CLINICAL RELEVANCE OF FERTILIZATION FAILURE AND NOVEL METHODS IN IVF

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1. Reproductive System

The reproductive system categorized as male and female reproduction in humans. The reproductive system in men includes a pair of testes, genital excurrent ducts, different accessory glands, and lastly penile. The two main functions of the testes are spermatogenesis and steroidogenesis. Spermatogenesis is the process of sperm cell development or in other word the production of the sperm cells which is called gametes. Rounded immature sperm cells undergo successive mitotic and meiotic divisions (spermatocytogenesis) and a metamorphic change (spermiogenesis) to produce spermatozoa. And secondly steroidogenesis which means synthesis of the androgens, also called sex hormones. Androgens, mostly testosterone which is substantially produced in Leydig cells that are located in the interstitial spaces of the testis are necessary for spermatogenesis and have crucial role in embryogenesis of the male embryo into phenotypic male fetus, and lastly responsible for sexual dimorphism. Accessory sex glands such as the seminal vesicles, prostate, and bulbourethral glands are taking place in male reproduction system by producing a several types of secretions that are attending to sperm to form semen.

On the other hand, female reproductive system counts in internal sex organs and external genital structures. The internal reproductive organs located in the pelvis and the outer genitalia participate in the anterior part of the perineum known as the vulva. The inner female reproductive organs are made up of pairs of ovaries, pairs of uterine/fallopian tubes, a single uterus and a vagina. External genitalia include mons pubis, labia majora and minora, clitoris, vestibule and vagina opening, hymen and external urethral orifice. Mammary glands can also be included as their functional status is directly linked to hormonal activity in the female reproductive system. Female reproductive organs exhibit cyclical monthly changes in both structure and function. These changes constitute the menstrual cycle and the appearance of the initial menstrual cycle in the maturing individual is referred to as the menarche. When the menstrual cycle becomes infrequent and eventually disappears, this change is called menopause. The menstrual cycle is mainly controlled by two hormones secreted by the adenohypophysis of the pituitary gland which are called follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and by two ovarian steroids which are called estrogen and progesterone.

2. Processes of Fertilization and Implantation

Fertilization and implantation are the natural life processes in the reproductive system, which is achieved by the fusion of male and female gametes (egg and sperm) to form a zygote. The process of fertilization in humans takes place in the ampulla of the uterine tube, and then it is implanted in the internal layer of the womb/uterus. After release from the ovary, the egg can survive for about 12-24 hours. After these above mentioned processes if the egg has not fertilized, it degenerates and sheds off from the uterine lining. Contrary to this, the sperm can live for about 72 hours. After the ejaculation the sperm cells are coming out into the vagina, and then sperms enter into the uterus through the cervical canal, and finally remaining surviving sperms swims upwards to the uterine tube to be more precise into the ampulla to fertilize the egg. The fertilization process is based on the principle of combining the haploid chromosome set of male and females to make it a single diploid cell called a zygote. In case of the absence of the fertilization, there will be no zygote formation.

The secondary oocytes released from the mature Grafian follicle of the ovary captured by fimbriae (small finger-shaped projections at the end of the fallopian tubes, through which the eggs move from the ovaries to the uterus) of the fallopian tube and get forward into the ampulla, where it is going to be fertilized by sperm within 24 hours after the release. Surrounded by multiple sperm cells, the oocyte will only be fertilized by a single sperm. The secondary oocyte completes its meiosis-II after the penetration of the sperm cell into the oocyte. Following this process, the secondary oocyte is referred to as the egg. The fertilization process happens in a few steps, including chemical and physical events. For instance; sperms incapacitation undergoes acrosomal reactions and releases chemicals called sperm lysins that are found in the acrosome. As a result of the acrosomal reaction, the membrane of the sperm and secondary oocyte are fused and subsequently the components of the sperm enter the oocyte. Calcium ions also play a significant role in the acrosomal reaction process. The optimal pH level, temperature and concentration of calcium and magnesium are the most important factors in acrosomal reaction. Immediately after plasma membrane fusion, the oocyte exhibits cortical reactions. These granules are located under the oocyte membrane, which fuses with the plasma membrane and releases cortical enzymes from the zona pellucida to the plasma membrane. Following this process, zona pellucida is toughened up by the cortical enzymes that prevent polyspermy (penetration of more than one sperm into the oocyte). Post-entrance of the sperm cell, the paused second meiotic division is completed by the secondary oocyte. This process gives rise to a haploid egg and a second polar body. The head of the sperm cell that holds the nucleus separates from the whole sperm and is called a male pronucleus. As a result, the tail and the second polar body begin to degenerate. The nucleus of the ovum is referred to as the female pronuclei. After this stage, the male and female pronuclei fuse together and their nuclear membrane degenerates. In brief, the fusion of the chromosomes of male and female gametes is called karyogamy. Now, after all these processes of the fertilization ovum takes the name zygote. The process of the entrance of sperm into the oocyte triggers the metabolism in zygote. Hereby, protein synthesis and cellular respiration are enhanced in this stage. Instantly after the fertilization, the cells start to divide and gradually multiply within 24 hours in the uterine tube, and this detached multicellular structure is called a zygote. Afterwards, between 3-4 days it migrates to the uterus, and at this moment we refer to it as an embryo. At this stage, an embryo which is in progress of the development undergoes through various stages and attaches itself to the endometrium and this process is referred as implantation.

3. Infertility

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility affects millions of people of reproductive age worldwide, and has an impact on their families and communities. There are many factors that cause male and female infertility, such as genitourinary anomalies, trauma, exposure to chemicals and being in an extremely hot environment for a long time. However, the factors that cause infertility in idiopathic infertility cases are not known.

4. Advanced Sperm Selection Techniques to Improve IVF and ICSI Outcomes

Approximately 50% of infertility cases are associated with a male factor. Assisted reproduction techniques (ART) tries to help to infertile patients' sperm to fertilize an egg and give normal birth with healthy offspring. However, the effectiveness of some techniques is still under the process of improvement. After the copula, while millions of spermatozoa are inseminated, only a few hundred sperm cells collide with oocyte for fertilization and reach the ampulla. This process shows that the sperm with the best structure and properties is naturally selected to support the development of the embryo.

Considering the risks of defective sperm resulting in reduced potential of the oocyte fertilization and even the development of congenital anomalies due to the challenges in selection of the sperm cells with good quality and characteristics, we can imagine how important the sperm cell selection is. For successful in vivo or in vitro fertilization, sperm must overcome natural fertilization barriers. However, Intracytoplasmic Sperm Injection (ICSI) technique that has been used during in vitro fertilization (IVF) bypasses natural barriers. The success of fertilization in this technique is strongly influenced by the quality of the sperm used for insemination. ICSI is considered absolutely required in the case of male factor infertility with an abnormal semen analysis. ICSI is an advanced assisted reproduction procedure used in an embryology lab during an IVF treatment in which a single sperm cell is injected directly into a woman's oocyte in order to create a fertilized egg.

The outer membrane of a sperm cell is very important in terms of their functionality as it is involved in some basic processes such as cellular metabolism, capacitation, oocyte binding and acrosomal reaction. The sperms are encapsulated in an extensive layer that provides the membrane its characteristic negative charge. Based on this, new techniques were developed to separate X and Y carrying and healthy pure headed sperms. Later, some other researchers started to modify and enhance the effectiveness of these techniques. These techniques are based on either the collection of charged sperm cells that adhere to the wall of a centrifuge tube or migration in an electric field. In both techniques, subsequent analysis of selected samples presents the huge rate of the sperm cells with high quality and higher DNA integrity. The procedure, known as the Zeta method, allows the selection of sperms with a lower DNA fragmentation than the "HA-coated plate selection" method. Despite the fact of these promising results, there are only a few published studies available related to the Zeta method selected sperm cells in ICSI patients.

The human body presents small channels containing dynamic fluid. Similar to these channels, developed microfluidic technology serves as a physiological platform for restructuring fluid channels and flows in living organisms. This technology is quantitatively controlled in a biophysical and biochemical environment, and the experimental results are visualized using optical microscopy. Moreover, this microfluidic technology provides the possible simulation of the journey of spermatozoa through the female reproductive tract, while allowing the quantitative assessment of the dynamics of spermatozoa motility when male gametes move in the biophysical and biochemical environment. Thus, this technology can help to develop new methods of gamete selection with minimal damage.

5. ROSI/ROSNI in IVF

Round spermatids are the earliest formed haploid male germ cells at the stage of before their development into tailed spermatozoa. The use of round spermatids in IVF has been suggested for infertile men who are unable to produce spermatozoa. This procedure is either called round spermatid injection (ROSI) or round spermatid nucleus injection (ROSNI) depending on the type of material used (whole round spermatid or only nucleus of the round spermatid). Several studies showed that the efficiency of ROSI became higher in recent years; however, the efficiency rate of the ROSI in comparison to the ICSI technique is low. Even the efficiency rate of the ROSI is lower than ICSI; ROSI technique gives hope that it could help azoospermic men to have their own genetic child's.

Although difficulties with the ROSI technique still persist and the overall low success rate of this technique continues to limit its use in clinical practice, recent studies show that outcomes have been significantly improved compared to previous studies. There are also a number of strategies available to improve the quality and effectiveness of round spermatids. One of these strategies is known as in vitro germinal cell maturation. Sertoli cells (SCs) transplantation in the testicles is also another strategy to overcome the male infertility. This strategy increases the number of testicular cells, sperm count and motility in azoospermia. As well, short-term germ cell co-culturing with SCs improves spermatogenesis. The stimulating factors produced by SCs in the co-culture system also have an impact on the differentiation of spermatogonial stem cells. For this reason, Sertoli Cell-Conditioned Medium in azoospermia is also another strategy which has the ability to recover the spermatogenesis.

6. Improved Techniques for Oocyte Stimulation in IVF

Poor oocyte response after stimulation for IVF is still one of the most important problems in reproductive medicine. Since the quality of the gametes affects the ability of the embryo to develop, it is very important to evaluate the morphological features of the oocyte in the embryological laboratory. Oocyte maturation consists of synchronous nuclear and cytoplasmic maturation processes that determine oocyte quality. Ovarian stimulation can be affected by intrinsic factors such as; oocyte growth ability, age, body mass index, lifestyle-related factors and by external factors such as; IVF laboratory procedures (oocyte retrieval, denudation, freeze-thaw, preparation procedures for ICSI), culture conditions (temperature, pH), and environmental conditions (light, air quality, humidity).

Several clinical trials have examined the role of androgens in improving poor oocyte response in IVF. On the other hand, certain studies argue against the use of androgenic supplements in improving fertility rates. Based on a meta-analysis, it was reported that clinical pregnancy and live birth rates increased following transdermal testosterone administration in patients with low response. In another experimental study, the paracrine regulation of steroidogenesis in theca cells by co-culturing theca and granulosa cells were evaluated and it showed that steroidogenesis is increased in theca cells. According to another research, a new protocol has been drawn up. In this protocol; to achieve intraovarian androgenization using the various mechanisms, they enhanced serum androgen levels by applying a daily transdermal testosterone gel. Then, they increased intrafollicular androgen levels by injecting hCG twice a week. And finally, an aromatase inhibitor called letrozole, has been used daily to prevent the androgen aromatization of estrogen with its daily application. Oral estradiol and vaginal progesterone have been favored for menstrual cycle control.

7. Preferred Embryo Selection Method to Enhance Embryo Implantation in IVF

The selection of embryos with the highest potential for implantation remains the main challenge of today's IVF labs. In this sense, various invasive and non-invasive methods have been developed to assess the morphokinetic, metabolic and chromosomal profiles of the embryo. According to current knowledge, frame-by-frame imaging is a promising non-invasive technique for facilitating embryo selection. Nowadays, this method is commonly used to identify embryos with high implantation potential to increase pregnancy rates, and to reduce the chance of multiple pregnancies by reducing the number of transferred embryos. In terms of the invasive techniques in embryo selection, blastocyst biopsy combined with complex chromosome analysis allows the identification of euploid embryos with minimal impact on the developmental potential of the embryo. This shows us that advances in technology and molecular biology allow the selection of embryos with high implantation potential in order to enhance pregnancy rate and abstain from multiple pregnancies.

8. Endometrial Scratching Method in IVF

It is known that one of the main problems underlying failed implantation is related to the receptivity of the endometrium, and therefore remains an important topic in the field of IVF. In this regard, recent researches have focused on the development of a variety of strategies to improve endometrial receptivity. Endometrial scratching (ES) is a technique used to improve the capability of an embryo to implant in the inner lining of the uterus, called endometrium after intrauterine insemination (IUI) or embryo transfer. In short, this technique involves endometrial scarring, in order to improve the receptivity of the uterus to the embryo. The ES is an inexpensive mechanical procedure for wounding the endometrium, which does not cause much discomfort to patients. This procedure can be performed using a variety of instruments such as a soft plastic endometrial biopsy catheter, Karman's cannula and vacuum aspirator, Novak's suction curette, and hysteroscopy. Mostly, in the luteal phase of the cycle preceding IVF, the endometrium is commonly scratched by using a 3mm in width small catheter known as the Pipelle®. Usually, the catheter is pushed forward through the cervix to the fundus, and then moved back and forth, and finally the process is completed by rotating the catheter to create a scratch on the endometrium in order to stimulate the endometrium.

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