Male Infertility – Scientific Background

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The Sperm Production System

The oocytes produced by the female are formed before she is born while she is still in her mother's womb. After puberty, some of these oocytes undergo a process of ripening and are freed each month during ovulation.

An adult male, on the other hand, is constantly producing sperm cells. The process of spermatogenesis is extremely complex. It lasts about two and a half months, and takes place in the testes.

The duct system in the male is divided in two: an inner duct and an outer duct. The inner part, in the testis, maintains a temperature of 34ºC – about 3º lower than body temperature. This lowered temperature is essential for the formation of sperm in the scrotum. At the conclusion of the process of spermatogenesis, the sperm cells are carried by the vas deferens to the ejaculatory duct. Here we find the prostate gland, which secretes about a third of the volume of the seminal fluid, and the seminal vesicles, a double-sided gland which secretes the remaining two thirds. The combination of the fluids of these two glands is known as the seminal fluid, or the "white substance" referred to by our Sages. The seminal fluid facilitates the exit of the sperm cells from the male - body and their entry into the female. We call this white substance semen, and it is ejected by the male during orgasm.

Inside the scrotum there are two testes, which produce sperm cells in a process lasting 64 days. Thereafter the ripe sperm cells spend an additional ten days in the epididymis, where they become mobile and fertile. Then they pass through the vas deferens, a very long duct which encircles the urinary bladder and terminates in the urethra, a duct for both urine and sperm.

In the abdominal cavity we see the prostate. This gland secretes acidic fluid while the seminal vesicles secrete a fructose containing fluid which enables the sperm cells to move. The secretion follows a certain order: during orgasm, sexual desire first arouses the sex

organ, increasing the blood flow to its spongy tissue and thereby causing it to become hard and erect. Thereafter the prostate gland secretes its fluid contents, which are acidic. The fluid cleans the urethra and contains special minerals, such as zinc, which have a very important influence on fertility.

Following the initial secretion of the prostate comes the issue of the sperm cells, which have gathered in the lower cavity of the epididymis, in the vas deferens and in the upper cavity (known as the ampulla). The contents of the seminal vesicles are secreted into the mixture.

Causes of Male Infertility

During the fifty years since the Second World War, researchers have noticed a decline in the capacity of fertile men to secrete sperm. While during the 1930's a fertile male was able to secrete around a hundred million sperm per milliliter of semen (on average, about three milliliters are secreted after four days of abstention from sexual relations), fertile males today secrete approximately half that amount. This means that from a quantitative point of view there has been a decline in the fertility potential of the semen, perhaps because of environmental factors. We shall discuss this further later on.

Some 10% to 15% of couples getting married today are expected to experience primary sterility, *i.e.* no children. An additional 5% to 10% will suffer from secondary sterility (which refers to a cessation of childbearing after one or two children are born). Hence the number of couples suffering from fertility problems is somewhere between 15-20%. This means that a substantial number of couples are expected to receive fertility counseling. In about 40% of these cases the cause of infertility is exclusively the female partner. In another 40% of cases the cause is exclusively the male. In the other 20% there are combined factors from both parties. According to researchers and based on my own professional experience, male sexual dysfunction contributes to about half of all fertility problems.

In general, there are four main categories of causes of male infertility. About 60% of the cases involve problems with drainage of the blood from the testes or problems of infection. Common problems include enlargement of the veins of the spermatic cord and obstruction of the blood flow from the testes towards the heart.

Instead of the proper blood circulation in the testes, which cools them, circulation in the opposite direction warms the testes and damages them. In 10% of the cases the problem is a hormonal imbalance. A further 3% involve genetic factors; 5% are caused by antibodies against the sperm; and in about 20% of cases the cause is unknown and perhaps can be attributed to environmental factors: heat, smoking, alcohol, drugs, pesticides, poisonous metals, etc.

Sterility due to mechanical reasons exists when there is a problem with transportation of either the sperm, the semen or what we refer to as the seminal plasma. Such sterility includes: congenital absence of vas deferens, surgical disconnection of the seminal ducts in the scrotum (which is a procedure commonly performed as a means of male contraception), and inverse flow of semen towards the bladder. (This sometimes occurs as a result of diabetes or brain damage. Instead of the semen flowing outwards through the urethra, it flows backwards towards the bladder. In order for fertilization to be attempted, the semen has to be removed, under appropriate conditions, from the bladder.) Like mechanical problems, impotence (which can result from psychogenic or organic factors) also prevents the flow of semen into the woman's body. Various drugs, including those which control blood pressure and anti-depressants, can also cause aspermia (an absence of sperm production), or a drop in sperm production. In all these cases sperm cells do exist, but they need to be extracted from the depths of the sperm duct or from the bladder in order to fertilize the oocytes, as will be explained later.

More common than mechanical problems is qualitative sterility, *i.e.* damage to the sperm cells themselves. The causes of this are manifold: a low level of sex hormones (the gondotropines, FSH and LH), or an absence of spermatogenic cells in the seminiferous tubules as a result of a birth defect, radiation, or chemotherapy. An additional cause is malfunction of the supporting cells for sperm growth: in order to ripen, the sperm cells in the testes require the support of somatic cells and sustentacular cells (cells of Sertoli). At the same time, the sperm cells also require the action of the cells of Leydig, which are responsible for formation of the male hormone, testosterone. When there is malfunctioning of any of these support cells, the ripening of the sperm cells and their fertility is impaired.

Often there is a cessation at a certain stage during the ripening process of the sperm cells. As mentioned, the sperm cell is formed

during the male's adult years, and there are proteins which are responsible for this process which appear only during the differentiation or during maturation of the sperm cells. Sometimes the male lacks one of these proteins and the development of the sperm cells is thus halted at a very specific stage, a phenomena known as spermatogenic arrest. The sperm cells cannot progress beyond this stage, and hence we find no mature sperm cells in the semen. The seminal plasma exists, but it contains no viable sperm.

Other causes of male sterility is excess heat in the testes as a result of prolonged sitting or exposure to heat. There are some professions in which infertility for this reason is quite common, for example drivers who sit in one place for hours on end, or men who work around furnaces. This also occurs in men who suffer from fevers or from varicosis of the testes (varicose veins which can damage the connection between the support cells and the developing sperm cells). Various other causes include undescended testicles, damage to the blood flow to the testes as a result of infections, pesticides, poisonous metals (mercury, lead, cadmium, etc.), a genetic defect due to extra sex chromosomes (*e.g.* XXY), illnesses such as mumps, impaired functioning of the thyroid gland, chronic kidney disease, and autoantibodies against the sperm cells. All of these factors can have an adverse effect on the production, function and development of the sperm cells.

A cross-section of the testis shows that it is comprised of long seminiferous tubules which are twisted inside the testes. This is visible both from above and from the lateral view. The sperm cells are formed in these tubules. Using a microscope we can distinguish those tubules which have a fleshy wall; spermatogenesis takes place inside this wall. The youngest sperm cells are situated around the outer perimeter of the tubule and have a spherical appearance. As they mature during the process of spermatogenesis, they pass from the periphery towards the center. When they reach the center of the tubule, we can already distinguish their tails. They are now fully formed in terms of structure, but still lack movement. They pass from the tubules via the efferent ducts of the testis to the epididymis, where they complete their maturation.

The young spherical sperm cell has a large nucleus which contains genetic material. During the remarkable process of spermatogenesis this nucleus undergoes a significant contraction, until it becomes very small and serves as the crystalline apex by

means of which the sperm cell penetrates the oocyte. The nucleus acts like a drill. During the contraction the head of the sperm cell reduces its mass, thereby allowing the tail to move it with relative ease towards the oocyte. But all the male genetic material – twenty-three chromosomes – remains tightly packed into the head of the sperm cell, in the nucleus. The spermatozoa pass the epididymis, resulting in sperm cells which are capable of movement and of fertilization.

Fertilization Process

The female oocyte is the largest cell in the human body.

The oocyte is comprised of a cell enveloped by a hard external covering known as the zona pellucida. When we peel back this external covering, an additional covering can be seen underneath, known as the vitelline membrane. During the fertilization process there is a meeting between the smallest cell in the human body – the sperm, and the largest – the oocyte. But from a genetic point of view the two are equal. Both the nucleus of the oocyte and the head of the sperm cell contain all twenty three chromosomes.

Once the sperm cell reaches the oocyte and connects with it, the process of penetration begins. The sperm penetrates the hard outer layer and reaches the inner membrane and the oocyte pulls it inwards.

Examinations for Infertility

In order to investigate the fertility potential of the sperm and to determine whether or not the male is fertile, the male must undergo an initial test. He undergoes a routine semen test including semen analysis or PCT, which is an attempt to detect sperm cells in the endocervix following sexual relations, a hormonal profile in order to determine whether the brain is issuing commands to the testes properly, and an examination of the size of the testes.

The most important test to determine whether the male is fertile or not is the semen test. The functions of the test are as follows: a) to determine whether the male has potential for fertility; b) to locate possible causes for weakening or canceling of fertility potential; c) to serve as a means of treatment follow-up in order to determine whether the treatment is improving the quality of the sperm, or weakening the factor that is impeding spermatogenesis.

Here we come to the issue of how the semen is to be obtained. I shall enumerate a number of methods and their respective advantages and disadvantages. From the point of view of the laboratory technician who has to determine the fertility potential of the semen, the ideal specimen is obtained using a sterile condom. This is not the type of condom which one purchases at a pharmacy, as a regular pharmacy condom contains spermicidal substances (if the pharmacist says that it contains no spermicides, he is almost certainly mistaken). I refer here to a special condom which is manufactured for the purposes of sperm tests. This condom must be sterile, and when the semen is collected inside it during normal sexual relations, we have a representative sample which resembles what takes place between the couple naturally.

Regular laboratories lack a suitably modest place for the couple to conduct normal sexual relations. Therefore the W.H.O. has recommended masturbation in the laboratory for convenience. From a medical point of view I am not convinced that masturbation is an ideal representative examination, because the process in which the male creates a specimen is unlike the regular process of the couple's relations.

The sterile condom containing the semen reaches the laboratory within about an hour. Regular semen is semi-coagulated (like jelly) at the time of ejaculation, and it undergoes liquefaction within less than an hour. The coagulation, which is important for the survival of the sperm cells in the female's vagina, is a product of the contribution of the seminal vesicles. They provide the special sugar and various movement characteristics which are connected with the exchange of substances in the sperm cells, processes which take place within seconds of the production of semen. When the semen is provided in the laboratory, the technician sees the coagulation immediately. When there is no coagulation, there is a possibility that there is an abnormality in the seminal ducts. However, when the semen arrives at the laboratory after more than an hour, even normal coagulation would have already disappeared and so this information is lacking.

There are those who, for *halachic* reasons, use a perforated condom. This makes it difficult to diagnose infections in the semen, since their source cannot be ascertained. It simply depends on the size of the hole. If it is large, and was pierced by the patient himself, then when we find an infection in the semen it may have

originated in the female, and we are unable to arrive at an accurate diagnosis from the semen examination.

Sometimes the semen is removed from the vagina; this examination is known as an improved PCT. In addition to the problem of infections, there is the additional problem that sometimes not all the semen is obtained. When the doctor extracts the semen from the vagina, he cannot be certain that the entire amount has been removed.

Another method is that of coitus interruptus performed at home; here too the problems described above complicate the examination.

Therefore, from a medical point of view, the most preferable method involves using an unperforated, sterile condom.

A routine examination of sperm quality is performed using a regular light microscope, which is only a slight improvement on the first microscope invented by Leeuwenhoek in 1650. Actually, the difference between them is not all that great. Leeuwenhoek's microscope, which was fixed to the table with a bayonet, magnified 350 times. Our modern light microscopes, because of the limitations of light rays, can enlarge only up to 1,000 times. A sperm cell, as mentioned, is the smallest cell in the human body, and therefore it is difficult to distinguish adequate detail even with this enlargement.

Nevertheless, using a light microscope we can see the sperm cells and we can count them quite easily. This is an important factor in determining fertility potential. In addition, we may observe their motility, and when there is a problem with the movement we can recommend various options for using those cells with better motility for artificial fertilization.

In the natural course of events, the semen is ejaculated into the vagina. Here it has to overcome three obstacles.

a. mucus found in the cervix;
b. the passage between the uterus and the fallopian tube, which is very narrow;
c. the penetration of the hard outer covering of the oocyte, the zona pellucida.

"Sperm Improvement"

Semen treatments are carried out when the sperm is weak. Sometimes it is sufficient to rinse the sperm cells of the other

components of the semen and replace them with artificial fluids which are rich in vitamins and sugars, and then to inject them directly in the uterus. The semen cannot be injected directly into the uterus, thus bypassing the obstacle of the cervical mucus, because the semen contains repellent substances which cause the smooth muscles of the uterus to contract. Instead of absorbing the semen, the uterus expels it and thus we have to rinse the sperm and replace its natural fluids with other fluids.

When the motility is even weaker and we have reason to believe that the sperm cells will not succeed in passing through the narrow passage between the uterus and the fallopian tube, then in addition to rinsing we also perform "improvement" of the sperm, which is really a sorting process. All the sperm cells are placed at the bottom of a test tube, and those with better motility are left to rise by themselves. Thereafter a piston with a hole in the middle is inserted, and when it is lowered we may collect the top layer from the test tube, containing the cells with the best motility. The term "improvement" is not really suitable as nothing is really improved; we are in fact sorting. We sort the cells with better motility from those which move less well and from other cells such as white blood cells, etc.

If after the "improvement," we have a sufficient concentration of cells, three to five million, then we can inject them into the uterus. If the concentration is lower, around a million cells, then we perform in-vitro fertilization. If the concentration is lower still with very weak movement and the sperm cell may be unable to penetrate the oocyte (especially when it has a defective head cap, as we shall see further on) then we may recommend micro-manipulation.

There are various methods of micro-manipulation:

a. We perforate the outer coating of the oocyte;
b. We insert the sperm cells under that layer by means of a microscopic syringe;
c. We insert a single sperm cell straight into the oocyte itself.

These procedures are known as PZD, SUZI and ICSI respectively. A significant breakthrough has recently occurred in the area of ICSI.

The routine examination using an ordinary light microscope has certain limitations. It is able to determine etiology in only 44% of males suffering from infertility problems. With regard to the

other 56% it remains difficult to arrive at a diagnosis, and these cases remain a "gray area." The reason for this is simple: because of its limited capability for magnification, the light microscope cannot distinguish the tiny details of the spermatazoam head cap. The head of a sperm cell is the most important element in successful fertilization.

Light Microscope *vs.* Electron Microscope

Here lies the difference between the magnification of a light microscope and that of an electron scan microscope. The electron microscope fills an entire room and magnifies several tens of thousands of times, many more times than an ordinary microscope. Thus we may distinguish the organelles inside the sperm cells, for example the mitochondria. We can see the inner nucleus of the cells and the outer dome by which the sperm penetrates the oocyte. We can see the ring by which the sperm cell attaches itself to the inner wall of the oocyte, and within the nucleus itself we can see the collection of genetic material.

The light microscope simply cannot supply this sort of information about the structure of the head of the sperm cell. For this we require an electron microscope which will enable us to diagnose additional reasons for infertility. We need the examination to tell us not only whether the subject has a fertility potential, but also what the possible reasons are for a reduction in this potential. For example, sometimes it is impossible to culture the bacteria in the semen because the natural antibodies in it inhibit their growth. But with the aid of an electronic microscope we can easily distinguish covering cells with colonies of bacteria on them, and sometimes we can see an "attack" of the bacteria on the sperm cells. We can also see how a white blood cell mistakenly destroys the actual sperm cell, as a result of natural antibodies against it.

Using an electron microscope we can not only see the organelles but also arrive at a much more accurate diagnosis than we could using a regular microscope, thus minimizing the number of sperm tests that will be required. We already have a very high level of diagnostic accuracy using this microscope – about 80%. Only 20% remain in the "gray area," with various factors requiring further clarification.

Using the electron microscope with its penetrating scanning ability, we can evaluate fertility potential, motility potential (as we

examine the organelles of the tail), potential for oocyte penetration and an indication of circulatory disease (varicocele). Each disease has its own characteristics, its own treatment, and its own chances of success, as for example the chances of success in operating for ligation of the veins in the case of dilated varicocele.

Summary of Modern Treatments

The innovative treatments available for defects in the heads of sperm cells can be summarized as follows:

1. Ligation of dilated veins.
2. Treatment using follicle stimulating hormone (pure FSH), even when the hormone profile in the blood flow is in order (it has recently been reported that FSH acts on the organelles of the head of the sperm cell, thus improving the fertility potential of the male).
3. Cooling of excessively hot testes – this is a new subject that is now under investigation.
4. Homeopathic treatment – certain treatment may assist in improving the quality of the head of the sperm cell.
5. Treatment of the sperm using density gradients, especially percoll. The head of a normal sperm cell, with its chromatin arranged properly, lies deeper within the density gradient and therefore may be separated from cells with defective chromatin density.
6. Micromanipulation, when the acrosome (the organelle which penetrates the oocyte) or the organelle for bonding with the lamina of the oocyte is defective, even if the internal structure of the nucleus is in order.

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