SEMINAL PLASMA - A SIMPLE ADD-ON, TO INCREASE THE LIKELIHOOD OF CONCEPTION

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ABSTRACT:

Although IVF/ICSI methods aid in helping couples conceive, there is no guarantee of implantation or clinical pregnancy. Many factors influence IVF success rates, including age and the cause of infertility. Overall, first-time IVF success rates for most intended parents' range between 25 and 30%. Lack of immunologic tolerance in early pregnancy leads to implantation failure, miscarriage, hypertension, and fetal growth limitation. Seminal plasma has the capacity to influence the mother immune system in order for the semi-allogeneic fetus to be accepted. (30). Additionally, it can facilitate embryo growth, increase the uterus receptivity. It is speculated that seminal plasma exposure has an impact on the health of the progeny. (16) In this article the use of seminal plasma as a treatment strategy to accelerate the development of embryo competency and rate of implantation, increase endometrial receptivity, and establish maternal immune tolerance has been discussed

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Keywords: Infertility, Seminal Plasma, Insemination, Implantation, Pregnancy,

OBJECTIVES:

The purpose of this study was to conduct a systematic evaluation and summary of the evidence on the use of seminal plasma (SP) in women undergoing IVF or ICSI to improve cycle outcomes.

METHOD:

SP exposure before embryo transfer by sexual interaction or intra-vaginal, intra-cervical, or intrauterine injection to the women of reproductive age with any reason of infertility who were having IVF or ICSI cycles were included in this review. The clinical pregnancy rate and the live birth or ongoing pregnancy rate attained in the index IVF cycle using seminal plasma insemination were reviewed in this article.

INTRODUCTION:

Human infertility is probably more prevalent than previously thought. After a period of regular, unprotected sexual activity of 1 year, if a couple facing difficulty in conceiving, it is known as infertility. In short failure to become pregnant. 15% of infertile couples experience 'unexplained infertility" and the remaining all 85% of infertile couples have an identifiable cause. Lifestyle and environment variables might be cause of increased infertility rate (Definition and prevalence of subfertility and infertility, may 2005).

In vitro fertilization has undergone numerous breakthroughs in recent years, but the success rates, clinical pregnancy and ultimately live delivery rates, remain relatively underwhelmingly low. The implantation rate, which is still low despite the transfer of high-quality embryos, is one of the multiple factors influencing the success of IVF. Poor uterine receptivity is one of the major reasons why implantation failure occurs (10). To prevent an immunological attack on the developing conceptus, a state of maternal immune tolerance is needed at implantation.

Traditionally, spermatozoa have only been considered to be transported in and fed on by seminal plasma (SP). In spite of the fact that seminal plasma has traditionally been thought of as nothing more than a vehicle for transporting sperm and providing a nutrient-rich fluid environment for them during this genetic material exchange, recent research has revealed a complex medium for communication between males and females. New research suggests, seminal plasma as a technique to increase early pregnancy success by regulating the cellular and molecular changes in the maternal environment necessary to support healthy, successful pregnancy outcomes (28). Seminal plasma (SP) is a complex substance composed of energy substrates for sperm, antioxidant agents, minerals, salts, and various protein moieties. It is expelled from the prostate gland and seminal vesicles, and it contains high levels of signalling substances like transforming growth factor-beta (TGF-), prostaglandins, interleukin-8 (IL-8), and interferon-gamma (IFN-), as well as bacterial polysaccharide (Robertson, 2005). It is also rich in estrogen, testosterone, and prostaglandins. The first time the female immune system is exposed to paternal antigens

that will later be encountered in the developing conceptus occurs during coitus, when seminal fluid is exposed. Seminal fluid probably interacts with the endometrial and cervical tissues. Low seminal fluid exposure has been related to human gestational problems like pre-eclampsia and foetal growth restrictions, which may have certain beneficial impacts on health. Amazingly, it seems that seminal fluid may influence the development of offspring and mediate disease transmission (4)

When seminal fluid is administered to the female reproductive tract during coitus, female reproductive tissues are first exposed to paternal antigens (Robertson, 2005). This shows that the female immune system can recognize and respond to male antigens in seminal fluid, and that seminal fluid may be involved in initiating the immunological response in preparation for a subsequent pregnancy (5). This hypothesis and the published literature support the concept that the seminal fluid plays an important role in orchestrating the changes in female reproductive tract (uterine or endometrium) that establish maternal immune tolerance. The absence of seminal plasma in the in vitro setting may contribute to higher rates of implantation failure and a decrease in embryo quality, according to data from IVF and associated reproductive technologies (6)

IMPORTANCE OF SEMINAL PLASMA:

We assumed that the fertility is determined not only by spermatozoa but also by the Seminal Plasma (SP). One may argue that this is what was proven when IVF was developed, with the emphasis on spermatozoa and the eradication of the native SP. IVF and intracytoplasmic sperm injection (ICSI) of ejaculated or epididymal spermatozoa, or even elongated spermatids that have never matured, have resulted in fertilization, embryo development, pregnancies, and births in humans (7) and animals (8), implying that the SP is not required. However, human fertility (as measured by infant deliveries) following embryo transfer of IVF/ICSI "fertilized" oocytes has remained stable at roughly 30% since 1994. Mammals' inflammatory responses may help to remove microorganisms from the reproductive tract or to remodel the tissue of the reproductive tract following fertilization in order to prepare for implantation (9) SP may potentially affect pregnancy, implantation, and fertilization by modifying the local immunity of the female reproductive tract, according to studies in rodents and pigs (26). The expression of active molecules in the female genital tract may change due to regulatory components in SP, which may have molecular, biological, and cellular changes in the uterus through particular pathways. Recent research has revealed that SP infusion alters the expression of immune-related genes in the peri-ovulating pigs' reproductive tract, indicating extremely early communication during mating/AI (27)

ROLE OF SEMINAL FLUID IN FERTILIZATION:

Seminal plasma was once thought of as a passive medium that carried sperm to the female reproductive system; but, over time, it started to be given credit for a more significant functional role in successful reproduction. Human seminal plasma is a rich source of antioxidants that may contribute to the prediction of sperm fertilization potentials. Seminal plasma components are in charge of controlling capacitation, survival of gametes in the female reproductive tract, and, last but not least, conditioning the female immune system to increase tolerance to allogenic embryos in addition to providing nutrition to sperm properly and protecting it from the harmful vaginal environment (10*)* The variety of seminal plasma components, especially the high concentration of seminal plasma proteins, shows that seminal plasma serves more purposes than just nourishing and protecting sperm during the normal fertilization processes that take place in females(9). The ejaculate instantly coagulates in the partner's vagina following coitus. Semenogelin and fibronectin, the two most prevalent seminal plasma proteins, combine to produce a web of cross-linked fibers that immobilizes the sperm by causing it to gel. After sexual activity, this cervical os clot gradually dissolves over the period of roughly an hour. In order to progressively release the sperm, seminal plasma proteolytic enzymes cleave the network of semenogelin and fibronectin polymers. Prostate-specific antigen (PSA) is the principal protease engaged in the process, which is assisted by metalloproteinases, primarily the MMP-9 and MMP-2 members of the gelatinase group. The idea holds that immunological tolerance development during fertilization and pregnancy is influenced by protein-sugar interactions linked to the existence of certain glycoproteins in the human reproductive system. Glycoproteins' sugar moieties are thought to control immunological responses and semen components are crucial for the growth of this kind of tolerance. The unique glycosylation profile of the proteins is thought to be responsible for the immunosuppressive impact. When glycans in the male reproductive system were examined, it was discovered that many oligosaccharide forms that are absent from serum glycoproteins in healthy humans were present (9). Proteins of the seminal plasma are relevant for sperm function particularly for their interactions with the various environments of the tubular genital tract. proteins act as signals for the immune system of the female reproductive tract (11)

Both immature or dysfunctional spermatozoa and leukocytes are intracellular sources of ROS in semen. If ignored, ROS can cause DNA, lipids, and protein damage in spermatozoa. Due to the high concentration of polyunsaturated fatty acids (PUFAs) in their plasma membrane and the insufficient inner antioxidant system, spermatozoa are particularly at risk for oxidative damage. (17,18) The spermatozoa are safeguarded by SP's powerful antioxidant defense mechanism, nevertheless, both during ejaculation and the beginning of their passage through the female reproductive tract. Inflammatory molecules from the testes, such as macrophages, somatic cells (Leydig and Sertoli cells), spermatogonia, leukocytes, and mesenchymal cells, are abundant in SP (19) Small proteins called cytokines are essential for cell signalling and play a crucial part in regulating fertilization. Interleukins (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-18), tumour necrosis factor-alpha (TNFα), tumour necrosis factor receptor 1 and 2 (TNFR1/2), interferon-gamma (IFN-γ), and granulocyte colony-stimulating factor (G-CSF), have all been found to accumulate in the SP which is responsible for fertilization (20)

ROLE OF SEMINAL PLASMA IN FEMALE REPRODUCTIVE TRACT:

A postcoital leucocytic reaction is immediately induced when semen is deposited in the vagina. The uterine epithelium is induced to produce proinflammatory cytokines during the process, primarily IL-6, IL-1, IL-1, and GM-CSF. The ejaculate contains a lot of immunomodulatory substances that are hypothesized to cause this reaction. As a result, immediately following coitus, monocytes, dendritic cells (DCs), and lymphocytes infiltrate the cervix in large numbers. DCs in particular appear to be at the epicentre of the immune response connected to conception and early pregnancy. (10)

In a 2012 study, Sharkey et al. used a biopsy to analyse the human cervix after unprotected vaginal coitus, vaginal coitus with the use of a condom, or no coitus at all. They proved that the introduction of SP during sexual activity (without the use of a condom) causes the release of pro-inflammatory cytokines and chemokines as well as a significant influx of macrophages, dendritic cells, and memory T cells. The seminal fluid-induced leucocyte and cytokine milieu in the cervix appears capable of starting changes in the female immune response that support conception.

ROLE OF SEMINAL PLASMA IN ENDOMETRIUM RECEPTIVITY:

Research has demonstrated that SP's function extends to the uterus in addition to the cervix. A healthy uterine environment is completely necessary for uterine receptivity to promote embryonic implantation. (21). Seminal plasma is thought to flow up through the cervix via sub endometrial and myometrium peristaltic waves (Leyendecker et al., 1996; Kunz et al., 1997). where it affects endometrial receptivity. In vitro effects of SP on stromal fibroblasts and endometrial epithelial cells were examined in a study by Chen et al. This proved that stromal fibroblasts and endometrial epithelial cells expression of genes and secreted proteins linked to cellular migration, proliferation, and viability when exposed to SP. By attracting leukocytes, particularly macrophages, seminal fluid aids in the regulation of endometrial tissue remodelling and uterine receptivity. The inhibitory components that might function as a barrier to an attaching embryo are lost as a result of these being further mediated by adhesion ligands like integrins, selectins, cadherins, and immunoglobulins. (2) Hidetaka Himura et al suggests that seminal plasma participates in the recruitment of $CD56^{bright}$ NK cells into endometrium. On the other studies using mice have shown that transforming growth factor (TGF)-b in seminal fluid drives the preponderance of T helper-2 (Th2) cells and causes uterine epithelial cells to release a variety of cytokines.7 These findings suggested that exposure of seminal fluid contributed to the uterine endometrium's immunological alterations. (24)

ROLE OF SEMINAL FLUID IN IMPLANTATION:

In order to support implantation and placental development, the female's response to seminal fluid stimulates the generation of Treg cells, which shield the conceptus from inflammatory damage. Additionally, oviduct and endometrium molecular and cellular changes induced by seminal fluid directly enhance embryo development and implantation competence (31). Paternal antigens, such as soluble human leukocyte antigens-G and sHLA class-I, can be detected in SP, influencing early embryo growth and implantation (16). Seminal factors are transmitted during insemination and act in the female reproductive tract to promote and "condition" the immune system of the female to tolerate the conceptus, and orchestrate molecular and cellular changes in the endometrium to aid in embryo development and implantation (15). Additionally, semen has been shown to facilitate embryo implantation when it has already been exposed to the female reproductive system (8-11).

ROLE OF SEMINAL FLUID IN CLINICAL PREGNANCY:

It contains chemokines, cytokines, and prostaglandins that can affect inflammation, tolerance, and angiogenesis to support pregnancy (16). One of the most significant components of seminal plasma that has been associated with controlling the maternal immune response is TGF- β. It is a potent immune modifying component that promotes active immunological tolerance. A putative involvement for growth factors found in seminal plasma in the endometrial decidualization and establishment of the pregnancy is supported by the fact that different growth factor receptors are expressed in the vascularized tissues of the female reproductive tract (Ejskjaer et al., 2005).

For successful implantation and ideal foetal and placental development during the pre- and peri-implantation stage of early pregnancy, the uterine cellular and molecular context is essential. Changes to this environment have an impact on infant health and viability as well as the success of pregnancy. The available evidence shows that seminal plasma serves as more than just a vehicle for sperm; it also regulates the environment of the reproductive tract, ensuring the best possible conditions for the development of the embryo and the long-term health of the progeny (1). Early or late pregnancy issues, such as implantation failure, miscarriage, hypertension, and fetal growth limitation, can be caused by a mother's lack of immunologic tolerance toward her child and in the placentation. The maternal immune system may be influenced by seminal plasma to accept the semi-allogeneic fetus.

Insemination of Seminal Plasma causes the transmission of seminal factors that act to promote sperm survival in the female reproductive tract, "condition" the immune system of the female to tolerate the conceptus, and orchestrate molecular and cellular changes in the endometrium to facilitate embryo development and implantation. These processes begin when signaling compounds, such as transforming growth factor-, along with other cytokines and prostaglandins secreted by the seminal vesicle and prostate glands, interact with epithelial cells in the cervix and uterus to activate cytokine synthesis and to cause cellular and molecular changes resembling a classical inflammatory cascade. The result is increased endometrial receptivity to the implantation of the embryo due to the recruitment and activation of macrophages, granulocytes, and dendritic cells, which play immune-regulatory and tissue-remodeling roles (5).

DISCUSSION:

There have been few investigations on the role of seminal fluid in the human peri-conceptional period. Early research found that artificial insemination (AI) of human sperm into the cervix causes an influx of leucocytes, primarily neutrophils, into the surrounding tissue (Pandya and Cohen 1985; Thompson et al. 1992). Seminal plasma is shown to be significant in this process, since in vitro and in vivo investigations reveal that adding seminal plasma resulted in the stimulation of GM-CSF, IL6, IL8, MCP-1, Macrophage inflammatory protein-3a (Mip-3a), and IL1a (Sharkey et al. 2007, 2012b). The cervix is a primary effector location for immunological responses in the female genital tract and is the site for seminal fluid deposition following coitus in women (Pudney et al. 2005). To protect the conceptus from maternal immune attack, an active tolerance state mediated by T regulatory (Treg) cells must be present from embryo implantation. During the peri-implantation phase of early pregnancy, male seminal fluid and ovarian steroid hormones are implicated in regulating the size and suppressive function of the Treg cell pool. In 1986 Bellinge et al included 152 couples (78 study group, 74 controls). Partner's fresh semen sample were used during IVF for any type of infertility.0.5–6.0 ml of untreated semen is injected 36–48 hours before embryo transfer. Absence of insemination in control. This trial's findings demonstrate that an IVF program's pregnancy rate is increased by the presence of semen in the reproductive system. It is hypothesized that insemination stimulates the inflammatory response because it is

known that the presence of sperm in the uterine cavity and fallopian tube commences a leukocytic invasion. This sensitizes the endometrium in some way to get it ready for the developing embryo to come out of the fallopian tube around 4 to 5 days after fertilization.

Tremellen et al. used 600 cases, 200 (102 study group, 98 controls) were in Center 1, and 400 (200 study group, 200 controls) were in Center 2. Couples receiving thawed embryo transfers in Center 1. Couples receiving a fresh embryo transfer from Center 2. This study included female from both the center, aged from 18 to 40, in a stable sexual relationship. Advice given to females from both the center to have sexual intercourse at least twice, once within 12 hours of OPU and once within 12 hours of ET. By this study it is proven that the likelihood of successful early embryo implantation and development is therefore increased by exposure to semen around the time of embryo transfer. Pregnancy rates are increased when seminal plasma is used in conjunction with IVF around the time of ovum pick-up or embryo transfer (29).

CONCLUSION:

The idea that seminal plasma affects fertility and pregnancy is supported by clinical research. The use of seminal plasma as an adjuvant therapy to increase the success rate of pregnancy following in vitro fertilization is an add on. Consequently, it can be said that seminal plasma constituents are involved in improving the condition of female reproductive tract and the uterus to increase the implantation rate and to support the pregnancy.

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