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MALE FACTOR INFERTILITY: A RATIONAL BASIS FOR TREATMENT

The treatment of male factor infertility is one of the true success stories in the field of reproductive medicine. Disorders of sperm quality range from a low count or motility to a complete absence of sperm production. Deformities of the sperm cell shape (morphology) are also important to its ability to fertilize the egg. Mild abnormalities of semen parameters can be effectively treated using techniques that “wash” out the seminal plasma and improve the concentration of normally shaped motile sperm, which are then transferred to the uterus via an intrauterine insemination. However, for more severe conditions this treatment is inadequate. With a total motile cell concentration of less than 10 million cells per ml or a normal morphology of less than 4% by strict Kruger criteria, the chance of fertilization failure is very high, even with IVF. Effective Treatments for Male Infertility are:

- Hormonal Therapy (Clomiphene, gonadotropins, corticosteroids, thyroid hormone)
- Non-Hormonal Drug therapy (bromocryptine, antibiotics)
- Surgery (varicocele, vasectomy reversal, surgical treatment of undescended testes etc.)
- IVF-Related procedures (intracytoplasmic sperm injection (ICSI), testicular sperm extraction (TESE))

As a general principle, if the male factor cannot be reversed in the man’s body by simple medical or surgical treatment, then IVF with ICSI represents the only rational approach, and as stated below, the results are excellent. Intrauterine insemination is *not* an effective way of treating moderate to severe male infertility. If the total number of sperm cells one obtains is less than 1 million, ICSI is the only treatment likely to be successful.

THE USE OF HORMONAL THERAPY:

In a relatively small number of cases of male infertility, the failure to produce an adequate quality of sperm relates to reduced secretion by the pituitary gland of those hormones necessary to stimulate sperm production. The pituitary gland in the man produces two important hormones with regard to testicular function. The first is called follicle-stimulating hormone (FSH), and the second is luteinizing hormone (LH). Luteinizing hormone's predominant function is to act on a particular variety of cells in the testicles that produces the male hormone testosterone. These cells are referred to as Leydig cells. A sustained reduction in FSH production, therefore, is capable of resulting in male infertility. Usually, if there is a reduction in either one of the components, LH

or FSH, the other one will also be low. In other words, if a man produces a normal amount of LH and has a normal blood male hormone (testosterone, androstenedione, dehydroepiandrosterone) level, it is very unlikely that he will have a reduced FSH production, and, accordingly, if his sperm function is reduced, it is unlikely to be the result of reduced FSH production by the pituitary gland.

The woman's cycle usually lasts about 28 days, and under normal circumstances, she releases one egg per menstrual cycle. In the man there exists a cyclical production of spermatozoa. In fact the entire spermatogenic cycle, from initiation to the production of the most mature forms of spermatozoa, takes approximately 100 days. Accordingly, any treatment administered to the man in order to improve sperm production can only be properly assessed after waiting for a period of approximately 100 days. In the man, as with the woman, the pituitary gland releases FSH and LH in response to need. In other words, if there is an abundance of male hormone being produced, then the pituitary gland (through messages received from higher centers in the brain) reduces its production of LH. This push-pull mechanism, referred to as a *feedback response*, helps the body regulate exactly how much stimulation is needed to keep normal testicular function going both with regard to the production of male hormones and with regard to the production of spermatozoa.

In order to assess the potential of a male to respond to fertility drugs aimed at stimulating the testicles to produce more spermatozoa and/or male hormone, it is therefore necessary to first measure both FSH and LH which are produced by the pituitary gland, as well as prolactin and the male hormones testosterone, androstenedione, dehydroepiandrosterone. Measurement of these hormones gives an indication as to the likelihood of the man responding to treatment aimed at: 1) inducing increased production of FSH or FSH/LH (e.g. clomiphene citrate) or, 2) the direct administration of gonadotropins which comprise of FSH, LH or HCG (e.g. Menopur, Bravelle, Follistim, Gonal F and/ or Novarel (HCG)).

- **Clomiphene Citrate** (The first approach) Clomiphene citrate is a hormone which, through its central action in the brain, stimulates the pituitary gland to produce natural FSH in large amounts. The FSH, as mentioned above, stimulates spermatogenesis. The treatment is very simple, and involves the administration of 1/2 tab (25 mg) of Clomiphene citrate every alternate day for a period of 100 days, to perform a baseline semen analysis, FSH, LH, and male hormone measurements immediately prior to initiating therapy, and then to serially repeat all of these tests throughout the treatment with Clomiphene. The final assessment of response can only be made approximately 100 days after initiating therapy. This administration of Clomiphene is essentially harmless to the man. He may experience some minor side effects such as spots in front of the eyes, dryness of the mouth, headaches, slight changes in mood, and, rarely, hot flashes. These side effects are all reversible upon discontinuation of therapy.
- **Gonadotropin Therapy**. In cases where Clomiphene therapy fails to be successful, or in certain situations where it is not possible for Clomiphene to stimulate the pituitary gland into action, it is possible to administer FSH alone or in combination with LH in the hope of stimulating the testicles directly. This therapy, in certain cases of male infertility, might be combined with the administration of the hormone human chorionic gonadotropin (HCG), which is also a natural hormone and has a function similar to that of LH. The basis upon which

HCG would be administered would be in order to further stimulate the production of male hormones in cases where failed masculinization is associated with reduced sperm production. Administration of these drugs is usually carried out 3 times per week, again for a period of about 100 days, and the same hormonal and sperm assessments as stipulated for Clomiphene therapy would apply. The treatment has very few risks, and the minor side effects which might occur are all reversible upon discontinuation of therapy.

- **Other hormonal therapies:** There is very little evidence that the administration of vitamin preparations or specific male hormone administration would be of benefit in the treatment of male infertility. In some cases, there may be systemic conditions affecting other areas of the body, which indirectly might impact upon the pituitary gland's ability to produce the hormones necessary to stimulate testicular function. Rare examples include administration of Thyroid Hormone in cases of involvement of the thyroid gland, severe diabetes mellitus, and collagen diseases amongst others. Sometimes the pituitary gland produces too much prolactin, which in turn inhibits the ability of FSH and LH to act on the testicles. In such cases, it may be necessary to administer a drug called Parlodel (Bromocriptine) to suppress prolactin production, and thereby remove the restraining effect that prolactin might have on the action of FSH upon the testicles. There are, of course, many other such examples of where treatment of unrelated conditions might improve overall male fertility; testosterone is only mentioned because it is prescribed so often to try and improve sperm function. Such treatment is in fact *contraindicated* because prolonged use (more than 2-3 months) of testosterone will almost always have the reversed effect, compromising sperm count, motility and even morphology.

If the man is fortunate enough to respond to one of the above treatment modalities for enhancement of sperm production, then it is possible for a number of masturbation specimens of sperm to be collected and frozen in liquid nitrogen in order to be kept for a number of years so that there will always be relatively good quality sperm on hand, even if the fertility treatment is discontinued, and you revert back to a relatively poor production of sperm subsequently. It is, of course, not practical to permanently treat an individual on potent medications such as Clomiphene, or gonadotropins.

IN VITRO FERTILIZATION

Intracytoplasmic Sperm Injection (ICSI): Although always a treatment of choice for male infertility, it was not until the introduction of ICSI in the mid 1990's that IVF became more successful when applied in cases of male infertility than for female related causes. ICSI is a procedure where fertilization is achieved through the direct injection of a single sperm into the substance of each mature egg. Even high concentrations of anti-sperm antibodies attached to the sperm (see below) or severe sperm defects such as absence or abnormalities of the acrosome (the enzyme-rich attachment at the top of the sperm-head, that enables the sperm to penetrate the zona pellucida, " the envelopment of the egg"), are offset by ICSI.

The performance of ICSI in cases of "male factor infertility" has been shown to slightly increase the risk of certain embryo chromosome deletions (leading to a slight increase in early miscarriages) as well as the potential for a resulting male offspring to have male infertility in later life. However, there is no evidence of any significant increase in the incidence of serious birth

defects in ICSI-offspring. More relevant is the fact that when ICSI is performed for indications OTHER THAN male infertility there is no reported increase in the risk of subsequent embryo chromosome deletions, miscarriages or in the incidence of subsequent male factor infertility in the offspring.

Testicular Sperm Extraction (TESE): is a procedure involving the introduction of a thin needle directly into the testicle(s), under local anesthesia, without making a skin incision. Hair-thin specimens of testicular tissue are removed (usually under local anesthesia) in the space of 15 to 30 minutes. Sperm are extracted from the tissue and each egg is injected with a single sperm using the ICSI technique. It is most commonly done in cases of spermatic duct (vas deferens) occlusion or absence but can also be performed in cases of ejaculatory dysfunction, such as might occur following spinal cord injuries, after prostatectomy, or in cases of intractable male impotency. TESE is simple, relatively low-cost, safe, and virtually pain-free. Most men can literally take off a few hours for the procedure and return to normal activity straight away. Aside from the remarkable success rates with TESE/ICSI is the fact that, unlike vasectomy reversal, the procedure allows the man to retain his vasectomy for future contraception.

Diagnosing and treating the causes of azoospermia (absence of sperm in the ejaculate): The Work-up includes semen cultures, and blood tests for Chlamydia antibodies, measurement of FSH/LH and Testosterone blood levels and selective testicular biopsy to confirm the diagnosis and plan treatment. If the FSH/LH is high (much over 12 MIU/ml) then it is likely that this is a testicular failure and probably little could be done to improve matters. If the FSH/LH levels are in the normal range (4-9 MIU/ml), especially if the testosterone blood level is also normal, obstruction of both sperm ducts (vasa deferentia) becomes a distinct possibility. Confirmation would require a thorough urological exam and treatment would be TESE/ ICSI. If the FSH/LH is on the low side (<4 MIU/ml), especially if this is accompanied by a blood testosterone level below normal, it is suggestive of under-stimulation of sperm production and could be amenable to improvement through stimulation with Clomiphene or gonadotropins.

Sperm DNA Integrity Assay (SDIA): The Sperm DNA Integrity assay (SDIA) like the Sperm Chromatin Structure Assay (SCSA) is a tool for measuring clinically important properties of sperm nuclear chromatin integrity. The results correlate fairly well with the potential of sperm from a given male to produce embryos that would be sufficiently “competent” to produce a live birth. The SDIA utilizes the metachromatic features of acridine orange (AO), a DNA probe, and the principles of flow cytometry (FCM).

SDIA data are not well correlated with classical sperm quality parameters (bulk semen parameters) and have been solidly shown to predict sub/infertility and poor reproductive performance. The SDIA measures DNA damage. The degree of abnormalities in the genetic material of the sperm is expressed numerically as the DNA Fragmentation Index (DFI). DNA damage may be present in sperm from both fertile and infertile men. Therefore, this sperm DNA damage analysis may reveal a hidden abnormality of sperm DNA in infertile men classified as unexplained based on apparently normal standard sperm parameters. Infertile men with abnormal sperm characteristics exhibit increased levels of DNA damage in their sperm. Sperm from infertile men with normal-appearing sperm may have DNA damage to a degree comparable to that of infertile men with abnormal-appearing sperm. The data suggests that an abnormal SDI assay is more likely

to occur in cases of abnormal semen parameters. Thus the assay is ideally suited to fertility clinics to assess male sperm DNA integrity as related to fertility potential and embryo development as well as effects of reproductive toxicants. Since SDI/ SCS assay parameters are independent of conventional semen parameters, results may allow physicians to identify male patients for whom IVF and intracytoplasmic sperm injection (ICSI) will be far less likely to result in initiation of a viable pregnancy.

Cancer treatments are well known to adversely affect male fertility. Reduction of sperm output arises from the cytotoxic effects of chemo- or radiotherapy upon the spermatogenic epithelium. However, even if the epithelium survives, there is a potential hazard to reproduction with effects ranging from infertility to miscarriage, and there is an association with infertility and reproductive performance. Optimal sperm chromatin packaging seems necessary for full expression of the male fertility potential. SDI assays emerge as predictors of the probability to conceive and carry the pregnancy to viability.

The improvement seen in sperm motility after sperm separation and Percol processing is not associated with a similar improvement in sperm DNA integrity (SDIA assay results). These data suggest that sperm processing techniques will not minimize sperm DNA damage and the potential transmission of genetic mutations in assisted reproductive cycles. Most current data available on the significance of abnormal SDIA results in infertile couples seeking treatment has emanated from non-IVF pregnancies. IVF data suggests the following:

- The viable (>12 weeks) IVF pregnancy rate (and thus presumably also the birth rate) could be as much as 2 times lower in women under 33 yrs of age, whose husbands have abnormal SDI assays (with a DFI of <30%). Results become progressively worse with advancing maternal age such that at 35 yrs+, the viable pregnancy rate could be as much as 3-4 times lower.
- Although it is possible for abnormal SDIA results to sometimes spontaneously revert back to normal, this probably occurs quite infrequently.
- Although abnormal SDIA results are detected in men with apparently normal semen analyses, abnormal results are more commonly seen in cases of men who have abnormal sperm parameters (abnormal sperm count, motility and/or morphology).
- There is some suggestion that the use of antioxidant therapy (Pycnogenol 200mg daily, L-Carnitine 3 grams per day, acetyl carnitine 500mg per day, Vitamin C 1,000mg per day and Vitamin E 800IU per day) taken for 6-8 weeks can cause the SDI assay to improve or even revert to normal. There is some suggestion that men who have varicoceles (a collection of distended veins in the scrotum) associated with an abnormal SDI assay may experience a reversion of the SDI assay back to normal, 3-6 months following surgical or radiological ablation of the varicocele.

In summary, an abnormal SDI assay augers rather poorly for the outcome of fertility treatment in general and IVF/ICSI in specific. In such cases, the fertilization rate and pregnancy rates are reduced and the chance of early pregnancy loss appears to be

increased significantly. However, it is important to emphasize that an abnormal SDIA result does not totally preclude a successful pregnancy. The prognosis worsens progressively as the age of the egg provider advances beyond 33yrs. Although abnormal SDIA results rarely revert to normal spontaneously this can and does happen on occasion. Selective surgical ligation of a varicocele and medical anti-oxidant treatment may be effective in restoring the SDIA to normal.

If an abnormal SDIA result fails to revert to normal in spite of treatment, the use of donor sperm should be seriously considered, especially when the egg provider is over 35 and facing a “rapidly ticking” biological clock. Another approach would be to divide eggs in half in an IVF cycle and use donor sperm for some of the eggs and husband’s sperm for the others.

ANTISPERM ANTIBODIES IN THE MAN:

Immunity to sperm, whether in the male or female, is not an absolute cause of infertility. Sperm antibodies reduce fertility, but do not invariably prevent conception. Rather, the effects are graduated; i.e., the larger the immunologic response, the less likely it is that a pregnancy will occur. Like any other kind of antibody manufactured by the body, sperm antibodies are formed in response to antigens. These antigens are proteins, which appear on the outer sperm membranes as the young sperm cells, develop within the male testes. Antigens can only stimulate antibody production when they come in contact with components of the blood. Under normal conditions, blood and sperm do not mix. Direct contact between the two is prevented by a cellular structure in the testes called the blood/testis barrier. This barrier is formed by Sertoli cells, which abut very closely against each other, forming tight junctions that separate the developing sperm cells from the blood and prevent immunologic stimulation. However, the blood/testis barrier can be broken by physical or chemical injury or by infection. When this barrier is breached, sperm antigens escape from their immunologically protected environment and come in direct contact with blood elements that launch an immunologic attack.

In the female's body, deposited sperm are regarded as foreign invader cells and as such would normally be targeted for attack and destruction by circulating antibodies. Yet sperm, which are immunologic aliens to the woman, do not usually cause an antibody response. Although usually exposed to billions of sperm during her lifetime, few women develop sperm antibodies. Why this is so is not well understood. It is known that the cellular construction of the vagina provides a physical barricade somewhat similar to the blood: testis barrier in the male. Here, too, physical damage or infection will increase the likelihood of sperm and blood mixing and subsequent antibody production.

Once sperm and blood come in contact, whether in the male or female, specific antibodies are produced against them by specialized blood cells called T- and B-lymphocytes. The three main types of sperm antibodies produced are Immunoglobulin G (IgG), Immunoglobulin A (IgA) and Immunoglobulin M (IgM). These antibodies bind to the proteins (antigens) on the sperm head, midpiece or tail. The antibodies formed may be of the circulatory type (in the blood serum) or secretory type (in the tissue). This is important because high levels of antibodies in the blood do not always antibodies will find their way to the semen where they can affect the sperm. For

example, the concentration of IgG is much lower in secretions of the reproductive tract than it is in the blood. Conversely, the local level of IgA is higher in the reproductive secretions than in the blood. This is an important point, which we will return to later.

Once sperm antibodies have formed, they can affect sperm in several different ways. Some antibodies will cause sperm to stick together (*agglutinating antibodies*). Agglutinated sperm clump together in huge masses and are unable to migrate through the cervix and uterus. Other antibodies mark the sperm for attack by Natural killer (NK) cells of the body's immune system (*opsonizing antibodies*). Some antibodies cause reactions between the sperm membrane and the cervical mucus preventing the sperm from swimming through the cervix (*immobilizing antibodies*). Antibodies can also block the sperm's ability to bind to the zona pellucida of the egg, a prerequisite for fertilization. Finally, there is evidence that the fertilized egg shares some of the same antigens that are found on the sperm. It is possible that sperm antibodies present in the mother can react with the early embryo, resulting in its destruction by phagocytic cells.

There are a number of diagnostic tests available to detect the presence of sperm antibodies. These are flow cytometry and the ELISA (enzyme-linked immunosorbent assay), the Franklin-Dukes sperm agglutination assay or the Immunobead Binding Test (IBT), to name a few. Acacio Fertility Center, Inc. (AFC), the Indirect Immunobead Binding Test (IBT) is used to detect antibodies present in the blood serum, in cervical mucus or on the sperm surface. Select patients are screened for sperm antibodies in the blood serum. If that test is positive (antibodies are present), a second direct test is sometimes recommended to determine if antibodies are present on the surface of male's sperm or in the secretions of the female's cervix. As mentioned earlier, certain antibodies are more likely to be found in some parts of the body than in others. The presence of high levels of antibodies in the serum does not mean that they will find their way to the semen or cervix. Antibodies present in the serum will have little effect on fertility if they are not also present where sperm are manufactured (testes) or deposited (cervix).

IgA is the most common antibody in secretions of the cervix, uterus and fallopian tubes. IgG may also be present, but IgM is found only rarely. In the male, IgA and IgG are found in the semen although there is controversy as to whether they originate locally (secreted by testicular cells) or cross over from the circulation. Antibodies of the IgM class are not found in semen.

Like the source of some antibodies, the question of the critical levels of sperm antibodies is also hotly debated among clinicians. There seems to be general agreement that blood serum levels above 40% by the IBT are associated with significant fertility problems.

Once an antibody problem has been identified, there are generally 3 options:

- In some patients, the administration of corticosteroids (prednisone) to temporarily suppress antibody production. Pregnancy rates are poor and steroid treatment carries with it the risk of significant side effects. Spontaneous fractures have been reported in 2 - 4% of cases. As such, we do not routinely recommend this treatment.
- The best option is a form of in vitro fertilization (IVF) known as intracytoplasmic sperm injection (ICSI) where each egg is injected with a single sperm), high pregnancy and birth rates have been reported.

Other treatments for sperm antibodies, such as prolonged use of condoms or antibiotic therapy, have also proven to be of no value in increasing the chances of pregnancy in antibody-positive couples.

Sperm antibodies occur in about 7% of infertile women and are even more common in men, especially those who have previously undergone reproductive surgery such as vasectomy or vasectomy reversal. In fact, when a vasectomy was performed more than ten years prior, more than 70% of such men will have high concentrations of sperm antibodies, representing a severe form of male infertility. Fortunately ICSI has optimized IVF pregnancy in cases of male immunologic infertility, to the point that success rates are virtually unaffected by the presence or concentration of antisperm antibodies.

Rev 08/19

This handout is intended as an aid to provide patients with general information. As science is rapidly evolving, some new information may not be presented here. It is not intended to replace or define evaluation and treatment by a physician.