Module

PGTO_US

Display

Intro to PGT-A

Backend Name: PGTO_US_01_Intro

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Prior to discussing preimplantation genetic testing for aneuploidy, it is helpful to first understand some background information about chromosomes, which are threadlike structures that carry genetic information in the form of genes. Egg and sperm cells contain 23 single chromosomes each. When a sperm fertilizes an egg, the resulting embryo has 23 pairs, or 46 total chromosomes - the sex chromosomes, X and Y, and 22 other non-sex chromosome pairs. Half of the chromosomes in the embryo are inherited from the egg, and half are inherited from the sperm. Embryos with extra or missing chromosomes, called aneuploidy, can result in a failure to conceive, spontaneous miscarriage, stillbirth, or a child with abnormalities. A common example of this is children born with Down's syndrome, which is caused by having three copies of chromosome 21, instead of two. Another common example of aneuploidy is Turner Syndrome, which is caused by having only one copy of the X chromosome instead of the usual two sex chromosomes. The risk of generating chromosomally abnormal embryos is increased in: Women with advanced maternal age. Couples who have experienced recurrent spontaneous miscarriage due to chromosomal abnormalities. Couples who have had implantation failure in previous pregnancy attempts. males or females who are known to carry a chromosomal abnormality, known as a "balanced translocation". In rare cases, some males with a low sperm concentration. Through preimplantation genetic testing for aneuploidy, or PGT-A for short, it is possible to test each individual embryo to determine if it has the correct number of chromosomes. This process helps doctors and patients decide which embryos to transfer, as chromosomally normal embryos are the most likely to develop to term and to be born as a healthy baby. This process will be discussed in detail throughout the module..

Biopsy for PGT-A

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In order to perform PGT-A, a small sample of the embryo, removed via a biopsy, is sent to a specialized genetics laboratory for analysis. The embryo biopsy is performed on either day five, day six, or rarely, on day seven after egg retrieval, on adequate quality embryos that have reached the blastocyst stage. At this stage, the embryo contains over 100 cells and several cells can be removed from the outer trophoblast layer of the embryo, which will eventually become the placenta. The cells are washed to remove any potential sources of contamination and transferred into small tubes for analysis. The embryos are then returned to the incubator and/or cryopreserved until the preimplantation genetic testing for aneuploidy results are returned. Thus far, babies born after procedures that include embryo biopsy have not had an increased rate of birth defects. However, the biopsy procedure does carry some risks. An embryo may be damaged during biopsy, which may cause it to stop developing or not be suitable for transfer. With a skilled embryologist, the risk of damaging an embryo is less than 1 to 2%. Although data has shown that embryo biopsy has no adverse impact on growth or medical outcomes, the technique is still relatively new, so there is potential for unknown consequences to live, born babies. While it is important to understand the risks involved in the process, embryos have been biopsied for over 25 years and have resulted in tens of thousands of healthy pregnancies..

PGT-A Analysis

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Once the biopsied cells arrive at the specialized genetic screening laboratory, the genetic material is amplified and testing is performed to determine the number of chromosomes. The report from the laboratory will indicate whether or not the embryos have the normal number of chromosomes and are candidates for transfer. The embryos may be euploid, aneuploid, or inconclusive. If the embryo is chromosomally euploid, it means that the embryo has the normal number of chromosomes and IS a candidate for transfer. If the embryo is chromosomally aneuploid, it means that the embryo has an abnormal number of chromosomes and IS NOT a candidate for transfer. The analysis may also be inconclusive, meaning that the testing could not identify the chromosomal complement of the embryo. These embryos are generally not transferred unless there are no other available embryos. There is a 1-2% chance of misdiagnosis due to the limitations of the test, either by false positive or false negative. A false positive means that an embryo is diagnosed as chromosomally abnormal, when it is in fact normal. A false negative means that an embryo is diagnosed as normal when it is in fact chromosomally abnormal. Uncertainty can also occur due to mosaicism, which occurs when there are cells with different chromosomal contents within the same embryo. This can cause a misdiagnosis if the cells that are tested are not representative of the embryo. In extremely rare cases, human error or natural forces beyond the control of your IVF center or genetic testing center, such as weather and air travel issues, can cause there to be no diagnosis if the cells are lost or impacted in transport to the testing laboratory. Rest assured that your embryos will still be safe at your IVF center. Lastly, there may be very subtle abnormalities where small segments of a chromosome are duplicated or deleted. These abnormalities are very difficult to interpret and are of unknown clinical significance; therefore, you may be advised to transfer other, more favorable, embryos if they are available..

Embryo Transfer

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In most IVF cycles in which PGT-A is performed, the blastocysts are biopsied and frozen on day 5, 6 or rarely, day 7. Once it is confirmed that there are chromosomally normal embryos available for transfer, a subsequent frozen embryo transfer cycle is performed. The percentage of chromosomally normal embryos can vary widely, from 0 to 100% in any given cycle. The older the woman, the lower the expected number of chromosomally normal embryos will be available for transfer. On average, 50-60% of blastocysts from women under 35 are chromosomally normal. This decreases to 45-55% for women aged 35-37, 30-40% for women aged 38-40, and 15-25% for women over age 40. For women of any age, it is possible that there will be no embryos available for biopsy, or that no biopsied embryos will be identified as chromosomally normal in a given cycle, meaning that there will be no embryos for transfer from that cycle. All patients doing IVF should be aware of the option of performing PGT-A and its advantages and disadvantages. There have been many studies evaluating the potential benefits of PGT-A and there is still debate as to the actual impact on clinical outcomes. The probable benefit of PGT-A is that, by knowing whether an embryo is chromosomally normal or not, you can avoid transferring an abnormal embryo. With the information provided by PGT-A, it is generally recommended that a single embryo is transferred as the pregnancy rate per transfer is increased and miscarriage rate is decreased. Also, with PGT-A, the risk of an ongoing pregnancy having a chromosomal problem is significantly reduced, although it is not completely eliminated due to the small chance of a false negative. The main disadvantages of a PGT-A cycle include: increased cost, a small risk of damaging an embryo in the biopsy or freeze/thaw process, and a delay in the embryo transfer until the PGT-A results are known. When an IVF cycle is performed without PGT-A, it is common to transfer more than 1 embryo to compensate for the expectation that depending on the patient's age, a portion of the embryos will be chromosomally abnormal, and therefore, will not implant or result in a miscarriage. In addition, there is a small chance of a false positive, where a normal embryo is misdiagnosed as abnormal and is not transferred. It is important to understand the benefits, risks, and alternative options in order to make an informed decision about pursuing PGT-A. While there is some risk involved, technological advances have made PGT-A an effective tool for improving IVF success rates.. 50.

Preimplantation Genetic Testing for Monogenic or Single Gene Defects

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Preimplantation genetic testing for monogenic or single gene defects, also known as PGT-M, is the process used to screen for specific single gene abnormalities. While PGT-M sounds a lot like PGT-A, there is a difference. As discussed earlier in the module, PGT-A is used to screen embryos for chromosomal abnormalities, while PGT-M is used to screen embryos for genetic abnormalities. Within our chromosomes, certain stretches of DNA are organized into genes. Since we have two copies of every chromosome, we also have two copies of every gene. Changes within these genes are called “variants”. Variants can be inherited from parents or can occur spontaneously. Some variants cause harmless changes, like differences in hair and eye color, but other variants, called mutations, can lead to genetic disease. When a child is conceived, the chromosomes and genes from the sperm and egg can combine in four possible variations, each with a 25% likelihood. If a person has a working copy and a non-working copy of a gene for a recessive condition, they are called a “carrier”, which is where the term “carrier screening” comes from. Carriers typically do not exhibit any symptoms of the condition they carry, and their carrier status typically has no impact on their health or well-being. In order for an individual to be affected by an autosomal recessive condition, individuals must have two non-working copies of the gene and no working copies of the gene. For this to occur, both parents must be carriers of the genetic condition. If both a mother and a father are carriers for the same autosomal recessive condition, they have a 25% chance of having an affected child, a 50% chance of having a child who is unaffected but is also a carrier, and a 25% chance of having an unaffected child. The process of PGT-M facilitates the testing of each embryo to identify if it is affected by the disease, completely unaffected by the disease, or just a carrier of the disease. With this approach, the affected embryos are identified and will not be transferred, thereby preventing the resulting child from having the disease. The same biopsy and analysis process is performed in a PGT-M cycle as is in a PGT-A cycle. Blastocysts are biopsied and then frozen. The specialized genetics laboratory will analyze the DNA and provide a report regarding the status of the embryo with regards to the specific genetic disease. Simultaneously, PGT-A can also be performed to assess the chromosomal status of the embryos. Once unaffected or carrier unaffected embryos are available for transfer, a frozen thaw embryo transfer cycle can be performed. There is a small, approximately 2-5% chance of an embryo having a false positive or false negative result with PGT-M. A false positive is when the embryo is diagnosed as being affected with the genetic disease when it is actually unaffected. A false negative is when the embryo is diagnosed as being unaffected but is actually affected. PGT-A and/or PGT-M cannot guarantee the birth of a chromosomally or genetically normal child, and is not a replacement for prenatal diagnosis via chorionic villus sampling (CVS) or amniocentesis. While there is some risk involved, technological advances have made PGT-A and PGT-M effective tools. It is important to understand the benefits, risks, and alternatives involved in order to make an informed decision on pursuing PGT-A and/or PGT-M. These topics should be discussed thoroughly with your genetic counselor and medical team.

Mosaicism

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Mosaicism is the presence of two or more cell types within a single embryo. A mosaic PGT-A result indicates that within the biopsied sample, some of the cells have the normal number of chromosomes while other cells have an abnormal number of chromosomes. Mosaicism is identified in approximately 10% of PGT-A tested embryos. The technology to detect mosaicism through PGT-A has only recently become available, and outcome data from the transfer of mosaic embryos is extremely limited. Prior to this technology, embryos were either classified as euploid or aneuploid. Studies to date show significantly increased rates of pregnancy loss and failed implantation after the transfer of mosaic embryos compared to the transfer of euploid embryos. Live births resulting from the transfer of mosaic embryos have been reported and appear thus far to be healthy, but it is important to note that it will be years before the long-term development and health of these offspring will be known. Euploid embryos are always chosen for transfer over mosaic embryos. If PGT-A results show that the only embryos available for transfer are mosaic, the preferred option is to undergo an additional round of IVF and PGT-A, with the goal of producing euploid

embryos. However, if additional treatment cycles are not possible, you may have the option of transferring certain types of mosaic embryos. If considering the transfer of a mosaic embryo, you will meet with a genetic counselor to review the specific chromosome abnormalities involved and potential risks, including failed implantation, pregnancy loss, or the birth of a child with intellectual or physical disabilities. The process of deciding whether to transfer a mosaic embryo is complex and personal, and should be carefully considered with the guidance of your medical team.