

The Coronavirus Disease 2019 pandemic as a threat to reproductive health and fetal life

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ABSTRACT

Objective: COVID-19 has spread rapidly across the world since its first appearance in 2019. At the beginning of the pandemic, COVID-19 was thought to affect only the respiratory system, although it has since been realized that it causes numerous transient or permanent problems in various body systems. One of these effects involves the reproductive system.

Several studies have investigated the effects of COVID-19 on the female and male reproductive systems. Embryological life depends on the fertilization of a healthy mature oocyte, a healthy mature sperm, and the continuation of pregnancy. The purpose of this article is to examine the effects of COVID-19 on the male and female reproductive systems and embryological life through a review of the current literature.

Keywords: COVID-19, Embryo, Reproductive Health, Pandemic

INTRODUCTION

The COVID-19 first appeared in China in December 2019 (1). Coronavirus causes various health problems, such as pneumonia, acute respiratory tract problems, kidney damage, myocardial dysfunction, and gastrointestinal diseases (2). Studies have also reported that COVID-19 can cause changes in the hypothalamic-pituitary-gonadal axis (3).

This axis is sensitive to insufficient sleep and to psychological and physical stress. Pulsatile release of hormones is necessary for a regular menstrual cycle, and irregularities in hormone secretion may result in menstrual disorders (4). Studies have investigated the effects of COVID-19 on male reproductive health, sperm parameters, and testicular tissue (5, 6). The regular functioning of the female and male reproductive systems is very important for a healthy embryological life (7).

COVID-19 and Its Effects on the Female Reproductive System

The female menstrual cycle is regulated by the hypothalamic-pituitary-ovarian axis, through the positive and negative feedback of hormones on these structures (8). The changes caused by COVID-19 in the hypothalamic-pituitary-gonadal axis will directly affect the menstrual cycle (3).

COVID-19 affects the target cell by binding to angiotensin-converting enzyme (ACE) 2 via the surface spike protein (9). ACE2 mRNA transcripts have been detected in the ovaries of reproductive age and postmenopausal women (10). ACE2 is a key enzyme in the axis that plays a synergistic role in the balance between Ang II and Ang-(1-7) levels. Ang II induces steroid secretion, facilitates follicle development and oocyte maturation, plays a role in ovulation, and maintains corpus luteum progression (11-15).

In addition, ACE2 mRNA has also been detected in the human and rat uterus (16, 17). Ang II initiates menstruation through spiral artery vasoconstriction (18).

The balance between Ang II and Ang-(1-7) plays a role in the regulation of myometrial activity and endometrial regeneration (16, 19). The normal function of Ang II in the endometrium is also essential for regular menstrual cycles (20). For all these reasons, COVID-19 affects the uterus, ovary, and oocyte and disrupts the functioning of the female reproductive system.

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COVID-19 and Its Effects on the Male Reproductive System

The male reproductive system is a complicated system consisting of the testicles, penis, duct systems, and accessory glands. The main task of the testicles is the production of sperm and the release of the hormone androgen. Sperm is stored and matured in the ducts. The production of non-sperm ejaculate substances occurs in the accessory glands. The principle factor in the formation of good-quality spermatozoa is proper spermatogenesis. Spermatogenesis is defined as the process of maturation of diploid male germ cells by meiosis and their differentiation into haploid male gamete cells. Spermatogenesis starts at puberty, once sperm maturation begins, and continues to the end of life. Four mature sperm are formed from each primary spermatocyte. A disruption in this system causes oligospermia, azoospermia, asthenospermia, and cryptorchidism, events that play a major role in male infertility (21-23).

ACE2 is expressed in the testes and epididymis, especially in Leydig cells, Sertoli cells, and spermatogonia (24). COVID-19 causes high fever and a possible cytokine storm, symptoms that affect male fertility. An increase in testicular temperature causes oxidative stress and sperm DNA fragmentation by increasing levels of reactive oxygen species (25). Postmortem macroscopic and microscopic analyses of the testes of 12 patients who died from COVID-19 in one study revealed damage in 11 cases, and that the mean Leydig cell count was significantly lower compared to that of a control group (26). In a recent study of 119 male patients of reproductive age, semen analysis of male patients diagnosed with COVID-19 revealed decreased sperm motility, sperm morphological disorders, and loss of libido. In addition, serum luteinizing hormone (LH) levels were significantly higher in the COVID-19 group compared to the control group, although no significant change was observed in serum testosterone levels. The authors concluded that gonadal functions were affected by the higher serum LH level and lower serum testosterone/LH ratio compared to the control group (27). Studies on this subject are still ongoing, and it is clear that the male reproductive system is under threat by COVID-19.

Effects of COVID-19 in the Embryonic and Fetal Period

Fertilization is a complex molecular chain of events in which oocyte and sperm nuclei and cytoplasmic components come together to form a zygote (28, 29). Fertilization begins with sperm capacitation, attachment of sperm to the zona pellucida, induction of the acrosome reaction, crossing of the perivitelline space, and fusion with the oolemma. The subsequent process involves the completion of the second meiotic division in the oocyte, the expulsion of the second polar body, the activation of the oocyte, the decondensation of the sperm nucleus and maternal chromosomes, and finally the cytoplasmic migration of the pronuclei. Processes including receptor-ligand interaction, ion-channel modulations, membrane fusion, and proteolysis occur during fertilization (28-30).

After fertilization, the oocyte becomes a blastocyst and adheres to the surface of the endometrium. The blastocyst implants into the endometrium on the seventh day. Implantation is followed by the formation of the placenta, which will support the embryo until the end of pregnancy (31, 32). The embryonic period, which is particularly sensitive to external factors (between the third and eighth weeks) involves the formation of numerous tissues and organ systems. The embryonic period is followed by the fetal period, which will continue until birth.

ACE2 is expressed in the placenta, placental villi, syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of primary and secondary villi. It is also expressed in the maternal stroma, intravascular trophoblast, and decidual cells. ACE2 is also found in the arterial and venous endothelium and the smooth muscle of the umbilical cord (33). ACE2 reaches its highest levels during early pregnancy, and is expressed in the primary and secondary decidual region and luminal and glandular epithelial cells. ACE2 has been observed in the placenta and amniotic and yolk sac epithelium during late pregnancy (34-36). During pregnancy, Ang2, ACE2, and Ang-(1-7) are principally involved in regulating blood pressure and fetal development. They also interact to maintain normal uterine physiology (37).

Ang-(1-7) and ACE2 are also thought to act as a local autocrine/paracrine regulator in the early (angiogenesis, apoptosis and growth) and late (uteroplacental blood flow) events of pregnancy (35). ACE2 controls the blood pressure balance in the pregnant woman (34). One previous study observed suppressed plasma Ang-(1-7) levels in pre-eclamptic women compared with normal pregnancies (38). Finally, low levels of ACE2 and Ang-(1-7) in the placenta have been associated with intrauterine growth retardation (36, 39).

RESULTS

COVID-19 exhibits its effect by binding to ACE receptors. It affects numerous body systems, such as the lungs, heart, kidneys, nervous system, and skin. The effect mechanism of the virus and its acute and chronic phase effects on different organs are still the subject of investigation.

Studies of male infertility after COVID-19 have shown that the disease exerts a deleterious effect on the male reproductive system. COVID-19 can also impair female reproductive functions, causing infertility, menstrual irregularity, and fetal distress. It has also been shown to infect the ovary, uterus, vagina, and placenta.

CONCLUSION

We therefore recommend that couples planning pregnancies be protected against COVID-19 infection. Close monitoring of the fetus and pregnancy is also highly important.

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