

Potential Involvement of Iron Overload in the Pathogenesis of Endometriosis-Associated Infertility

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ABSTRACT

Endometriosis is a common gynecological disease affecting women of childbearing age and closely related to infertility. Pelvic iron overload caused by ectopic periodic bleeding is one of the typical pathological features of endometriosis. Endometriosis-related pelvic iron overload may mediate infertility by affecting the microenvironment of gametes and zygotes and causing defective endometrial receptivity. The aim of this study is to review the current literature associating iron overload with endometriosis-associated infertility and to discuss the potential damage of iron overload on the functionality of key cells during the reproductive process, thereby contributing to the development of the infertility.

Keywords: Endometriosis; Infertility; Iron-Overload; Spermatozoa Quality; Ovarian Function; Embryo Development; Endometrial Receptivity

Mini Review

Endometriosis is defined as the appearance of intimal tissue, including both endometrial glands and stroma, outside the uterine, the main symptoms of which includes dysmenorrhea, abnormal menstruation, infertility and sexual intercourse pain. Endometriosis is an estrogen-dependent condition, primarily found in women of childbearing age and is highly correlated with infertility [1]. Epidemiology study revealed that the incidence of endometriosis in women of reproductive age is 10%~15%, whereas the incidence is as high as 30%~50% in infertile patients [2]. Women with endometriosis tend to have a lower monthly fecundity rate compared to normal women [3]. In addition, there is also a link between endometriosis and lower live birth rates [4]. Despite an increasing number of studies on endometriosis-

associated infertility, its etiopathology remains largely unknown. Indeed, a growing body of evidences suggests that mechanisms such as distorted pelvic anatomy, endocrine abnormalities, and altered cell-mediated functions in the endometrium may play a role in the pathogenesis of endometriosis-associated infertility [5].

Iron is an important metal for virtually all living organisms due to its presence in a large number of iron-containing proteins [6]. Excess accumulation of iron within tissues or cells, however, can contribute to toxicity and is associated with the pathogenesis of a variety of diseases such as thalassemia, hemochromatosis, cardiovascular or neurodegenerative diseases [7]. Moreover, in the case of hemorrhage, lysis of iron-rich erythrocytes leads to excess iron, which is directly toxic to target tissues and cells,

causing iron-mediated oxidative damage and inflammation [8]. It was recently suggested that iron-overload could be associated with endometriosis-associated infertility [9]. In this manuscript, presence of excess iron in peritoneal fluid from patients with endometriosis are summarized, emphasizing the origin of iron overload in this disease. Current literature on iron involvement in endometriosis-associated infertility is reviewed and potential damage of iron overload on reproductive processes are reported on the basis of current data collected from both clinical study and biological models.

Presence of Excess Iron in Peritoneal Fluid from Patients with Endometriosis

Iron deposits are typical features of endometrial lesions and increased iron concentration are observed in the pelvic cavity of patients with endometriosis [10-12], and the concentration of iron is related to the severity of disease [11-13]. It has been reported that the concentration of free iron in endometriotic cysts was higher than that in non-endometriotic benign cysts, suggesting that endometriosis lesion may be the source of increased pelvic iron [14]. The periodic shedding and bleeding of lesions by the cyclic variation of estrogen and progesterone accumulates a large number of red blood cells, part of which are swallowed up by macrophages, stored in the pelvic cavity in the form of hemosiderin, and the rest was breaks down and leads to the release of hemoglobin. Digestion of hemoglobin leads to releasing a large amount of free iron, which is suggested to excess the iron-binding ability of ferritin and transferrin [15]. When decompensation occurs, the excess free iron which cannot be completely bound by transferrin and ferritin was released into pelvic fluid, resulting in iron overload in pelvic fluid of patients with endometriosis [8].

Evidences of Adverse Effects of Iron Overload on Reproduction

Pelvic fluid closely participates in the formation of microenvironment for oocyte maturation, fertilization and embryo implantation and development [16]. Langendonck et al. reported that compared to controls, the significantly increased pelvic iron concentration found in patients with endometriosis was only observed in secretory phase, but not in proliferative phase or menstrual period [12]. The secretory phase coincides with the timing of ovulation, fertilization, and implantation and development of early embryo, which means that any adverse alteration occurred during this process, including overload of iron in pelvic cavity, should be detrimental to the reproductive outcome.

Spermatozoa Quality: High dose of iron found in the patients with endometriosis may hinder the process of fertilization. A study by Arumugam et al. investigated the association between iron concentration in peritoneal fluid from patients with endometriosis and acrosome reaction rates of spermatozoa [17]. This study found that an increased iron concentration is responsible to the

decreased acrosome reaction rate, suggesting the increased iron concentrations found in patients with endometriosis may have adverse effects on the fertilization [17]. More recent data suggest that iron could produce biphasic effects on spermatozoa quality. In this study, low concentration of iron prompts spermatozoa motility and DNA integrity whereas high concentration of iron exerts toxic effects [18]. In addition, iron uptake by peritoneal macrophages may prompt the spermiophagy and lead to the subfertility found in patients with endometriosis [19].

Ovarian Function: Endometriosis, especially at the ovarian site has been reported to have detrimental effects on ovarian function. Sonographic, histologic, and biochemical data have shown that patients with endometriosis tend to have diminished ovarian reserve [20,21]. Moreover, this tendency of diminishing ovarian reserve also accompanied by a decrease in oocyte quality [22]. This deleterious effect on ovarian reserve together with the decline in oocyte quality suggest a general decrease in ovarian function in patients with endometriosis, which has been proposed to be associated with the iron-mediated toxic damage to the surrounding follicles, as higher levels of iron was observed in the follicular fluid from follicles growing close to the lesion compared to that in contralateral unaffected ovaries [23]. However, despite these findings, it remains uncertain whether iron overload may exert adverse effect on ovarian function, with one study concluding that iron diffusion from endometriosis lesion into the adjacent ovarian tissue does not markedly affect ovarian function [24].

Embryo Development: Potential effect of iron on preimplantation embryo development has also been reported. Studies using in vitro mouse embryo found that iron at very low concentration was beneficial to elicit an improved blastulation rate and support preimplantation embryo development [25,26]. Zhao et al. recently found that iron is essential for porcine embryonic development, but redundant iron impair the embryonic development [27]. This finding was compatible with the study by Naes et al. who noted that the high non-physiological levels of iron had toxic effect of embryonic development [18]. Nonetheless, it worth noting that still some other studies do not tend to support the idea that iron overload could compromise preimplantation embryo development [23,24].

Endometrium Receptivity: It has long been well accepted that changes in the receptivity of endometriosis affected embryo implantation [16]. Deferred histologic maturation, biochemical disturbances or immune disorders may contribute to dysfunction of endometrium [28]. However, to the best of our knowledge, there is only one study linked the iron overload to the defective endometrium receptivity. In this study, haemosiderin deposition in the endometrial glandular epithelium in the patients with beta-thalassaemia major has been considered to be a potential cause of the defective endometrial receptivity and associated with the infertility of these patients [29].

Summary and Prospect

Although increasing evidences on the association between iron-overload and endometriosis-related infertility are available, thoughtful research is still lacking and some unresolved aspects should be considered. First, conflicting results have been reported for some of the aforementioned observations, especially in the study of association of iron overload with ovarian function and preimplantation embryo development. Second, future study including both randomized controlled clinical trials and biological investigations are necessary to elucidate the precise mechanisms through which iron exert adverse effects on reproductive processes and will facilitate further explorations of the possible benefits of iron chelation therapy to treat endometriosis associated infertility.

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Conflict of Interest

The authors declare no conflict of interest.

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