected by endometriosis, although this figure is likely to underestimate the true prevalence [1]. The number rises to 35 to 50% in patients with pelvic pain and infertility or both [2,3]. The prevalence is not affected by race, ethnicity or geographical distribution. Typical clinical symptoms include severe chronic pelvic pain, painful periods (dysmenorrhoea), discomfort during intercourse

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(dyspareunia), and infertility. The symptoms of endometriosis do not correlate with the extent or the severity of the disease. Even microscopic or subtle endometriosis can cause incapacitating symptoms. The debilitating symptoms pose a significant impact on the individual's quality of life, impairing work strength, women taking disease-related days off work (absenteeism) or decreased productivity and therefore contributing to high annual cost on the system and society [4].

2. SITES OF ENDOMETRIOSIS

Mostly, the ectopic endometrial tissue is present in the pelvis, but it can be found anywhere in the body. Common sites of endometrial implants include pelvic peritoneum (including uterosacral ligaments and Pouch of Douglas) and ovaries (Fig. 1). Often the rectosigmoid colon and appendix are also involved. Rare and remote sites include laparotomy and episiotomy scars, pleura, kidney and ureter.

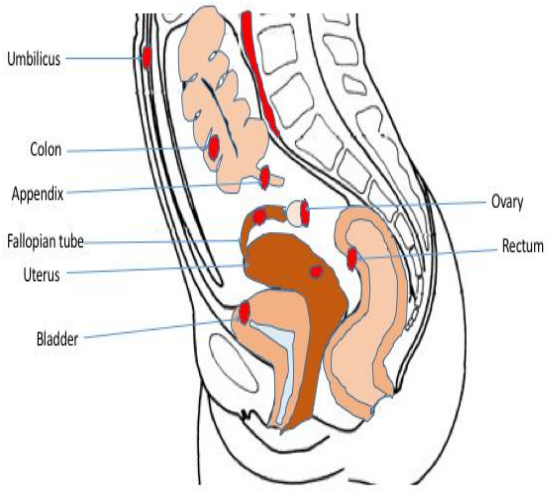

Fig. 1. Sites of endometriosis

Common sites of endometriosis in decreasing order of frequency: (1) ovary, (2) Pouch of Douglas, (3) uterosacral ligaments, (4) broad ligaments, (5) fallopian tubes, (6) uterovesical fold, (7) round ligaments, (8) vermiform appendix, (9) vagina, (10) rectovaginal septum, (11) rectosigmoid colon, (12) cecum, (13) ileum, (14) inguinal canals, (15) abdominal scars, (16) ureters, (17) urinary bladder, (18) umbilicus, (19) vulva, and (20) peripheral sites. Source: (31)

3. PATHOGENESIS OF ENDOMETRIOSIS

Though the first description of endometriosis was given by Daniel Christianus Schrön in 1690 and the first researcher to ascertain the disease was Thomas Cullen, the disease will eternally be associated with Dr John A. Sampson because of his surpassing work in endometriosis in discovering its pathogenesis [5]. He coined the term endometriosis from ancient Greek: 'endo' means inside, 'metra' means womb and the suffix '-osis' means disease. The pathogenesis of endometriosis is not entirely understood. Several theories have been proposed which include retrograde menstruation and implantation, coelomic metaplasia, the induction theory, direct transplantation and vascular dissemination (Box 1). No single theory can adequately explain the pathophysiology of endometriosis and experts believe that multiple mechanisms operate simultaneously in the initiation and spread of the disease [1].

Regardless of the cause that incites the disease, many key questions remain unanswered: Why does endometriosis develop only in few women when retrograde menstruation is seen in 90% of women [6]? Why do the symptoms of endometriosis not correlate with disease severity?

4. CLASSIFICATION OF ENDOMETRIOSIS

Since the severity and the extent of the disease vary widely among individuals, attempts have been made to design a uniform classification system which can help in diagnosis and treatment of women with endometriosis. The revised classification given by the American Society of Reproductive Medicine (ASRM) is most widely accepted. The goal of this classification was to evaluate the fertility potential using the revised ASRM classification score [7] (Fig. 2). It is based on the allocation of points for disease visualised and sites involved. It describes the disease extent, differentiates between superficial and deep infiltrating endometriosis, describes the morphology and colour of the endometriotic patches and describes ovarian endometriomas in detail. However, it fails to correlate well with the symptoms of endometriosis like pain and infertility [7].

5. ENDOMETRIOSIS AND INFERTILITY

One of the significant consequences of endometriosis is infertility, and the possibility of being infertile is very agonising to a woman. Though, endometriosis has been identified as a disease for centuries; the sequential events leading to infertility are still obscure. The

prevalence of endometriosis in women with infertility rises to 25%-50% and about 30%-50% of women with endometriosis are infertile [8,9].

5.1 Biological Mechanisms in Endometriosis Leading to Infertility

Several mechanisms have been suggested to provide a piece to the puzzle of mechanism causing infertility in endometriosis, but none has been proven. The mechanisms are discussed below, though the cause of infertility is still obscure.

5.1.1 Distortion of pelvic anatomy

Pelvic adhesions in endometriosis deform the pelvic anatomy. Adhesions disturb the relative position of tubes and ovaries and impair ovum pick-up. Tubal motility is impaired due to an elevated level of cytokines and the transfer of gametes and embryos in the required directions is affected [9]. The binding of sperm to the inner lining of the fallopian tube is affected which further impairs their capacitation [10]. The adhesions and inflammation (chronic salpingitis) in the tubes have the potential to occlude the tubes and cause hydrosalpinx which further minimises the possibility of pregnancy either spontaneously or through assisted reproductive technology. There are several hypotheses by which hydrosalpinx affect the pregnancy rates. The fibrotic wall and the distorted epithelial lining hampers pregnancy [11]. It is also hypothesised that the presence of inflammatory mediators and macrophages in the fluid within the hydrosalpinx are toxic to the embryo and hamper its development [12]. The proximal end of the tube in hydrosalpinx is free which not only allows the entry of pathogenic microorganisms but also becomes a path for the fluid to drain thus hampering implantation and escalating the abortion rate [13]. Therefore, bilateral tubal ligation increases the success of IVF-ET in such patients [14].

5.1.2 Ovulatory abnormalities in endometriosis

Ovaries are the commonest organ to be involved in endometriosis. They are the most apparent reason leading to infertility from the disease. The amount of oestradiol secreted is decreased along with the reduction in the count of follicles and their growth. The granulosa cell function is also impaired due to alteration in the level of cytokines which also impair follicular growth and oocyte maturation. The apoptosis of granulosa cells is also found to increase in proportion to the stage of the disease and cause a decrease in the pregnancy rates with the higher stage of the disease [15]. It has also been observed that the markers of oxidative stress are raised in the cytoplasm of granulosa cells in patients with endometriosis [16]. The milieu of the follicular fluid has abnormal concentrations of various

1. Sampson's retrograde menstruation theory is based on the assumption that endometrial cells shed during menstruation regurgitate transtubally and implant onto the pelvic viscera and the peritoneal cavity (5).

2. **The coelomic metaplasia theory** suggests that due to some unknown stimuli, the mesothelial cells of peritoneum undergo spontaneous metaplasia into endometrial cells. This theory explains pleural and pulmonary endometriosis as the shed endometrial cells have no access to the thorax (32).

3. **The induction theory** is a variation of coelomic metaplasia and suggests that some biologic factor induces the differentiation of undifferentiated cells into endometrial cells (33).

4. The lymphatic theory by Halban predicts that endometrial tissue is carried to distant sites by the lymphatics draining the uterus. Vascular dissemination of the cells also explains endometriosis at remote sites (34).

5. The theory of embryonic Mullerian rests or Müllerianosis proposes that the misplaced embryonal remnants of the Mullerian duct, under the influence of oestrogen at puberty, develop into endometriotic patches (35).

Box 1. Theories of pathogenesis of endometriosis

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete	
		4	40	
OVARY	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Fig. 2. Revised ASRM classification of endometriosis
Source: ASRM 1997

cytokines and hormones. The amount of oestrogen, progesterone and androgen are also decreased, and the proportion of activin is increased impairing the oocyte development and promoting the growth of the ectopic endometrium [17]. Ovulation is affected as the luteinising hormone (LH) surge is altered, and there is a deficiency of LH receptors in the follicles. The pituitary-ovarian axis is disrupted which leads to the lengthening of the follicular phase. Luteal phase deficiency with low LH levels has been reported in patients with endometriosis, and the LH surge is delayed. This furthermore hinders with follicular growth, secretion of oestrogen, the formation of corpus luteum and secretion of progesterone [18]. The incidence of luteinizing unruptured follicle syndrome (LUFs) is also high in women with endometriosis [19,20]. Due to the above constellation of problems associated with ovulation, increased doses of gonadotropins and ovulation induction drugs are necessitated in women with endometriosis. are known to require higher doses of ovarian induction medications for a longer period compared to people without the disease [21]. The endometriotic cysts present in the ovary, known as endometriomas or chocolate cysts are found in women with ovarian endometriosis. It has been shown that women with bilateral endometriomas undergoing IVF (in-vitro fertilisation) responded poorly to ovarian hyperstimulation regimes with decreased follicular count and reduced oocyte yield [22].

5.1.3 Defective peritoneal function

Peritoneal fluid is produced as a result of transudation from the capillaries and is vital in the for lubrication of the abdominal viscera. It is a dynamic milieu rich in various cytokines, inflammatory cells and growth factors. Women

with endometriosis have been reported to have increased amount of peritoneal fluid. Not only the amount of fluid increases but also the concentration of various prostaglandins and interleukins and activated macrophages and reactive oxygen species increase [23]. In women with endometriosis, the peritoneal fluid has been noted to contain an increased number of macrophages, inflammatory cytokines and reactive oxygen species and reduced concentrations of antioxidants. The abundant phagocytic cells engulf the sperm and thus alleviating the chances of fertilisation [24]. Due to the oxidative stress, the quality of the sperm is also hampered as evident by increased fragmentation. Increased sperm DNA fragmentation has been noted in the peritoneal fluid from patients with endometriosis. Also, the macrophages cause the Fas-ligand expression by the endometrial cells and thus mediating apoptosis of the immune cells and eluding the immune surveillance of the body [25].

The quality of embryos from women with endometriosis is reduced. They are more likely to get arrested developmentally at the cleavage or 4-cell stage. It has been postulated that the ovarian endometriomas secrete products pernicious to the developing oocytes which affect cleavage of the embryo [26]. There is also an increased incidence of spontaneous abortions at varying gestational ages due to the impaired development of the embryo or inadequate endometrial support to the developing embryo. Significant abnormalities in oocyte or embryo grading have been reported, but no difference is seen in oocytes from the ovary affected by endometrioma as compared to the normal contralateral ovary, which suggests the role of endometrial factors [26]. Studies have found that embryos from women with endometriosis have aberrant nuclear and cytoplasmic events including cytoplasmic and nuclear fragmentation [27], abnormal distribution of microtubules and increased cellular stress [17].

5.1.4 Implantation defects

An intricate system of cellular and humoral immunity and various other factors play a crucial role in implantation. Increased autoantibodies and phagocytic cells are found in the endometrium of women with endometriosis which impacts the implantation rates [28]. Delayed and out-of-phase histological maturation of the endometrium and hormonal abnormalities also affect implantation. Increased uterine contractility due to abundant prostaglandins are also a contributing factor to impaired implantation. L-selectin, a protein that covers the trophoblast on blastocyst exterior is also expressed poorly in endometriosis. $\alpha v\beta 3$ integrin is a cell adhesion molecule important for implantation is also reduced in such patients [29,30].

6. TREATMENT OF ENDOMETRIOSIS

Women with endometriosis present with varying symptoms and the treatment is directed towards the amelioration of the symptoms like pain and infertility and to prevent recurrence. The treatment options can be expectant, medical or surgical depending on the age of the patient, the severity of symptoms, desire for fertility and the site of endometriosis. The treatment of pain which usually suppresses ovulation renders the patient infertile. The treatment details are beyond the scope of this review.

7. CONCLUSION

The disease, endometriosis is full of theories and hypotheses. The cause, pathogenesis and the mechanisms of infertility are not completely understood. A lot of research is going on in this field, and various treatment have been successful. But the disease is still an enigma.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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