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Review Article

Paternity Test

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Abstract

The article presents modern data on the properties of seminal fluid creating the primary conditions for the development of a healthy pregnancy. Actual pathophysiological theories based on the study of cell lines, proving the direct role of paternal material in the formation of an allogeneic environment, are considered. Literature data on the influence of dosing and quality of the partner's biological material are given.

The subject of fertility is the interaction between male seminal fluid and female tissues during sexual intercourse, the effect on fertility, pregnancy and the health of the child. It has been established that the biological contribution of the father to pregnancy and his ability to influence the reproductive outcome goes beyond the simple provision of male mi gametes at conception. The key questions of the study are: whether the seminal fluid delivered during sexual intercourse affects gene expression and immune responses to the endometrium; the completeness of the identity of the molecular agents by which seminal plasma and sperm interact with the cells of the cervix and endometrium; the physiological significance of semen priming in women and its potential contribution to unexplained infertility, embryonic development and pregnancy outcome; clinical factors, lifestyle and environmental environments that affect seminal fluid composition and signaling function. Ultimately, a better understanding of the role of seminal fluid in shaping reproductive success could provide new avenues for diagnosing and treating infertility in couples and improve recommendations for couples planning a pregnancy or in assisted reproduction settings.

Keywords: DNA-paternity test; paternity; paternity testing; fatherhood; moral interest; genetic relatedness

The Paternity Test

The matters encountered in this topic converge in one particular matter: alleged paternity. What does it mean? This means that you cannot debut in a sexual sense with a woman whom you do not understand asthe mother of your children and the person that you wish to take care of as a biological being. This is the union of many disciplines: religious, psychological, moral and ethical, medical, molecular biological changes necessary for conception.

Here we conduct research on changes in the femalegenital area with the onset of sexual activity. They areunited by one thing: the readiness of the female genital organs for pregnancy.

Probably the development of this topic can lead to global economic decisions, such as: reducing the cost of assisted reproductive technologies, hormonal contraception and, consequently, increasing the satisfaction of the population with other treatment anddiagnostic options, the improvement of demographic policy is inevitable, the reduction of the stress factor as a catalyst for morbidity, the stabilization of the moral and legal component of the institution of the family and reproduction.

Introduction

Currently, there is a tendency to reduce the birth rate, the percentage of infertile couples is increasing, despite the development of reproductive medicine and an active state demographic policy. Modern public and private clinics offer their services for pregnancy planning, infertility treatment, including through assisted reproductive technologies [2,3]. To date, there are more than 200 clinics in Russia that provide services using assisted reproductive technologies in the treatment of infertility. At the same time, approximately 60% of the total number of IVF cycles are carried out in private clinics, 40% in state medical institutions. The indicator of the availability of assisted reproductive technologies is the number of ART cycles performed per 1 million population. Onaverage, 1500 IVF cycles per

1 million population areperformed in Europe. In Denmark, this figure is 3000 cycles per 1 million population, in the Czech Republic

- 2500, a number of European countries performmore than 2000 cycles, resulting in 3-6% of the total number of pregnancies. In Denmark, with the help ofART, 5% of the total number of newborns are born. Then fewer cycles, the lower the result. According toRosstat, in 2016 the population of Russia was 146,804.4 thousand people, and the number of IVF cycles is only 839 per 1 million people. This means that the population's need for this type of service is not actually fully satisfied. Therefore, the issues of fertilization associated with maternal tolerance to thefetal antigen become relevant [1].

The purpose of the study: systematization of scientificdata on the frequency and pathogenetic mechanisms of interaction of seminal fluid and female organs to create conditions for a successful pregnancy.

Theory of "maternal modulation"

The transmission of spermatozoa through the male reproductive tract, the ascent along the female reproductive tract to the waiting oocyte is the primary role of seminal fluid. However, studies conducted back in the 1920s suggested a secondary role for seminal fluid in the reproductive process. Pioneers inthe field of reproductive biology, Ryuzo Yanagimachiand M.K. Chang, in the study of the seminal fluid of the golden hamster, stated, in addition to the destruction of bacteria and spermatozoa, about otherfunctions of leukocytes in the uterus under the influence of seminal fluid [4,5]. In parallel, the immunological paradox of pregnancy has been a source of discussion for decades: how does an allogeneic fetus survive in an immunologically hostilematernal environment during pregnancy?

In the 1950s, Nobel Prize winner Sir Peter Medawar put forward a number of hypotheses designed to explain the survival of aphetus in an immunologicallyincompatible host. One of Medawar's hypothesessuggested "immunological lethargy or inertia of the mother," but this theory suggests the mother's vulnerability to infections or autoimmunity.

Although Medawar's hypothesis of the separation of the fetus and mother may be predominant to explainthe reasons for fetal survival, it becomes clear that themother has no immunological idleness, and the existence of a so-called maternal modulation (or tolerance) of the immune system, which helps in the survival of the conceptus. The question remains, howis maternal immune tolerance to conceptual antigensestablished in order to remain active during embryo implantation? One possible mechanism for establishing maternal tolerance to implantation may include helping the father at conception, namely the potential for paternal-maternal seminal fluid-mediated communication to optimize pregnancy success [15,17,18].

The seminal fluid (cell-free fraction of sperm) derivedfrom the male extra glands is rich in simple sugars, buffers, antioxidants, hormones, and proteins of unknown function that are thought to be present to facilitate sperm survival and transport through the female reproductive tract. Research has now begun highlighting the importance of some of these seminal fluid proteins as potential mediators of paternal- maternal communication provided during fertilization.

Postcoital inflammatory response

Observations dating back to the 1960s demonstratedthe acute ability of sperm to modulate the cellular environment of the female reproductive tract of mice,humans, cattle, pigs, horses and sheep. Afterinsemination in rodents for the next 72 hours, there isa sharp influx of leukocytes. This influx of white bloodcells is accompanied by an increase in the expression of inflammatory mediators in the endometrium, including the C-C motif ligand (CCL) 2, CCL3, CCL5,and colony-stimulating factor (CSF) 2. Other studies in rodents have shown that seminal fluid is an active component of the ejaculate, causing these changes in the mother's tissues. At the same time, it was proved that the active substance is the transforming growth factor beta (TGFβ), originating from seminalvesicles in the seminal fluid, responsible for the increased expression of mediators of endometrial inflammation and, ultimately, for inflammation after insemination.

Similarly, a postcoital inflammatory reaction in the cervix after contact with sperm was observed in people where there is no inflammation after sexual intercourse, protected by condoms. In parallel with mice, TGFβ derived from seminal fluid is responsible for inducing increased expression of inflammatory mediators' interleukin-6 and CSF-2 in human cervical epithelial cells [6,22].

One recent study was aimed at evaluating the effect of seminal fluid supplementation (or TGFβ) during artificial insemination on the incidence of pregnancy in cattle. Despite the statistical inadequacy, the studysuggested that artificial insemination with the addition of seminal fluid or TGFβ could improve pregnancy rates, especially in bad herds. The infusion of seminal fluid into the pig's uterus causes significant cellular inflammation 36 hours after the infusion, which still manifested itself after 8 days, which is significantly different from the acute inflammation observed in other species. The same research team described a significant increase in the number of complete and viable embryos collected from sows after the introduction of sexual fluid. Horses and sheep also experienced increased acute endometrial inflammation after applying seminal fluid or semen [6].

The question remains, what is the significance of this inflammatory reaction caused by seminal fluid after fertilization? The proposed role would be to proactively clear sexually transmitted pathogens or non-viable sperm. It is interesting to note that many inflammatory mediators activated in the endometrium or fallopian tube by seminal fluid are also embryo trophic in nature, specifically CSF-2, the leukemia inhibition factor, and IL-6. The temporal expression of these so-called embryokines can be partially regulated by the effect of seminal fluid on the coordinated development of the embryo with fertilization {7,8,9,10].

An even more intriguing significance of this inflammatory event is associated with the induction of maternal immune modulation necessary for successful pregnancy in viviparous species [19,20].

Immunomodulatory ability of sperm As mentioned earlier, Medawar hypothesized the need to suppress or modulate maternal immunity to facilitate the survival of the allogeneic conceptus.

There is a possibility that this immune modulation will be controlled by ovarian or placental hormones or by the conceptus itself. However, none of these scenarios allow for potential maternal immune adaptation to be specific to the paternal antigens expressed by the conceptus and/or exist during embryo implantation (at least in rodents and humans). A curious possibility remains that insemination may act as the first "targeting" event of the maternal immune system to the paternal antigen potentially expressed by the conceptus. It is assumed that the main mechanisms of immune tolerance necessary for pregnancy are clonal deletion, anergy and clonal immunity of alloreactive T lymphocytes.

These mechanisms should prevent the cytotoxic effects of certain alloreactive lymphocytes in peripheral circulation during pregnancy. In many mucosal tissues, the predominance of the immune response with a biased Th2 is associated with a state of functional tolerance, and this is likely to also occur during pregnancy. Seminal fluid has been shown to enhance

changes in the immune function of T cells, B cells, NK cells, and macrophages in mice, cattle, and humans. It is evident that exposure to semen, and indeed seminal fluid, causes acute hypertrophy of the spleen and lymph nodes draining the uterus in mice. The quality of any immune response, including the phenotypes of effector T cells and the state of the cytokine profile, is determined during exposure to the primary antigen. and depends on the state of activation of antigen-presenting cells. It has been suggested that the lymphocyte activation site is of great importance for the functionality of downstream effector cells.

However, most of the evidence supports the idea that antigen-presenting cells play a fundamental role in lymphocyte programming and that local cytokine expression is a key factor in regulating the behavior of antigen-presenting cells. Could it be that activating specific cells in the draining lymph nodes of the reproductive tract could help "fuel" the maternal immune system with the paternal antigen?

It is believed that the frequency of exposure to the antigen in combination with the dose contributes to the formation of tolerance of the mucous membranes. A single exposure to high doses or small repeated doses of the antigen has been shown to be most beneficial for the development of tolerance, a paradigm consistent with the effect on the uterine epithelium of seminal antigens during sexual intercourse. Although studies have shown that lymphocyte populations become anergic to paternal antigens during pregnancy, one study demonstrated that this hyporeactivity is achieved in a father-specific way. Robertson et al. demonstrated that tumor growth in female mice can be induced by interbreeding with males with a main histocompatibility complex (MHC) haplotype coinciding with the haplotype of an injected tumor cell line.

The use of uterine ligation before mating in this model also excluded the possibility that the conceptus was responsible for the observed systemic changes in immune tolerance. Tumor growth in virgin mice or mice paired with the incomparable MHC haplotype with the tumor was suppressed. This is direct evidence that sperm exposure can cause systemic immune tolerance to potential paternal antigens.

Seminal fluid is rich in immunodeficient cytokines, such as TGFβ and PGE2, which can lead to a change in the cytokine profile of the T cell population in the direction of Th2, which is considered beneficial for pregnancy success. In a landmark experiment, the depletion of positive T-regulatory cells fork head box P3 (FOXP3) led to the complete failure of pregnancy. TGFβ has been demonstrated to activate FOXP3- positive T-regulatory cells in vitro. Interestingly, our own research has demonstrated that exposure to seminal fluid plays a significant role in the generation and attraction of FOXP3 cells in female reproductive tissues [12,13,14].

Resume

Seminal fluid is considered only as a means of sperm transfer for fertilization of the oocyte. Itis now clear that a more complex function affects the female reproductive physiology. It is noteworthy that seminal fluid contains soluble signaling agents originating from exosomes that interact with the female reproductive tract, triggering an immune response, which has implications for fertility and pregnancy outcome. Experiments in rodent models demonstrate the key role of seminal fluid in ensuring reliable embryo implantation and optimal development. Experiments in rodent models demonstrate the key role of seminal fluid in ensuring reliable embryo implantation and optimal development. Placenta. In particular, seminal fluid contributes to the attraction of leukocytes and the formation of regulatory T-cells, which facilitate the implantation of the embryo, suppressing inflammation, contributing to the adaptation of the vessels of the uterus and maintaining tolerance to fetal antigens. There is evidence of comparable effects in women, when seminal fluid causes an adaptive immune response in the tissues of the cervix after contact during sexual intercourse, and spermatozoa entering the upper tract can directly affect the endometrium. These biological responses may be of clinical importance, explaining why sexual intercourse in IVF cycles increases the likelihood of pregnancy, inflammatory pregnancy disorders are more common in women who are conceived after limited exposure to the intended father's seminal fluid, and the incidence of preeclampsia increases after the use of donor oocytes or donor sperm, when there was no previous contact with the alloantigen’s of the conceptual cells. it is important to identify the mechanisms by which seminal fluid interacts with female reproductive tissues to provide facts that can aid in the preliminary planning and treatment of infertility. Normal spermatozoa are not a guarantee of fertility, and cytokine signaling agents may, at least in part, constitute the additional competence needed for seminal fluid. Significant research has focused on identifying additional biomarkers of male fertility in seminal plasma, with several studies having proven them., whether there are differences in their absolute and relative levels between fertile men and men classified as infertile based on the parameters of the World Voluntary Association. Some seminal cytokines can reduce sperm quality and function, such as CXCL8, which is usually elevated with a bacterial or viral infection, is present at elevated levels in the seminal fluid of men with leukocytospermia, and has been shown to have a negative effect on sperm motility. In men with leukocytospermia, it is also possible decreased TGFB in seminal fluid, although the link between this and the insufficient fertility associated with leukocytospermia remains unclear. Several studies have failed to identify significant relationships between cytokines and sperm parameters, suggesting that different regulatory pathways are at the heart of their synthesis. A recent study comparing the content of cytokines in the seminal plasma of healthy people in the control group and men in sub fertile pairs, despite the normal parameters of spermatozoa, including the partners of women with repeated miscarriage, revealed a decrease in IL1B levels and an increase in inhibitory IFNG in seminal plasm a. Given the lack of communication with sperm parameters, this experimental plan seems more fruitful, and similar studies to study the relationship between the composition of the seminal fluid and preeclampsia or other gestational disorders seem justified. Similar studies will require the establishment of adequate normal ranges for fertile men, as well as a set of seminal fluid of more than one sample. The relative content of TGFB and other cytokines in seminal plasma varies significantly from person to person, and also fluctuates depending on the individual over time beyond the control of biological factors and factors. environments. Whether these differences in the stimulating capacity of seminal fluid are physiologically significant or have important implications for the context and transmission of signals between men and women is currently unknown.

The issues covered in this topic are combined into one common problem: alleged paternity. The topic of the so-called recognition of the ideal partnership has been covered many times. This is confirmed by the biological and immunochemical results of many studies that have shown the need for histocompatibility of partners for a healthy pregnancy and childbirth.

Our study involves evidence and behavioral reproduction. It's a combination of many disciplines: religious, psychological, moral and ethical, medical and health problems, fundamental biological spheres, including molecular biological changes in the body of a girl prepared for conception.

Probably, the development of this topic can lead to global economic solutions, such as: reducing the cost of assisted reproductive technologies,

hormonal contraception, and possibly increasing the satisfaction of the population with other therapeutic and diagnostic capabilities. In addition, the improvement of demographic policy, the reduction of the stress factor as a catalyst for morbidity, the stabilization of the moral and legal component of the institution of the family and reproduction are inevitable.

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