

# Association of inflammation with female reproductive system disorders

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## Highlights

- Inflammation is the body response against injury and infection.
- Inflammation can affect fertility potential of women.
- Inflammatory state has essential roles in physiological reproductive functions in females.
- Inflammatory mechanisms are associated with disorders of female reproductive system.

## Article Info

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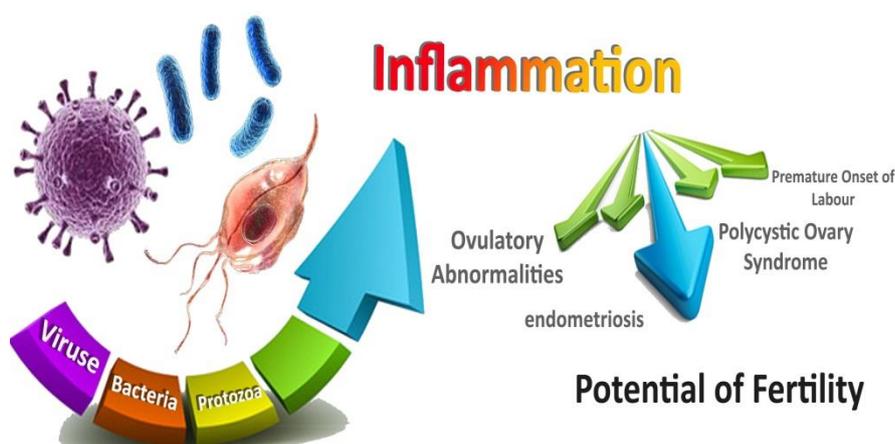
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## Graphical Abstract



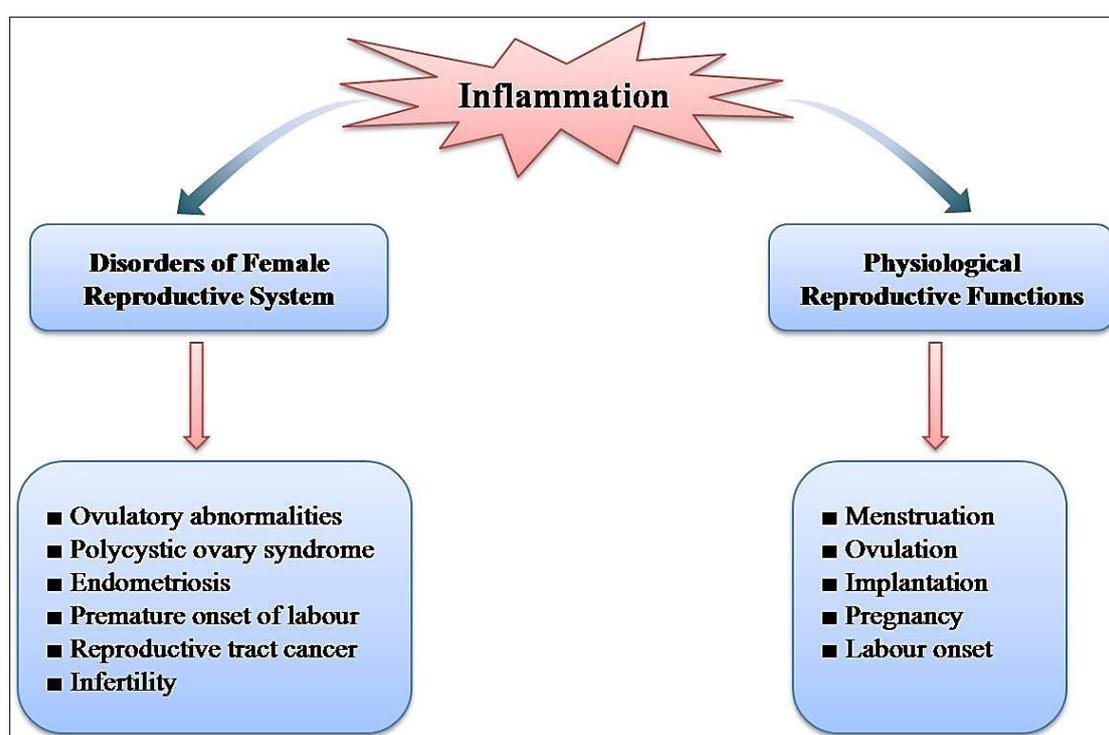
## Abstract

Inflammation is the body response against infection, injury and illness. It is a significant factor which can affect reproduction processes. Inflammatory state has key roles in physiological reproductive functions in women like menstruation, ovulation, implantation and pregnancy. Previous studies evaluated the association of inflammatory mechanisms with disorders such as ovulatory abnormalities, polycystic ovary syndrome, endometriosis, premature onset of labor and infertility in women—the present review summarized association between inflammation state and some reproductive disorders in female. Based on available findings, the inflammation state can be associated with various female reproductive disorders, which finally can affect fertility potential. Thus, assessment of inflammatory mechanisms and their association with processes of reproductive in treatment strategies of female infertility can be efficient. More comprehensive studies with a large number of patients and consideration of inflammatory pathways are required to provide more definitive evidences.



## Introduction

Reproductive disorders and infertility is a main challenge in female health and is related to adverse pregnancy outcomes, from implantation process until term. Among these disorders, we can mention polycystic ovary syndrome (PCOS), uterine fibroids, endometriosis, adenomyosis and inflammation. Inflammatory mechanisms play significant roles in the major processes of physiological reproductive in women such as menstruation, ovulation, implantation of embryo and pregnancy (Figure 1) (1, 2, 3). In fact, hyperinflammatory condition might result in disorder in the cross talk of immune-endocrine at female reproductive system, which predisposing to derangements of pregnancy (3).



**Figure 1.** Inflammation is involved in both physiologic events and pathogenic conditions in female reproductive system.

In fact, inflammation is a complex, active process for response to detrimental stimuli as well as is a type of nonspecific immune response. During inflammatory response from infection, components of immune system to the infection site are guided. After steps, in a small tissue space, phagocytic cells including macrophages and neutrophils inhibit the infection (4). Moreover, inflammation may lead to acquired anatomic abnormalities that this also might be associated with pelvic adhesions and infertility (1). It has been reported that inflammation state can reduce the infertility in women via damage to essential components of the oocytes, disorder in the processes of follicles maturation and fertilization, hormonal alternation, impairing the embryo implantation (5). Therefore, controlling the inflammatory pathways is important factor in the reproductive tract pathologies of women. This review has focused on the association of the inflammation state with some reproductive-related disorders in women.

## Infection agents

In reproductive female tract, infection agents such as viruses, bacteria and protozoa, can lead to inflammation and effect on reproductive processes in female. Among we can mention Chlamydia trachomatis, Neisseria gonorrhoeae, Treponema pallidum, Mycoplasma, Ureaplasma, HHV6 (Human herpes virus 6), Human papillomavirus (HPV), ZIKV (Zika virus), Herpes simplex virus (HSV), Trichomonas vaginalis, Toxoplasma gondii (6, 7, 8).

Chlamydia trachomatis infection is the most common reason of inflammatory infertility, which in developed countries can lead to infertility in 10 to 30% of couples. However, in developing countries, infertility associated with pelvic inflammatory is about 85% (1). The chlamydia infection prevalence mainly is not the same in various ethnic populations and it has been proposed that the genotypic dramatically can be effect in this context. In fact, various genotypes lead to variable expression of inflammatory cytokines that may be facilitatory or protective in the pelvic inflammatory disease (PID) progression (1). Thus, the genotype can characterize susceptibility than infection from chlamydia. Generally, some infection agents by the various mechanisms can lead to dysfunction in female's reproductive system, which the recognition of these factors and their effects on reproductive events is significant in the treatment of infertile couples.

### Ovulatory abnormalities

In the ovary, the various factors that are responsible for the inflammatory cascade such as leukotrienes, prostaglandins, histamine, leukotrienes, and different cytokines have been characterized (9). It has been shown a relationship between inflammation markers and function of ovarian so that ovulation is related to a mid-cycle reduction in inflammation however, anovulation is related to high inflammation early in the ovarian cycle (10). Therefore, ovulation process is comparable to the inflammatory state (9). The premature ovarian failure (POF) is significant factor in link of ovulatory infertility and inflammation, which can effect reproduction. In women lower the 40 age, the POF incidence is 1%. About 25% of the POF women can spontaneously ovulate (1). Various factors are associated with POF including intrinsic agents such as chromosome abnormalities and genetic disorders like galactosemia, and extrinsic agents include chemotherapy, ovarian surgery, smoking, irradiation, and toxins. Moreover, it has been suggested that inflammation might play an important role in ovulatory abnormalities. So that, the redistribution of dendritic cells and active monocytes to ovary might contributes to POF (11).

### Endometriosis

Endometriosis is a common disorder in which endometrial tissue is found outside the uterine cavity (12). It has been reported that 30–50% of the female with endometriosis, are infertile, and also among infertile female, 30- 71% have endometriosis (13, 14). Therefore, endometriosis can has the undesirable effects on process of female fertility. It can impact on reproduction steps including folliculogenesis, ovulatory and fertilization, implantation and embryonic development (15, 16, 17). Moreover, the endometriosis can result in enhancement of pregnancy loss risk, decreased of implantation capacity, anatomical obstruction related to endometriotic lesions. Endometriosis is related to inflammation and in women with endometriosis; the factors of host response to inflammation are enhance in their peritoneal fluid (18). In the endometriosis, pelvic inflammation might result in formation of adhesion and scarring, and also anatomical disorder in the reproductive system. Inflammation also decreases the level of progesterone and impairs the endometrium function. Moreover, cytokines of inflammatory cells can influence in the maturation of oocytes and process of fertilization.

It has been reported that in women with endometriosis, the cytokines including TNF- $\alpha$ , IL-1, IL-6 and IL-8 have enhanced (19). In fact, the genetic variations in these inflammantory factors can associate with risk of endometriosis. For example, TNF- $\alpha$  that is a multifunctional cytokine contributed in the inflammatory and immune processes, its levels increases in peritoneal fluid of women with endometriosis (20). Moreover, several polymorphisms have been reported in the promoter of TNF- $\alpha$  gene, which may associate with the pathogenesis of endometriosis. For example, Ahsgar et al., and Teramoto et al., showed the association of the polymorphism of TNF- $\alpha$  1031 T/C endometriosis risk (21, 22). Also, another study has reported that in women with the IL-6-174 G allele, prevalence of endometriomas is elevated (23).

### Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) as the most prevalent endocrine disorder in women is associated with the infertility due to anovulation. PCOS is a heterogeneous disorder and women with this syndrome, the

menstrual irregularities and signs of androgen excessive are demonstrated (24). In the process of ovulation, the inflammation is involved and uncontrolled inflammation might results to the PCOS development (25). It has been reported that the anovulation is main cause of female infertility in PCOS and the morphology of polycystic ovarian is more prevalent in women with ovulation-related infertility (26, 27). Low-grade chronic inflammation is underlying the ovarian dysfunction in the PCOS (28, 25). The evidences show that visceral adipose tissue can play an important role in PCOS-related inflammation (25, 29). Moreover, in PCOS, some dietary triggers can induce the oxidative stress in order to the inflammatory response stimulation. Inflammation stimulates the production of excess ovarian androgen and hyperandrogenism might be associated with low-grade chronic inflammation state. As well as the enhancement of abdominal adiposity associated with the inflammatory state in PCOS (30).

Some proinflammatory genotypes are related to PCOS such as those that encode IL-6 and TNF receptor 2 (31, 32). IL-6 as a main proinflammatory cytokines has an essential role in the process of inflammation. It has been shown that IL-6 level closely related to the obesity as well as its serum levels is higher in the women with PCOS than healthy women (28, 33). Given to the prevalence of PCOS in women and the implications on fertility process, thus, the syndrome and its association with inflammation can be important to female infertility management.

### Pregnancy

In general, pregnancy immunology is the result of the composition of responses caused by the immune systems of maternal and the fetal-placental (34). The implantation of embryo is an essential process in reproduction, which various cytokines, growth factors, chemokines and adhesion molecules are characterized in this process (35, 36). Cytokines may is secretes by the cells of endometrial and the immune system which are recruited to the implantation site. The cytokines balance of Th1 and Th2 is characterized during pregnancy via the Th2 cytokines initial prevalence. However, the processes of Inflammatory/infection alter this balance via the progressive change toward predominance of Th1 and exacerbate the production of inflammatory cytokine that is contributed in adverse outcomes of pregnancy (37). Also, hormones of maternal and placental can influence the inflammatory state (37). Generally, the cytokines network dysregulation may results to adverse consequences in pregnancy such as preeclampsia, spontaneous abortion, preterm labor and fetal growth limitation (38, 39, 40).

### Conclusion

Inflammation is the response of body to injury and infection that mediators such as cytokines, chemokines and growth factors play important roles in this process. These inflammatory mediators can also effects on the immune function. Generally, in condition of the damage to body and inflammation that promote via pathogens, the inflammatory mediators release, then the various cells are activated including endothelial and epithelial cells, macrophages, neutrophils, platelets and mast cells in order to repair the injury and resolve the inflammation in body. In female's reproductive system, the inflammation is involved in the physiological processes including menstruation, ovulation, pregnancy and labour onset. The reproductive tract in order to the establishment of the normal reproductive functions is able to eliminate the inflammatory state by clearance of leukocytes and tissue debris. Moreover, inflammation can relate to pathophysiology conditions in reproductive system of women such as ovulatory abnormalities, endometriosis, polycystic ovary syndrome and infertility.

The female reproductive disorders can due to excessive activation of inflammatory pathways or its dysregulation. According to review of literature, during ovulation the inflammatory mediators release and play the important roles in this process as well as ovarian follicular dynamics, however, dysregulation of the inflammation can result the PCOS development. The inflammation also can be a main agent in endometriosis-related infertility, so that the leukocyte infiltration and cytokines play significant roles in reproduction process (12). In addition, the cytokines dysregulation can results to adverse consequences of pregnancy. Therefore,

determine the accurate molecular mechanism of inflammatory pathways in the reproductive system of women can be helpful to the therapeutic strategies in the reproductive tract disorders.

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