Editorial

Immunological Infertility

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The ability to produce antibodies against invading foreign proteins is a protective defence mechanism necessary for survival of the species. Introduction of sperm in the vagina can produce an isoimmune response giving rise to antibodies against sperm resulting in infertility. In the male, sperm are normally confined to the genital tract. This blood-testis barrier is breached due to infection, trauma, obstruction or unexplained reasons resulting in leakage of sperm ending in production of autoantibodies against sperm. Various reports attribute 15-40% of unexplained infertility to such immunological problems. It is possible that breaching of blood-testis barrier is not uncommon. But immunological tolerance induced by long term physiological leakage of sequestered sperm antigens or activation of non-specific T-suppressor cells by testicular germ cells or genetic polymorphism of the immune response could possibly prevent development of clinically significant problem.

Antibodies against zona pellucida block receptor sites on the zona pellucida interfering with sperm - egg interaction, zona penetration and fertilisation. This can now be overcome by intracytoplasmic sperm injection(ICSI). Zona pellucida antibodies can be ruled out by demonstrating in-vitro fertilisation. In fact, this is one of the basis for advocating one-IVF cycle as a test for fertilisation before resorting to intra-uterine insemination (IUI).

Autoantibodies against sperm are present in the male in the serum and/or seminal plasma. Isoantibodies against sperm can be found in the female in the serum and/or genital fluids like follicular fluid, tubal secretions, endometrial fluid and cervical secretions. The action of the antibody depends on its isotype, titre, production site, and binding site. Antibodies can cause immobilisation and agglutination of the sperm, affecting its motility, transportation and viability. Even spermatogenesis may suffer due to antibodies. Antibodies in the female genital tract can inhibit sperm cervical mucous penetration, affect capacitation and interfere with sperm selection process and fertilisation.

Sperm antibodies should be suspected and looked for in cases of oligo-or asthenozoospermia, otherwise unexplained infertility and failure of intrauterine insemination. If a sample of semen presents clumps giving an appearance of falling snow sperm antibodies should be looked for.

Over the years a number of laboratory tests including RIA and ELISA have been devised to detect sperm antibodies in the sera, seminal plasma and cervical secretions. But mere presence of antisperm antibody does not mean failure of fertilisation. Besides these tests do not given us extent of fertility impairment. They are difficult to standardize and interprete and lack immunological validity and clinical significance. Hence they have very limited utility in clinical practice. It must be emphasised that pregnancy is probabilistic event and

no test can accurately predict the precise impairment in fertility.

Cervix is an important major site of immunological activity and being readily accessible we depend on post-coital test (PCT) and sperm cervical mucous penetration test (SCMPT) for indirect evidence of antibodies against sperm. PCT is done 2-24 after intercourse (without use of any lubricant) during the preovulatory period. It should be preceeded by 2-4 days of abstinence. Cervical secretion is collected by a pipette, cannula with a balloon, tuberculin syringe, forceps or bacteriological loop. Presence of 8-10 progressively motile sperm under a high power field indicate a satisfactorry test and rule out sperm antibody problem. A negative test is indicated by no sperm, non-motile sperm or sperm without forward progression. A negative test is a reasonable guide for sperm antibodies in the seminal plasma or cervical mucus. Yet when PCT is negative pregnancies are recorded in 10%. A poor PCT may be due to genital abnormalities absent or incomplete penile penetration, retrograde ejaculation, wrong timing of PCT, chronic cervicitis etc. A negative test should be repeated for confirmation.

SCMPT is carried out by placing coverslip over a drop of preovulatory cervical secretion leaving the peripheral 2 mm free. A drop of semen is placed at each of the 4 edges of the cover slip. Capillary action brings into contact the sperm and the cervical secretion and normally the phallanges of sperm penetrate into the cervical secretion. If sperm antibodies are present the sperm fail to penetrate into the cervical secretion and start shaking or quivering on coming into contact with cervical secretion.

When SCMPT indicates antibody problem crossover SCMPT is carried out wherein husband's sperm is tested with antibody free donor cervical mucus and wife's cervical mucus is tested with antibody free donor sperm. Sperm and cervical secretion from fertile subjects may be presumed to be free from antibodies. Cross over SCMPT indicate whether the antibody is in the seminal plasma or cervical mucus.

Lastly, recovery of sperm from the peritoneal cavity, by colpopuncture or at laparoscopy, following intercourse reasonably excludes immunological problems.

Treatment for sperm antibody in the male -

1. Since male genital tract infection is associated with sperm autoantibodies it should be treated vigorously. Semen culture and study of prostatic secretion could detect the infection in stubborn cases.
2. Sperm antibody level gradually decreases if the antigen is withdrawn. Suppression of spermatogenesis by testosterone substantially decreases the antibodies. Pregnancy can now be attempted after stopping the suppression.
3. Intrauterine insemination (IUI) - In the belief that antibodies bind sperm soon after ejaculation, ejaculating directly into the media to dilute the antibodies and rapid processing of the semen is advocated by many. Addition of galactose (to interrup the interaction between galactose residue on the sperm and galactose recognition sites on the antibody) or chymotrypsin (to cleave the Ig molecule of the antibody and modify it so that motility and fertilisation potential of the sperm are not affected) to the media is also recommended by some.
4. Immunosuppression by corticosteroids - Various regimes with methyl prednisolone are recommended. High doses upto 96 mg/day cyclically from day 1 to 7 or day 22 to 28 of the wife's cycle is one of the regimes recommended. Another regimen recommended is high dose for 2 weeks followed by a medium dose of 16 mg for 3 to 12 months. High doses or prolonged treatment carry the risk of hip necrosis.
5. AID - use of donor sperm is a reasonable treatment
6. IVF-ET and ICSI can be logically resorted to for poorly responding obstinate cases.
7. Adoption

Treatment for the female:

1. Occlusion therapy: Use of condom for 6-9 months prevents persistent antigen exposure and significantly brings down the antibody titre. PCT should now be positive. It should be emphasised that use of condom has no effect on autoantibodies in the male.
2. IUI This bypasses the hostile cervix with antibodies in its secretions and hence seems to be a rational treatment
3. Immunosuppression with corticosteroids is advocated for circulating antibodies. Cyclic treatment in the earlier part of the menstrual cycle is advocated by many while some advocate continuous treatment. Apart from osteoporosis, one is worried about potential dangers to zygote, early embryo and even unfertilised ovum.
4. IVF-ET
5. Adoption

Choice for treatment in a couple depends on chance for success and time needed for success (age of the female is relevant here) besides cost, invasiveness & risk of treatment. Lastly, an increased incidence of spontaneous abortion in immunised women who subsequently conceive is reported by some workers.

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