Seminal fluid and fertility in women

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Seminal fluid is often viewed as simply a vehicle to carry sperm to fertilize the oocyte, but a more complex function in influencing female reproductive physiology is now evident. Remarkably, seminal fluid contains signaling agents that interact with the female reproductive tract to prime the immune response, with consequences for fertility and pregnancy outcome. Experiments in rodent models demonstrate a key role for seminal fluid in enabling robust embryo implantation and optimal placental development. In particular, seminal fluid promotes leukocyte recruitment and generation of regulatory T cells, which facilitate embryo implantation by suppressing inflammation, assisting uterine vascular adaptation, and sustaining tolerance of fetal antigens. There is emerging evidence of comparable effects in women, where seminal fluid provokes an adaptive immune response in the cervical tissues after contact at intercourse, and spermatozoa accessing the higher tract potentially affect the endometrium directly. These biological responses may have clinical significance, explaining why [1] intercourse in IVF ET cycles improves the likelihood of pregnancy, [2] inflammatory disorders of gestation are more common in women who conceive after limited sexual activity with the prospective father, and [3] preeclampsia incidence is elevated after use of donor oocytes or donor sperm where prior contact with conceptus alloantigens has not occurred. It will be important to define the mechanisms through which seminal fluid interacts with female reproductive tissues, to provide knowledge that may assist in preconception planning and infertility treatment. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

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Seminal fluid is generally viewed as having just one biological function—delivering spermatozoa to fertilize the oocyte at conception. The plasma fraction, derived from the male accessory sex glands, acts to promote the survival and integrity of sperm as they are transmitted from the male to the female genital tract (1). However, carriage of sperm is not the only action of seminal fluid in mammalian species. Studies over the past two decades demonstrate that bioactive signaling agents in the noncellular fraction of semen interact with the female reproductive tract after coitus, evoking gene expression and cellular changes in the immune system that in turn actively influences fertility and fecundity and even offspring health. The effect in mammals is analogous to mating events in invertebrates, where male fluids intromitted at coitus increase the likelihood of female reproductive investment, maximizing the chance of transmission of genes to subsequent generations (2). An expanding body of evidence shows seminal fluid interaction with female tissues is a feature of every mammalian species (3), albeit with variation depending on the reproductive anatomy of each species.

Perhaps unsurprisingly then, several clinical studies backed up by in vitro experiments provide evidence that seminal fluid exerts biologically comparable effects in women. The cervix, and potentially also the endometrium and fallopian tube, can respond to seminal fluid signals in ways that may have consequences for fertility and pregnancy progression. The gene expression and immune cell changes identified to date reflect those in other mammals, implying similar actions on the female immune response. Given the difficulties of studying seminal fluid effects in women, the molecular and cellular mechanisms are incompletely defined and any physiological significance is not proven. Notwithstanding these limitations, there is tantalizing evidence that seminal fluid signaling may explain clinical observations of links between duration of sexual cohabitation and protection from pregnancy disorders including preeclampsia and fetal growth restriction (4) and benefits of seminal fluid contact for embryo implantation reported in an IVF setting (5).

This review paper will summarize the evidence for effects of seminal fluid on reproductive function in women, discuss existing knowledge of signaling agents and their molecular effects, and identify knowledge gaps for future research.

MALE SEMINAL FLUID SIGNALING: INSIGHT FROM ANIMAL MODELS

The plasma fraction of seminal fluid is produced by the male accessory sex

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organs (prostate, seminal vesicle, and epididymis) and contains a complex mixture of bioactive agents that act to nourish and protect sperm during traversal of the female tract. In addition it contains soluble cell-cell signaling cytokines, prostaglandins, hormones, and other factors that exert actions on female tissues (6). In mice, where these effects are best described, seminal fluid interacts with luminal epithelial cells on the endometrial surface to differentially induce or suppress several hundred mRNAs (7). Among these are many differentially expressed noncoding microRNAs (miRNAs) (7). Strikingly, many of the mRNAs and miRNAs induced have known actions in the immune response, causing local synthesis of an array of cytokine and chemokines that are released into the stromal and luminal compartments (7). Within hours, these agents recruit immune cells (macrophages, dendritic cells [DCs], and granulocytes) from the blood into the endometrial stroma and lumen (8, 9). The neutrophils and macrophages help to clear debris and pathogens introduced at coitus and may engage in selection of sperm most competent for fertilization. The DCs have an additional function—they take up seminal fluid antigens, traffic to local lymph nodes, and through a process of cross-presentation, activate and expand inducible regulatory T cell (Treg cell) populations that are reactive with seminal fluid antigens including major histocompatibility (MHC) antigens (10, 11).

Subsequently the newly generated Treg cells migrate via the blood into the endometrium, where they promote endometrial receptivity for embryo implantation. The implanting embryo expresses the same paternally derived antigens present in seminal fluid. If the Treg cells induced by seminal fluid have sufficient stability and suppressive competence, they will support invasion of trophoblasts and the vascular changes required for robust placental development, while suppressing the inflammation that would otherwise prevent maintenance of the semiallogenic embryo (12). The Treg response to seminal fluid depends on seminal plasma factors originating in the seminal vesicle gland (8), notably the key immune-regulatory cytokine transforming growth factor beta (TGFB), which is synthesized in the latent form and activated in the female tract after ejaculation (13). The actions of seminal plasma may be reinforced through the $\gamma\delta$T cell/IL17A pathway (14).

Meanwhile, the immune cells recruited by seminal fluid in mice also exert direct effects on endometrial receptivity, with macrophages secreting angiogenic factors and inducing expression of embryo attachment ligands in epithelial cells (15, 16). Actions of seminal fluid extend to the oviduct where, as in the endometrium, synthesis of cytokines and growth factors that support preimplantation embryo development is induced (6, 17). The ovary is also impacted such that seminal fluid contact promotes leukocyte recruitment to accelerate ovulation and advance corpus luteum development (6).

Seminal plasma is not mandatory for successful reproduction in most animals, since viable pregnancies can be initiated using epididymal or washed ejaculated sperm in artificial insemination or IVF followed by ET. However, studies in several species indicate that fertility and fetal development are compromised if females are not exposed to seminal plasma. Experiments in which seminal fluid signaling is disrupted by surgical removal of seminal vesicle, prostate, or coagulating glands from mice, rats, or hamsters before mating each show that seminal fluid contact affords optimal reproductive outcomes (6). In mice and rats, ET protocols routinely employ recipients mated to vasectomized males, but fetal loss and abnormality is considerably greater when recipients are not exposed to seminal fluid (6).

The effects of seminal fluid exposure extend beyond fertilization and implantation, with consequences for the quality of the ensuing pregnancy and the lifelong health of the offspring. Recent experiments in mice show that when pregnancy is conceived in the absence of seminal plasma contact at conception, not only is the pregnancy rate reduced but offspring health is profoundly affected (17). After birth, offspring displayed altered growth trajectories and disturbed metabolic function, with male pups substantially more affected than females. Altered offspring phenotype is characterized by increased central adiposity, disrupted metabolic hormones, reduced glucose tolerance, and hypertension (17). Oxidative damage to sperm without the protective effect of seminal plasma is implicated in the reduced fertility in this model, but the detrimental programming effects in offspring were at least partly attributable to effects on embryo development of the altered cytokine environment seen when seminal fluid signaling is ablated (17). As well as metabolic effects, conception without seminal fluid has been linked with altered genetic imprinting in hamster embryos and elevated anxiety in offspring (18).

EFFECTS OF SEMINAL FLUID IN THE CERVIX OF WOMEN

The primary tissue shown to respond to seminal fluid in women is the uterine ectocervix. This is unsurprising, given that this is where seminal fluid is deposited at coitus and the significance of the cervix as a major inductive and effector site for immune responses in the female genital tract (19). The cervix plays a key role in the defense against infection by bacterial and viral pathogens and may be critical for the initiation and maintenance of immune tolerance toward spermatozoa and other antigenic material present in the ejaculate.

The earliest evidence demonstrating a response to seminal fluid in periovulatory women used donor insemination followed by cervical smears to show recruitment of leukocytes into the cervical mucus when whole semen, but not sperm-free seminal plasma, was administered (20). A subsequent study used immunohistochemistry to identify the leukocytic efflux as mainly neutrophils, with lesser numbers of macrophages and lymphocytes (21). Neutrophils accumulated within the cervical mucus as early as 4 hours postinsemination, with maximal leukocytosis observed at 12 hours before almost complete resolution by 24 hours.

A limitation of the first studies was the artificial seminal fluid administration and the superficial sampling site. In 2012, we published the first evidence that insemination at vaginal coitus elicits an inflammation-like response within