Seminal fluid in infertility: more than just a vehicle

Infertility, which affects 15 % of couples worldwide, is defined as failure of conception despite unprotected sexual intercourse during a period of more than twelve months. Focus on infertility studies has been taking place for decades, however, such spotlight was mostly given towards the female counterpart. Nevertheless, the male contributes up to 50 % of infertility cases.

Male infertility is a multifactorial syndrome, incorporating genetic, molecular and anatomical abnormalities which are phenotypically demonstrated in male genitalia and spermatozoa. For instance, genetic anomalies include chromosomal alterations, gene mutation and Y chromosome microdeletions. Eventually, these can be manifested as ejaculatory failures or as varicocoele; i.e. distention of the scrotal veins which disturb sperm production. The latter can result in low or total lack of sperm production termed oligozoospermia and azoospermia respectively. There are also abnormalities in sperm quality, whereby sperm have no tail, thus being unable to move adequately (asthenozoospermia).

Increasing evidence is showing that sperm integrity is not the only factor responsible for successful conception. The seminal fluid produced in the male reproductive system plays a vital role, especially when it is present in the female reproductive tract. Nowadays, infertile couples are turning towards assisted reproductive techniques (ART) such as *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). However, the drawback of these modalities is that they bypass all the seminal fluid contents and involve only the sperm during the procedure.

Whereas previously, seminal fluid has been regarded only as the carrier of sperm, latest studies have shown that the fluid's role is also related to embryo development by preparing the female immune system to tolerate it. In fact, insertion of seminal fluid either by natural intercourse or via intravaginal delivery during ART resulted in an improvement in clinical pregnancy rates (up to 23 %) and live birth rates.

Seminal fluid also contains a vast array of molecules; such as ions, sugars and proteins. The latter are the most abundant, accounting for 50 % of all the seminal fluid and help the development of the embryo in its early stages after implantation in the uterus. Hence, IVF procedures that may lack seminal fluid in their program might be affected negatively. In a cohort study, whereby two groups of men were investigated, it was shown that sperm from the group which resulted in pregnancy following ART had proteins (e.g. A2LD1, ATP1B3 and FBXO2) which were expressed significantly more than those in the other group of men.

Other proteins, such as TFGβ1 and TFGβ3, induce an immune response in the female by recruiting white blood cells. This is beneficial because the expectant mother becomes protected against any contaminants from her partner which might induce an infection. Additionally, cytokines and hormones in seminal fluid indirectly induce endometrial changes for the preparation of embryo implantation. Seminal fluid contents also set immunotolerance towards the semen, i.e. the female immune system tolerates the semen and sperm of her partner better, especially if the female has had frequent sexual relationships with the same male. Hence, avoiding immune-mediated infertility.

Additionally, recent evidence suggests that there is also a link between the duration of sexual relationships and protection from pregnancy defects such as preeclampsia.

Numerous studies have been carried out which suggest that seminal fluid plays a major role in male infertility. Seminal fluid proteins are being investigated as potential biomarkers for diseases. However, more research need to be carried out in this field due to the complexity of the subject. These will provide indications towards the best choice of counselling and ART that might be available for partners when they choose to start a family.

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