MEditorial May 2011

"Pollination"

Thanks in good part to a healthy 2010-2011 rainy season, the greens of the grass, the horticultural color diversity, and one of my favorites, the fragrance of jasmine, seem especially intense and beautiful this spring: pollination at its best.

I think the analogy of pollination to human reproduction is more appropriate than ever, since our growing knowledge of sperm and egg function, as well as incredible assisted reproductive technologies (abbreviated as "ART") not infrequently require an intermediary (akin to the pollinating bee) to effect fertilization. Reproduction in humans is not always the same as "successful" [depending on your point of view] sex. Sex is fun; reproduction can be a chore!

Let's look at the male part of the fertility equation. Sperms are produced by the testicles in an incredibly high quantity, the tens of millions per cc. of semen; but most are "wasted" on the way to fertilize the egg (ovum) usually in the fallopian tube. Production of sperms goes on continuously, sometimes for a man's whole lifetime, and [as opposed to the limited supply of eggs, petering out toward menopause, in the female] are produced anew to fully develop in a given cycle. The ova on the other hand, exist, a priori, in a state of so-called meiosis, a biologic process in which only one-half of the 46 human chromosomes and one "X" chromosome exist.

Research suggests sperm problems/male infertility are very dependent on genetics and chromosomal function. Men have two "sex" chromosomes, an "X" and a "Y". The "Y" chromosome has portions of gene sequences that control sperm production. "Deletions" or acquired absence (in the DNA splitting and recombination processes) of some of these gene sequences, may determine a man's capability of fathering a child, especially in cases where the sperm count is exceptionally low or zero. See more below.

Although most authorities feel a sperm count of below 20 million per cc. is low, this is controversial. Remember fertility is determined by the ability to cause

pregnancy, not by a sperm count itself. Some doctors do not consider a man "infertile" unless he and his partner have gone 6-12 months without conception. We do see pregnancies in couples where sperm counts are well below 20 million per cc.; and difficulties conceiving in other couples where the man has more than 100 million sperms per cc. Some other factors that bear on fertilization include the morphology (appearance) of the sperms (can also be genetically-linked), with odd-shaped sperms being ineffective at penetrating the "thick" barriers around the human ovum. Strange-looking sperms do not, however, lead to babies with birth defects. Motility of sperms relates to how fast sperms progress in a forward direction through the cervix after ejaculation. Speed and direction are important here. Furthermore, some fast/normal-appearing sperm seem to lack enzymes needed to penetrate the egg. In other cases, thick cervical mucus (not normal at the time of ovulation) slows down even hearty sperms on their way to the fallopian tube.

There are risk factors for poor sperm counts and function. How these factors interfere with sperm production/function is less than clear but they may work by inducing production of toxic substances in the testis such as "free radicals". Adverse conditions include presence of a varicocele (varicose veins inside scrotum--usually worse on the left side, since the anatomy/angle of the left vein entering the body from the scrotum is different than the right): history of testis cancer; history of undescended testis at birth; history of testicular torsion—an acute painful twisting of the testicular blood supply, more often seen toward puberty but occasionally seen in younger boys and adults. <u>Varicoceles</u> associated with poor sperm counts/male infertility can be fixed as an outpatient surgery with an anticipated 70% chance of improving the sperm count/motility/morphology and an improved chance (perhaps 1.5 to 2x as high versus NOT fixing the varicocele) of a subsequent pregnancy. Despite all the studies on this controversial issue, we still cannot predict which infertile men with which sized varicosities will benefit (and to what extent) from tying off these abnormal veins--which may act as a "heat sink" raising the relatively low scrotal temperature above that at which sperms can be properly produced.

This leads back to genetics. Further research on the "Y' chromosome, motivated by the Human Genome Project, will undoubtedly lead to better predictions as regards male fertility and hopefully some treatments to improve sperm counts and function (so-called "seminal parameter"). The available medical therapies right now are limited and often do not help. Men with "untreatable" sperm dysfunction/infertility are often referred nowadays, with their wife, for "couples therapy" to a GYN/Infertility doctor who can often achieve a pregnancy using such reproductive technologies ranging from IUI (in-utero insemination) to IVF (in vitro fertilization, which used to be referred to as "test tube babies") to ICSI (intra-cytoplasmic sperm injection, where a single sperm can be injected using a piston-like pipette under microscopy into the wife's harvested egg—with the resultant embryo implanted into the wife's uterus). The sperms used to achieve this can be harvested, even in their "immature" predecessor state, from the testicle in some men with <u>zero sperm counts</u> (no sperm at all in the ejaculate, referred in this instance as "NOA" or non-obstructive azospermia). Open and percutaneous (through the scrotal skin) techniques permit such sperm retrieval. A whole other important issue is whether "ART" will lead to more birth defects including an increase in male infertility in babies so produced. Genetic testing, such as those for certain "Y" chromosomal microdeletions, help predict in which cases such retrieval will likely lead to a pregnancy. Deletions in certain areas of the "Y" sex chromosome called "a" and "b" portend a bad outcome, whereas deletion in the "c" region is more favorable for a pregnancy using assisted reproductive techniques.

My feeling is that for a while, perhaps another decade or so, we as urologists will depend heavily on our GYN/Infertility colleagues to "rescue" infertile couples (by "pollination") who suffer poor sperm function--but eventually, my specialty will be able to improve sperm production and function directly within a man's body.

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