REVIEW ARTICLE

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# Female Autoimmune Disorders with Infertility: A Narrative Review

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## ABSTRACT

Autoimmunity is a condition in which the immune system cannot recognize the self from non-self-antigens. Autoimmunity is relatively more common in females than males. The process of embryo implantation is considered the most significant restricting factor in female reproduction. The immunological system of the females may affect the success or failure of pregnancy by its effect on extremely important steps from ovulation to implantation processes, thus ensuring the importance of autoimmunity for women in sub-fertility. The association between autoimmunity and female reproduction receives increased attention nowadays. A successful conception is a result of multiple complex interactions between the developed embryo and the receptive uterus and is usually under immune-hormonal control. In certain circumstances, the female ovary can be a target of an autoimmune attack, like some organ-specific or systemic autoimmune disorders subsequently resulting in clinically significant ovarian dysfunction, implantation failure, and sub-fertility. Consequently, the effect of a specific auto-antibody on the etiology of infertility remains unknown. This review focused on auto-antibodies that may affect female fertility.

**Keywords:** Autoimmunity; Sub-fertility; Auto-antibodies; Pregnancy; Implantation Failure.

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## INTRODUCTION

Female reproductive potential tends to be organized by coordinated and simultaneous interactions represented by the Hypothalamic-Pituitary-Ovarian (HPO) axis. The fertility of the female can be affected by multiple organ systems dysfunction, immunological disorders, reproductive tract dysfunctions, neuro-endocrine system disorders, multi-systemic disorders, and any exhausting or severe illness [1, 2].

The immunological system may affect the success or failure of pregnancy in any of the extremely important steps of female reproduction and embryo implantation; starting from the blastocyst hatching out of the zona pellucida (ZP) to the attachment to the uterine epithelium [3].

In the process of implantation, the trophoblastic layer of the embryo and the endometrial layer of the female uterus mutually interact. This occurs when L-selectin on the trophoblast interacts with its ligands in the uterine endometrial layer, which may induce troponin expression in the human endometrial epithelium [4].

For successful implantation to happen, the external trophoblastic layer should interrupt the uterine endometrial epithelium, and expand through the underneath stroma and blood vessels to be involved in maternal blood circulation. Implantation occurs only during (the implantation window); in which the uterine endometrium is highly receptive and usually extends between days 19 and 23 of a 28–day menstrual cycle [5].

The implantation process is the most significant restricting factor in woman reproduction. Pre-implanted embryos can express histo-compatibility antigens (MHC) which theoretically can induce an immune response. Thus, the possibility of maternal immune responses playing a role in the failure of

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implantation is accepted [6, 7].

Autoimmune mechanisms and increased auto-antibodies production can be explained in some causes of female sub-fertility: premature ovarian failure (POF), polycystic ovarian syndrome (PCOS), endometriosis, spontaneous and recurrent pregnancy loss (RPL), repeated implantation failure (RIF) following several assisted reproduction trials, and unexplained infertility [8–10].

POF is defined as absent menstruation in women younger than the age of 40 with elevated gonadotropin levels. It can be seen in about 1%–2% of females in the general population. It is anticipated that POF will be linked to immune system disorders [1]. The predominance of anti-ovarian antibodies (AOA) in POF and unexplained sub-fertility seem comparable. It has been suggested that unexplained sub-fertility might characterize the initial step of POF autoimmunity [11]. Over time, ovarian follicles have been depleted by targeted antibodies from the immune system against ovarian tissue. The high prevalence of anti-ovarian antibodies in between 30 and 60% of affected females may help to explain this [11, 12].

Normo-gonadotropic anovulation (WHO group II) affects about 50% of women, mostly those with PCOS. It affects 5%–20% of all reproductive-age females. An autoimmune mechanism has been implicated in several cases of PCOS. The prevalence of AOA is increased in PCOS together with some organ and non-organ-specific auto-antibodies [13]. Additionally, a link between PCOS, autoimmune oophoritis, and premature ovarian failure (POF) has been established [14, 15]. Tubal sub-fertility contributes to 10%–30% of female causes of infertility. Impaired fertility is attributed to fimbria damage and/or pelvic adhesions that impair the transport of sperm and oocytes. The tubal disease can be caused by multiple factors, which include pelvic and genital tract infections, endometriosis, and previous pelvic surgery. Bacterial infection is not uncommon; *Chlamydia trachomatis* is diagnosed in 20%–40% of cases, followed by *Neisseria gonorrhea* in about 25%–50% of cases [16].

In some instances, the occurrence of tubal damage depends on the activation of autoimmune inflammation. Similar to most infections that occurred elsewhere in the body, Chlamydia infection is associated with strong upregulation of the synthesis of heat shock proteins (HSPs). HSPs are the major antigens and can induce a strong immune response. This induced immune response, which is directed against HSPs can elicit an autoimmune inflammatory reaction that culminates in tubal damage [17].

Endometriosis is a disorder that occurs due to the growth of endometrial tissue elsewhere in the female body organs outside the uterine cavity. It is a common reproductive disorder that usually affects 10%–20% of all reproductive-aged females [18].

It was believed that an alteration in the cell-mediated and antibody-mediated immune systems might contribute to endometriosis-associated impaired fertility [19]. Endometriosis has been given the name autoimmune syndrome due to polyclonal B-cell activation and the production of different auto-antibodies [20]. Around 40% of endometriosis females had increased serum auto-antibodies. They often tend to specifically target uterine endometrium (anti-endometrial antibodies), however, anti-ovarian antibodies (AOA), anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-phospholipid antibodies (APA) are seen in some patients [21]. Unaccounted sub-fertility is a diagnosis given to 10%–20% of infertile. Unexplained sub-fertility is applied when the infertile couples' investigations are completely normal. Immune system dysregulation with enhanced production of auto-antibodies as a possible etiologic candidate for those couples has been suggested [22].

Useful clinical laboratory tests for AOA could be used as indicators of immune system response versus ovarian antigens, however, the identification of some antibodies doesn't suggest a causal association [23, 24]. In addition, auto-immune system activation and the presence of numerous auto-antibodies may be regarded potential causes of in vitro fertilization (IVF) failure [25, 26]. In light of this, the purpose of this review is to examine how female auto-immunity exhibited by various forms of auto-antibodies might impact her reproductive potential and conception rate.

## FEMALE CONCEPTION

For a successful pregnancy to have occurred, every step of the human reproduction process must proceed correctly. A mature egg should be released from one of the two ovaries, the released egg is gathered up by the fallopian tube to be united with the sperm that swim up through the cervical canal to be fertilized at the ampulla of the fallopian tube. The fertilized egg moves down the fallopian tube reaching the uterus, to be implanted within the endometrium of the growing uterus [27]. Any defect in one or more of these steps may result in infertility in women [28]. Female conception and fertility are often influenced by the following variables: age, body mass index (BMI), quality of gametes, and embryo implantation [29]. Although the failure to get a pregnant after 12 months of regular, unprotected intercourse in healthy partners with a female age less than 35 years is considered infertility, the conception rate during the 1st year of marriage is 80% and approaches 90–95% during the second year of marriage [30].

## ANTI-PHOSPHOLIPID ANTIBODIES (APAs)

Anti-phospholipid antibodies are heterogeneous antibodies, present in nearly 2–5% of reproductively-active females [31], 14% of females with recurrent first-trimester abortions [32], and 10% in females with unexplained sub-fertility and recurrent miscarriages [33]. They attack the negatively-charged phospholipids with a phospholipid-binding plasma protein (PLBP) [34]. Although they have been related to different autoimmune diseases of connective tissues; rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), they may exist as an isolated entity called primary anti-phospholipid syndrome (APS) [35].

The presence of APA exhibited a tremendous impact on female fertility potential, reacting with the mother-fetus crossing point in numerous parts, leading to recurrent miscarriages, fetal growth restriction, and fetal death [36].

It has been hypothesized that the link between APA and the probability of conception is more than an immunological malfunction. During spontaneous abortion, placental intravascular or inter-villous clots might be identified histologically as evidence of thrombophilic insult (Figure 1) [37].

Studies found a link between APA and low release of human chorionic gonadotropin (hCG) from placental extracts of a human female, inhibition of trophoblastic cell adhesion molecules, prevention of in vitro trophoblastic migration, invasion, and activation of complement on the trophoblastic surface which induces an inflammatory response [38].


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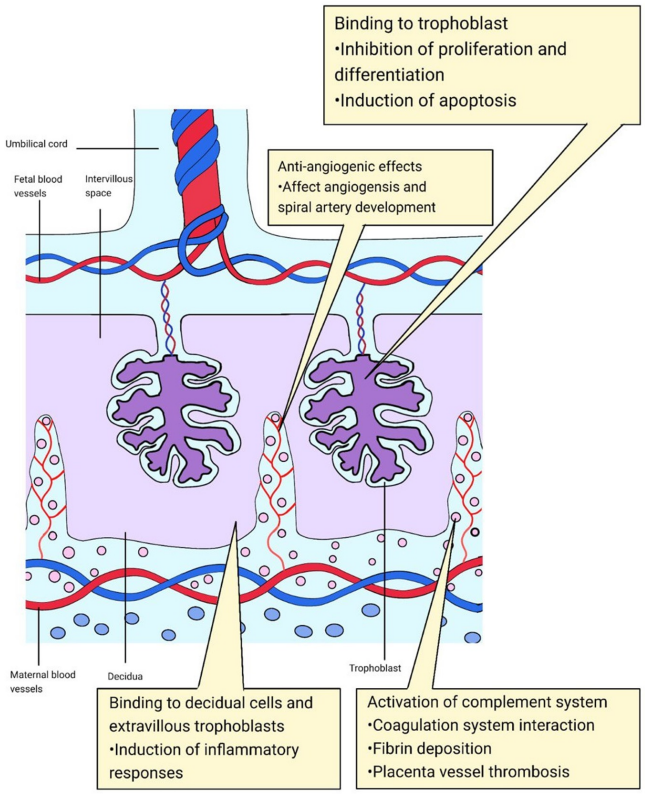


**Figure** 1. Anti-phospholipid antibodies (APAs) affect the endometrium resulting in the failure of implantation. Different mechanisms by which APAs results in implantation failure have been recognized, APAs bind to trophoblast, inhibit its proliferation, differentiation, and induce apoptotic cell death. APAs also bind to decidual cells, stimulate both inflammatory and coagulation system which ends in placental vessels thrombosis due to fibrin deposition. Together, APAs inhibit angiogenesis within uterine endometrium and lead to abnormal development of spiral arteries [39].

## ANTI-THYROID ANTIBODIES (ATAs)

ATA (anti-thyroglobulin and thyroid peroxidase antibodies) have been present in healthy females and are more frequent in those of reproductive (childbearing age) [17]. ATA accounted for 16%–20% of typical pregnant females and ladies undergoing assisted reproductive techniques (ARTs) compared to 20%–24% in females with recurrent pregnancy loss [32] and 45% of pregnant females with hypothyroidism [40].

Curiously, a number of researchers have demonstrated a fundamental role of thyroid autoimmunity among females with endometriosis which further reduces their conception rate [41, 42]. Others demonstrated a connection between this and sub-fertility owing to ovarian causes, such as PCOS [43].

## ANTI-NUCLEAR ANTIBODIES (ANAs)

Anti-nuclear antibodies attack several nuclear and cytoplasmic antigens that are necessary for different cell functions like gene transcription, translation, and cell cycle regulation. The most common autoimmune disorder that is associated with the presence of ANAs is systemic lupus erythematosus (SLE) [44].

The exact role of ANAs in female reproduction is generally undetermined, however, their existence may be related with failed implantation [45]. Successful conception and enhanced implantation have been described as being improved by short-term immune-suppressive medication, however, this medication failed to increase the live birth rate [46].

## ANTI-OVARIAN ANTI-BODIES (AOAs)

These are heterogeneous auto-antibodies target a cluster of antigens, including granulosa cells, theca-interna layer, ooplasm, and ZP proteins [24, 47].

Many correlation exist between the presence of AOA and decreased female fertility, include a reduced response to stimulation medications, decreased fertilization rate, altered normal development of oocytes and embryos, and failure of implantation [24].

## ANTI-SPERM ANTIBODIES (ASAs)

Male seminal fluids contain sperms that contain antigens that are considered foreign antigens by both male and female immune systems. ASAs are identified in 10%–15% of males with sub-fertility and in 15%–20% of females with unexplained sub-fertility. When sperms are exposed to the immune system, ASAs are produced either in the male seminal plasma or the female (serum and cervical mucus) (Figure 2) [48]. Several mechanisms have been proposed to explain why ASAs interfere with the fertility process. They interfere with sperm motility within the woman's cervix, uterus, and tubes, adversely affect fertilization, altering sperm capacitation and acrosome reaction, and finally inhibit early embryonic implantation [36].

## ANTI-FOLLICLE STIMULATING HORMONE (FSH) ANTIBODIES

Researchers had observed a physiological occurrence of antibodies directed at FSH in the serum of healthy non-pregnant

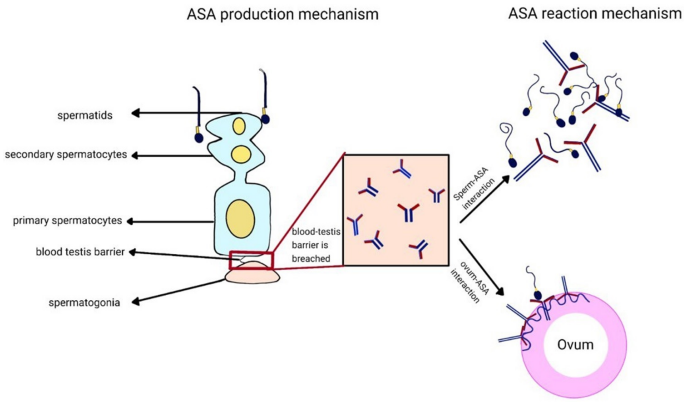


**Figure** 2. Anti-sperm antibodies (ASAs) and conception failure. ASAs are usually produced when blood-testis barrier is interrupted. The produced antibodies are released to circulation. Following intercourse, fertilization failure occurs either due to antibody binding to the sperm head, inhibiting sperm motility by forming sperm agglutinate or binding to the surface of oocyte and preventing sperm binding and penetration of the oocyte [49].



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women [50]. The production of auto-antibodies can be enhanced when an elevated level of auto-antigen is present, such as elevated FSH levels and AOA in cases of premature menopause [13]. Therefore, anti-FSH antibodies primarily tend to be naturally occurring antibodies rather than markers for autoimmunity against the FSH. However, it was observed that anti-FSH antibodies were predominantly produced in women with sub-fertility compared to healthy females [51, 52]. In addition, its presence may reflect ovarian autoimmunity, by causing some impairment in folliculogenesis and altering the function of endogenous FSH by forming immune complexes with FSH and accelerating its clearance [53, 54].

## ANTI-ZONA PELLUCIDA ANTIBODIES (AZAs)

The ZP of the human oocyte has an essential role during the process of conception. The cellular ZP is a glycoprotein moiety that surrounds the oocyte following ovulation and remains till implantation. Three receptors (ZP1, ZP2, ZP3) have been recognized for each ZP layer [11, 55]. It facilitates comparatively species-specific sperm-oocyte recognition and stimulation of the sperm acrosome reaction. ZP protects the early embryo during its passage within female genital tracts before implantation [56, 57]. As ZP demonstrates a strong immunogenicity, it might be a target antigen in ovarian auto-immunity [11, 56]. The AZAs have been distinguished in fertile and infertile women and men because of their high occurrence [8]. AZAs seem to be implicated in the etiology of unexplained infertility (due to their blocking impacts on sperm ZP binding [58–60].

ZP physically separates the germinal and the somatic constituents of the oocyte. Certain antibodies can stop sperm from binding to and penetration of oocytes and may be the cause of failed fertilization either naturally or following assisted reproduction [61].

The incidence of AZAs in females who complained of sub-fertility is 7.5–36.5% [62]. There are some arguments about the exact role of fertilization failure following (ARTs) especially intra cytoplasmic sperm injection (ICSI) as the ZP problems are bypassed by artificial injection of the sperm in the ooplasm [63], However, a higher incidence of 39–91% of ARTs failures is related to AZAs [64]. This was proven by the fact that women whose IVF attempts kept failing had a higher level of AZAs in their blood. (Figure 3) [65, 66].

## CONCLUSION

The association between auto-immunity and female reproduction is receiving more attention these days. A successful conception is a result of multiple complex interactions between the developed embryo and the receptive uterus and is usually under immune-hormonal control. In certain circumstances, the female ovary can be a target of an autoimmune attack, like some organ-specific or systemic autoimmune disorders subsequently resulting in clinically significant ovarian dysfunction, implantation failure, and sub-fertility. Thus, the impact of a particular autoantibody on female infertility pathogenesis is still not well known.

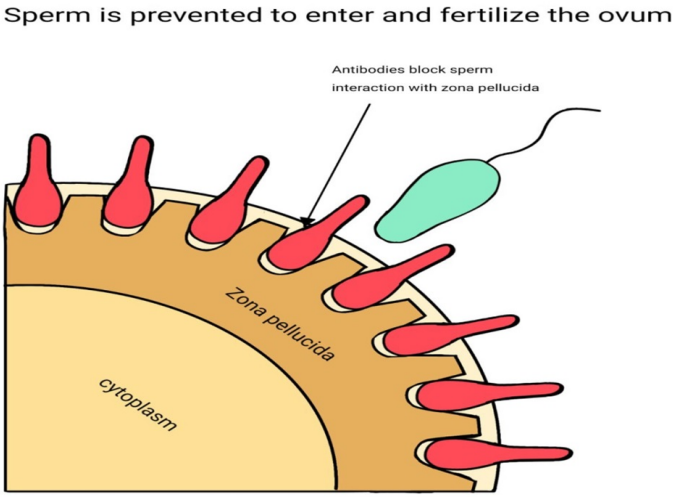


**Figure** 3. Immune response caused by anti-zona pellucida antibodies (AZAs). AZAs bind to ZP (zona pellucida) that surrounds the oocyte, altering ZP structure and composition, preventing sperm bind to and penetrate ZP of the oocyte, and ends with fertilization failure [67].

## ETHICAL DECLARATIONS

### Acknoweldgements

None.

### Ethics Approval and Consent to Participate

Not required.

### Consent for Publication

None.

### Availability of Data and Material

None.

### Competing Interests

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