REVIEW ARTICLE

Genetic Counseling in Reproductive Issues: Emphasis on the Genetic Aspects

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Abstract

Aim: To provide information regarding contributing genetic factors and emphasize the importance of genetic counseling in reproductive issues.

Background: Genetic counseling is a communication process, where a trained genetic counselor helps educate the client about the genetic background and comprehend the options available to deal with the risks and guides them to choose an appropriate line of action that is relevant in their perspective. A client could be indicated for genetic counseling for reproductive issues such as recurrent spontaneous abortions or infertility (primary and secondary infertility or subfertility). There are various etiological factors responsible for these issues, regarding the pregnancy itself or the environment, but genetic factors are a major cause and account for approximately 5% of pregnancy loss.

Conclusion: There is poor awareness and knowledge with regard to the role that genetics plays in reproductive issues, which could cause miscarriages, recurrent abortions, or fertility issues. Obviously, there is a requirement for generalized education of communities and targeted interventions at the primary level itself, but in the clinical setting, it is the responsibility of the genetic counselor to counsel in a nondirective and nonbiased way so that the client has authority to make a decision in complete autonomy.

Clinical significance: Out of all the clinically recognized pregnancies, 10–15%, globally, end in a miscarriage and the recurrence risk increases with each consecutive pregnancy loss. Chromosomal abnormalities account for around 50–66% of all miscarriages. Infertility is also a major problem in India and it affects 10–14% of Indian population. In order to clearly understand the causes of reproductive issues in the Indian context, all the above factors need to be further investigated.

Keywords: Chromosomal abnormalities, Genetic counseling, Genetic factors, Infertility, Recurrent spontaneous abortions, Reproductive issues.

International Journal of Infertility and Fetal Medicine (2019): 10.5005/jp-journals-10016-1182

Background

Genetic counseling is a communication process between a client and a trained genetic counselor; it's a professional evaluation of certain risk factors concerning one's family history and/or pregnancy. Genetic counselors are allied health professionals who work in a number of clinical backgrounds including cancer genetics, clinical genetics, prenatal genetics, etc., and are responsible for educating their clients, other medical professionals, along with the general public about a particular genetic disorder.

Reproductive genetic counseling can be indicated for advanced maternal age (>35 years) if there is elevated risk of aneuploidy (most commonly done for trisomy 21, 18 and 13) or neural tube defects indicated in the maternal serum screening, or if there is presence of soft markers indicated by ultrasound. Other indications for counseling to be advised could be if one or both parents are carriers for a particular genetic condition (balanced chromosomal rearrangements) or if they have an affected first child or a family history of mental retardation, chromosomal abnormalities, cleft palate, congenital heart defects, single gene disorders, neural tube defects, recurrent pregnancy losses (stillbirths, miscarriages, premature infant deaths), subfertility, or various alternative disorders that could be genetic. Couples who are close blood relatives (consanguineous marriages) are also advised for genetic counseling. Premarital counseling or preconception counseling is advised to couples at a higher probability for genetic disorders based on family history or couples experiencing infertility.

The counselor needs to make the patient understand that they do not treat the patient but instead help them get to the bottom of the medical facts, which include the diagnosis, the likely foundation of the disorder, and the management that is available for the same along with the implications that the suggested course of action may have on themselves, their family, and their future generations. They also explain how the disorder is inherited and how it can possibly affect the future generations and help comprehend the options available so as to deal with the recurrence risks and guide them to choose an appropriate line of action that seems relevant in their perspective of the risk involved and act with respect to that choice.[1]

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How to cite this article: Pargaonkar AP, Talagadadeevi R, Parvathi VD. Genetic Counseling in Reproductive Issues: Emphasis on the Genetic Aspects. Int J Infertil Fetal Med 2019;10(2):21–27.

Source of support: Nil

Conflict of interest: None

Reproductive Issues

Abortion

Abortion or pregnancy loss refers to the termination of a pregnancy and can be stated as "the illegal or forcible expulsion of the product of conception from the mother's womb, with or without the consent of the mother at any time during the period of gestation." Pregnancy

loss transpires due to various etiological constituents wherein the growing embryo is unable to survive and is expelled from the pregnant woman at different gestational ages.[2]

Abortions are actually of two types, namely, induced abortions and spontaneous abortions. Induced abortions are actually intended pregnancy terminations that are undertaken for whatever reason the woman wants to end the pregnancy. Spontaneous abortion, or miscarriage, is a complication of pregnancy and is an unintended pregnancy termination where around 70% of human conceptions are unsuccessful in achieving viability. The World Health Organization (WHO) has defined miscarriage (which usually occurs around 20–22 weeks of gestation) as the loss of a fetus that weighs less than 500 g. Patients with early pregnancy loss usually present with a combination of a defective placentation, a hypoxic environment, as well as oxidative stress.

Recurrent spontaneous abortion (RSA) is the condition where there is loss of two or more successive pregnancies prior to 20 weeks of gestation and is roughly estimated to have an impact factor of ~1% on all couples trying to conceive. The causes of RSA remain idiopathic in 50% of cases. In RSA, there could either be problems taking place with the pregnancy itself, which include chromosomal aberrations, or there could be other etiological factors with respect to the environment of the pregnancy such as uterine abnormalities, endocrine malfunction, immunological disorders, infections, and other unknown factors. But genetic factors, although poorly understood, are a major cause and account for approximately 5% of pregnancy loss.[3]

Chromosomal Abnormalities

Genetic abnormalities such as balanced chromosomal translocations within the embryo (the most common causes of spontaneous abortions) may be errors of mitosis, meiosis, or fertilization. Maternal meiotic errors also lead to autosomal trisomies, which represent about 20% of the total population of first-trimester spontaneous abortions. Studies done on sperm have also shown that paternal meiotic errors have a possibility of causing an abnormal fertilization. A common reproductive problem is aneuploidy in the fetus, which is reported to occur in 5–10% of all pregnancies. Most of the aneuploid fetuses die *in utero*, which thereby result in an early pregnancy loss.[4,5]

The analysis of the karyotypes done in recurrent abortions suggested that RSA in women can also be a cause of chromosomal anomalies taking place recurrently in the fetus as a result of balanced (reciprocal and Robertsonian) translocations within one parent, which the fetus then inherits in the unbalanced form. The carriers of balanced translocations have a risk of conceiving an embryo with a chromosomal abnormality due to anomalous segregation at meiosis, which ranges from 20 to 80%.

The most common aneuploidy is [45,XO] Turner syndrome, having an incidence of 14.6%. Trisomies are the largest group of chromosomal abnormalities, which are associated with miscarriages among which the most common trisomy is trisomy 16, followed by trisomy 21 and 22. About 6% of miscarriages are a result of trisomy 16 and 20% of genetic abnormalities are triploidies. These chromosomal abnormalities can be passed down one generation to another or may arise because of abnormal oocyte spindle formation and meiotic division in the germ cells, which takes place *de novo*. The translocations where two chromosomes are involved in a mutual exchange of broken-off fragments, are considered to be the most discerned paternal chromosomal aneuploidies that contribute to miscarriage.

Down syndrome (trisomy 21) is known to be the most common reason of mental retardation (mean intelligence quotient = 24) and has the greatest incidence at birth out of any other chromosome anomaly (about 1 in 700 live births). All children with Down syndrome have a very high risk of infectious morbidity and congenital defects and have a noticeably shortened life span, with a 10- to 20-fold elevated risk for early-onset dementia along with leukemia.

Although most fetuses with aneuploidies are nonviable and thereby lead to premature miscarriage, a few have the potential to survive to the newborn period. Most cases with trisomy 13 and 18 correspond to serious clinical morbidity and an elevated rate of mortality just shortly after birth. For these reasons, significant efforts have been spent over the years to identify such fetuses earlier in the pregnancy so as to appropriately counsel the couples so that they have sufficient time to consider their reproductive options.

X Chromosome Inactivation (XCI)

It is the condition where out of the two X chromosomes that are present in all somatic cells of a healthy female, one X chromosome is rendered inactive during primary embryogenesis. It's crucial for appropriate dosage compensation in females and it occurs such that the X chromosomes (derived paternally or maternally) are rendered inactive with around the same incidence, wherein the dosage imbalance of the X-linked genes between males and females is functionally equalized. Therefore, women are mosaics for two cell categories: one for those cells where the active X chromosome is acquired paternally and the other for those cells where it's acquired maternally. When there is a deviation occurring from this distribution, it's called the skewed XCI—the phenomenon of preferential inactivation in approximately 80% or more of the cells of any one of the two X chromosomes, which maybe a probability event or maybe because of any genetic factors that are associated with the original X inactivation process.[6]

Other propositions that have been done also state that X-linked mutations (fatal in males) give rise to skewed XCI in the female carriers, which include microphthalmia with linear skin defects (MLS) syndrome) and oral-facial-digital syndrome type I (OFD1). These types of mutations have an outcome where there is a loss of the male fetus and thereby give a higher frequency of miscarriage in the carrier females. Immensely skewed XCI of greater than 90% has been reported in females with a history of RSA.[7,8]

Gene Mutations and Polymorphisms

There are mutations taking place in a number of genes that contribute to recurrent miscarriages. One such gene is the *methylenetetrahydrofolate reductase (MTHFR)* gene that codes for the *MTHFR* enzyme, which is in charge of converting homocysteine into methionine via a multistep process. It is responsible for catalyzing the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, which plays a part in the vitamin B12-dependant remethylation. It's responsible for the conversion of homocysteine to methionine, which is further converted to S-adenosylmethionine (methyl group donor in the methylation of proteins, DNA, phospholipids, and neurotransmitters).

Individuals with *MTHFR* gene mutations have an accumulation of homocysteine, which causes blood clots and is linked to recurrent miscarriages. There is a firm association between neural tube defects (NTD) and elevated homocysteine concentrations, which has led the way to the theory that elevated homocysteine

concentrations could be toxic to the embryo and thereby lead to decreased fetal viability. Also, low concentrations of vitamin B12 (cobalamin) or transcobalamin give rise to hyperhomocysteinemia (correlated with NTD and trisomy 21); it has transcobalamin 776C>G polymorphism and MTHFR 677C>T and 1298A>C polymorphisms. Neurological abnormalities and mental retardation occur due to hereditary deficiency of transcobalamine. The importance of supplementation before conception, in women who are still planning a pregnancy, with vitamin B12 and folate could perhaps reduce miscarriage incidence.[9]

Alternative genes have also been correlated with pregnancy loss. Mutations of the *SCO2* gene (cytochrome c oxidase (COX) assembly gene) located on chromosome 22, have been identified in the heterozygous state in aborted fetuses and are suggested to cause miscarriage.[10]

Infertility

Infertility is a condition of the inability or incapacity to bear a live birth where there is lack of genetic productivity in either one or both partners to give birth to a child even after unprotected coitus for a period of time. The complication leading to this condition could be due to a male or female factors or both. A successful fertilization occurs when the sperm fuses with the ovum and this could be obstructed due to certain genetic or environmental factors in the individual, which gives rise to infertility. The genetic factors include mutations in genes that code for specific proteins, which are responsible for spermatogenesis or ovulation. Mutations can also lead to the reduced motility of the sperm or can give rise to different shapes of the sperm head: pinheaded, roundheaded, double-headed, no head, etc.

In males, the underlying cause of infertility is due to genetic factors that include chromosomal disorders and recently it has been realized that the gamete formation in human males is dependent on the orderly arrangement of genome. When there is a mutation in the gene, it may lead to the production of abnormal gamete. When the genes obstruct the gametogenic process, it prevents the relocation of the germ cells that takes place from the yolk sac to the gonadal ridges of the early embryo. The action of such genes seems to have severe effects on gametogenesis in adults.

In females, the underlying basis for infertility is failure in the ovulation process or tubule blockage. A female cannot conceive when there is absence of ovulation as it's the only process that helps in the germination of eggs. Similarly, when the fallopian tube is blocked, it is impossible for the sperm to reach the ovum for fertilization.

Types of Infertility

Infertility is basically of three types:

- Primary infertility: The situation where a couple have been unable to conceive even after repeated sexual intercourse for a minimum of 1 year.
- Secondary infertility or acquired infertility: The situation where the couple have already experienced a pregnancy and have a child previously but due to the decreased rate of fertility, they fail to conceive again. This means they have acquired infertility after a certain period of time. This condition can be improved by medical treatment.
- Subfertility: It's a form of reduced fertility and is a prolonged time of undesired nonconception.

In Males

Infertility in men could be due to genetic or environmental factors. Primary infertility in males can be caused due to globozoospermia, which is a condition where the sperm lacks an acrosome and is roundheaded. Usually a healthy sperm has an oval-shaped head with an outer layer of covering called an acrosome, which contains certain enzymes that help in the breakdown of the outer membrane of the ovum leading to fertilization. In case of the absence of an acrosome, the fertilization of an egg does not occur and leads to infertility. The gene that is involved in this condition is *DPY19L2* and it is responsible for the production of certain proteins that are in turn responsible for the oval-shaped head and the elongation for the sperm cell and its maturation. Hence, the mutation in the *DPY19L2* gene will obstruct the production of the DPY19L2 protein and result in nonelongated and roundheaded sperm cells leading to infertility. Through the research analysis, they found that the cause of infertility is due to the deletion of 200kb on chromosome 12 of the gene *DPY19L2*, which has occurred due to consanguineous marriage of their grandparents.[11]

Asthenospermia is also one of the possibilities leading to primary infertility in males. A healthy sperm usually has appreciable motility (25 micrometer per second), an acrosome, an oval-shaped head, and passes through the outer membrane of the ovum. But in case of asthenospermia, the motility of the sperm is known to be less than 5 micrometer per second, which leads to infertility.

With respect to secondary infertility, in recent studies it has been reported that azoospermia factor microdeletions on the Y chromosome could lead to infertility in men. The Y chromosome has genes that code for certain proteins that take part in spermatogenesis. When a deletion occurs in the specific region of the Y chromosome, it results in the arrest of spermatogenesis. To study this condition in detail, few scientists conducted an experiment in which they made seven divisions in the Y chromosome. These were further divided into subintervals—A, B, and C. With the help of the tagged sequence sites, the whole Y chromosome has been spanned. The genes involved in spermatogenesis present on the Y chromosome were found to be deleted at the intervals 5 and 6. This region was called the azoospermia factor. The azoospermia region contains three nonoverlapping loci (AZFa, AZFb, and AZFc). When there was a deletion in this region, it resulted in spermatogenic arrest.[12,13]

The commonly identified contributing factors associated with subfertile couples include sexual dysfunction or abnormal semen quality, which affects 1 in 20 males. The most common cause of male subfertility is idiopathic oligoasthenoteratozoospermia (iOAT), which affects around 30% of all infertile men. There is considerable reduction in the fertilization capacity due to the increase in the concentrations of reactive oxygen species in the semen, which eventually damage the cell membrane. Therefore, the morphological changes in the sperm are an indicator of reduced fertilizing capacity.

The possible causes of iOAT are known to be age, infective agents, noninflammatory functional alterations in post-testicular organs, variations in the genome of the gamete, alterations in the mitochondria, environmental pollutants, and hormonal changes. Autosomal Robertsonian reciprocal translocations are caused because of the poor sperm quality and subfertility. Most cases of severe iOAT are also a result of idiopathic testicular disorders. Severe iOAT is a result of idiopathic testicular abnormality. Genetic tests were seen to be normal in around 7–10% men (who have sperm

counts accounting to less than 5 million/mL). Treatment of severe iOAT scarcely improves the semen quality, but intracytoplasmic sperm injections (ICSI) are frequently successful. Testicular or genital tract disorder, systemic constituents, along with other extrinsic factors (which could include lifestyle changes or drugs) can also cause male subfertility.

Furthermore, a number of drugs also impede sexual function or spermatogenesis, such as anabolic steroids and sulfasalazine, colchicine, chemotherapy, etc. But fortunately, the effects are known to be reversible, thereby enabling fertility to revert back to normal within 6–12 months once they are withdrawn.

The serum analysis is done for the assessment of male fertility and based on the results, the patients are recommended for a specialist opinion. A specific diagnosis is to be sought. The clinical diagnosis includes a 66% incidence of congenital bilateral absence of vas deferens along with nonobstructive azoospermia (which refers to absence of sperm in semen) as a result of 47, XXY (Klinefelter's syndrome) with an incidence of 15–30% and severe oligozoospermia (reduced sperm numbers) as a result of 47, XXY (Klinefelter's syndrome) having an incidence of 1–2% and Y-chromosome micro deletions with an incidence of 7–10%.[14]

In Females

Female primary infertility could arise due to oocyte maturation arrest. This condition was found to be present in 30% of individuals, due to the mutations in the gene *TUBB8*. Various studies have provided evidences for the phenotypic characteristics of oocyte germinal vesicle arrest by the gene *PATL2* in a homozygous nonsense mutation. A phenotypic variability is seen in individuals having gene mutations in a heterozygous condition. The gene *PATL2* is responsible for producing certain proteins that guide the oocyte maturation. The process of oocyte maturation is obstructed, due to the mutation, thereby leading to infertility in the individual.[15]

When it comes to secondary infertility, premature ovarian failure takes place in about 1% of women and is a condition that leads to hypergonadotropic hypogonadism. Hypogonadism is a condition caused when there is a damaged response in the gonads targeting the gonadotropins and hormones, which will inhibit the sex steroid production and accumulate the gonadotropin levels. Premature ovarian failure (POF) and leukodystrophy are the co-occurring conditions of ovarioleukodystrophy. The change in a specific gene due to mutation is the reason behind ovarioleukodystrophy. The genes that are responsible for this condition is *EIF2B1* to *EIF2B5*.[16]

According to a study conducted in Germany in September 2014, it was found that the basic components that are responsible for diminishing the chances of pregnancy in subfertile women are age, diabetes, endometriosis, dysfunction of the ovaries, PCOS, or any infection that has happened previously in the genitourinary tract. A few factors have also been shown to improve pregnancy rates, specifically, the utilization of hormonal contraceptives, prior pregnancy, or birth and progesterone therapy.[17]

The most common causes of female subfertility include anovulation, blockage of the tubes (which can happen after the woman is suffering with a sexually transmitted infection or can also arise due to ectopic pregnancy), and cervical hostility. Anovulation is when the ovaries fail to release a mature ovum or oocyte during the menstrual cycle, leading to anovulatory cycles and can manifest in various clinical presentations, such as luteal insufficiency, oligomenorrhea (irregular periods) or amenorrhea (absence of periods). Complications of anovulation comprise of endometrial hyperplasia, cardiovascular disease, arrhythmia, insulin resistance, or type II diabetes mellitus, among other constituents.

The most common cause of anovulatory subfertility is polycystic ovary syndrome (PCOS) and it accounts for around 70% cases. Excess production of androgen within the ovary seems to be the primary abnormality, which leads to the recruitment of small preovulatory follicles, which do not respond to normal concentrations of follicle-stimulating hormone (FSH). Even if the women with PCOS ovulate, the chances of conception for them is reduced because of the fewer ovulatory events occurring within a particular time. Obesity increases the chances of women with PCOS developing anovulation. The most common genetic cause includes Turner's syndrome (45,XO) in which there is primary ovarian failure or premature menopause, which is a result of underdeveloped ovaries.[18] A tabulation summarizing the common genes involved in infertility in males and females is given in Table 1.

Inheritance Patterns and Recurrence Risks

The significance of accurate diagnosis cannot be overemphasized. The principle component of the process of genetic counseling begins with a correct diagnosis, which depends upon diagnostic decision making, the identification and recognition of crucial phenotypic signs, application of the principles of medical genetics, and proper laboratory diagnosis. For conditions defined by a specific laboratory marker, which could include an abnormal karyotype or a biochemical assay, the procedure of diagnosis is straightforward, but for many genetic disorders, where there are no well-established criteria, the diagnosis can be fairly challenging.

The inheritance patterns of single gene disorders can either be sex-linked or autosomal dominant/recessive. Every gene has a pair of alleles, which controls its expression and function that exist in a homozygous or heterozygous condition. In case of a heterozygous dominant variant, a dominant allele is found in combination with a recessive allele, which overshadows the phenotypic expression of the recessive allele. Recessive alleles on the other hand need to be present in a homozygous condition in order to be expressed. An individual has a pair of alleles, one inherited from each parent. A few changes in either of the alleles might or might not lead to phenotypic expression. The former is called a single nucleotide polymorphism, whereas the latter is called a mutation. The diseases caused by mutations are usually inherited based on the location of the gene or the requirement of one or two normal alleles. Certain conditions involve individuals with the same mutation showing different symptoms. Conversely, individuals suffering from different mutations show similar phenotypic characteristics, which could be attributed to the influence exercised by the genes or various other environmental factors.

Autosomal dominant diseases are inherited in every generation as a dominant allele expresses itself in a heterozygous condition whereas autosomal recessive diseases are not observed in every generation as recessive alleles express themselves only in the presence of their recessive counterparts. There are a lot of carriers of the mutation that are observed in this type of inheritance pattern. X-linked disorders are inherited in a dominant and recessive manner as well. Since males possess a single X chromosome, it makes them more susceptible. Females are usually carriers and phenotypically express the mutation only when it is present in a homozygous

Table 1: Genes involved in infertility of males and females

In males	*Genes involved*	*In females*	*Genes involved*
Globozoospermia	*DPY19L2*	Oocyte maturation arrest	*TUBB8*
			PATL2
Asthenospermia	*CATSPER1*	Premature ovarian failure	*EIF2B1* to *EIF2B5*
Azoospermia factor	*DAZ*	Anovulation	*BMP15*
	CFTR		
	CDY		
	PRY		
	PRY2		
	RBMY		
Idiopathic oligoasthenoteratozoospermia	*GSTP1*	11 beta-hydroxylase deficiency	*CYP11B1*
	GSTM1		
	GSTT1		
Kallman syndrome/hypogonadotropic hypogonadism	*KAL1*	Hypergonadotropic ovarian failure	*BMP15*
	LEP		
	GNRH1		
	FGFR1		
	CHD7		
	NSMF		
	KISS1		
Oligozoospermia	*NR5A1*	Fragile X syndrome	*FMR1*
	KLHL10		
Azoospermia	*HSF2*	Endometriosis	*HSD17B2*
	ETV5		*STAR*
	PRM2		*SF1*
	SOHLH1		*CYP19A1*
	GILZ		
Myotonic dystrophy	*DMPK*	Polycystic ovarian syndrome	*PCOS1*
			INSFBN3
			INSR
			SRD5A1
			SRD5A2
			CYP11A1
			FTO
			DENND1A
Testicular disorder of sex development	*SRY*	Leiomyomas	*MED12*
	SOX9		*COL4A5*
	NR5A1		*COL4A6*
	SOX3		*HMGA2*
	RSPO1		*RAD51B*
	DAX1		

dominant or recessive form. Y-linked inheritance affects males only. The recessive allele is expressed in its singular form in males as there is no dominant counterpart to suppress its effect.

The risk associated with autosomal dominant inheritance is 50% wherein there are high chances of half of the total progeny present to be afflicted with the particular condition. In case of autosomal recessive inheritance pattern, the risk assessment involves 50% of the progeny being carriers, 25% of the progeny being affected, and the remaining 25% being completely unaffected.

In the X-linked dominant inheritance pattern wherein the female is affected in a heterozygous condition and the male is unaffected, 50% of the progeny are affected whereas the other 50% remain unaffected. The progeny of a heterozygously affected female and an affected male will show 100% affected and the progeny of a homozygously affected female and a normal male will also show 100% affected. In X-linked recessive inheritance, the progeny of a heterozygous carrier female and an unaffected male will show 25% affected, the progeny of a heterozygous carrier female and affected male will show 50% affected, and the progeny

of a homozygously affected female and affected male will show 100% affected.

Another independent risk factor that is observed for miscarriages is advanced maternal age (usually of >35 years), irrespective of reproductive history, wherein, the risk surges rapidly after the age of 35. The chance of stillbirth and ectopic pregnancy also escalates with maternal age. Elevated maternal age has an increased risk of the occurrence of aneuploidy conditions such as Down syndrome, Edward syndrome, and Patau syndrome.

Human Fetal Tissue Research

The cells or tissues derived from a fetus after an induced (elective) or spontaneous (natural) abortion or a stillbirth are known as human fetal tissues. These cells are then harvested either for establishing cell lines or to be utilized as transplantation material. Fetal research refers to research with embryos. Fetal research includes invasive and noninvasive techniques, and these have led to major advances in the diagnosis as well as the treatment options of the conditions that have a high rate of clinical morbidity and conditions that can eventually threaten the survival of a pregnant woman or a fetus. Once the cell lines are established after culturing, they can then be used either to evaluate a drug's capacity to damage genetic material or simply to assess the effect of certain infections.

The instigation of polio vaccine through the use of fetal cell lines in the 1950s has been one of the greatest medical innovations of our time done via fetal tissue research. It was first used in 1982 for transplantation in a patient suffering from Parkinson's disease, when Swedish physicians transplanted fetal brain cells into the patient. Since then, many experiments have been conducted to examine the effectiveness of fetal cells as transplanting materials and to find a cure or minimize the effects of some blood disorders, diabetes, and neurological disorders.[19]

It holds promise as a therapy for a lot of conditions, namely, DiGeorge's syndrome, diabetes mellitus, and also for neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, etc. As these diseases do not have a cure, many scientists have pushed forward with research including transplant therapies in this field to find a solution. As materials salvaged from abortions are the only source of the fetal tissue, there are a group of people who are naturally opposed to the research, and it has obviously raised a number of ethical concerns.

Obtaining the woman's voluntary and informed consent is absolutely necessary. The woman who makes a donation of the fetal tissue should first sign a statement proclaiming that the donation has been made for therapeutic research and that the identity of the recipient is unknown to the donor.

The attending physician must also sign a statement declaring that they have acquired the tissue with the donor's signed statement and that they have explicitly communicated to the donor their intent to use the tissue in research and that the technique used for inducing the abortion and the point in time of the abortion in association to the gestational age of the fetus are based on concern for the pregnant woman.

The physician's statement must explicitly declare that they have the woman's consent for the abortion before obtaining or requesting consent for the tissue to be used if the tissue is obtained in accordance to an induced abortion, and that they did not make any alterations to the timings, the method, or the procedures that were used to terminate the pregnancy (just for the purpose of obtaining the tissue for research) and that the woman's decision to terminate the pregnancy was made independent of any discussion of using the fetal tissue for research purposes.[19–21]

Discussion and Conclusion

The desire to have a child is a part of human life cycle; failure to conceive is, in consequence, a very disheartening situation. The physical, emotional, as well as the financial toll of a pregnancy loss is huge. In the Indian context, it is not possible to have an authentic evaluation regarding the ratio of pregnancy loss as the records are generally incomplete. Most of the studies that we have come across have suggested that there is no well-grounded estimate to the extent of abortions that occur in India. Women or men in India do not have a control over their fertility as a consequence of poor health (as around 25% of people in India are below poverty line), and hence they have a very high probability of experiencing abortions, either once or recurrently.

There is a significantly lesser degree of awareness and knowledge with regard to the role that genetics plays in reproductive issues, which could cause miscarriages, recurrent abortions, or fertility issues. Obviously, there is a requirement for generalized education of communities and targeted interventions at the primary level itself, but in the clinical setting, it is the duty of the genetic counselor to counsel in a nondirective and nonbiased way so that the client has the authority to make a decision in complete autonomy. They provide psychological, social, and emotional support by being empathetic towards the condition of the patient and by discussing new coping-oriented strategies to help accept and manage the situation.

Genetic counseling for infertility or recurrent miscarriages in India is a sensitive issue as it carries a social stigma. Infertility can evoke feelings of hopelessness as they are unable to conceive a child even after unprotected coitus for a repeatedly longer time. The complication leading to infertility could be due to male/female or both. In India, it was earlier considered that only women were infertile and responsible for not conceiving but studies have proved that even men contribute toward infertility.

The goals of counseling in reproductive issues differ with respect to the predicament of the patient and the treatment options that they wish to go forward with such as assisted reproductive technologies (ART). They help individuals be familiar with their choices when it comes to treatment continuation or termination. If the patient or their partner are indicated to be carrying genetic defects that could be transmitted to the child, then the doctor will advise against proceeding with ART but if not then the couple can choose for ICSI and PGD to have a baby. But if the couple decides to have a child with a genetic defect (e.g., AZF microdeletion), then the counselor will make them aware of the interventions that they need to take so that their son can preserve his fertility in the future.

They will encourage preimplantation genetic diagnosis that permits the individual to give birth to a baby, along with pre-ART counseling that will identify the dormant teratogens and risk factors and thereby prevent transmission of the same to the offspring. They should also cover the effects of ART. Thereby, they will encourage preimplantation screening and prenatal screening.

Clinical Significance

Out of all the clinically recognized pregnancies, 10–15%, globally, end in a miscarriage and the recurrence risk increases with each consecutive pregnancy loss. Miscarriages still remain the most

common complication of pregnancy despite the fact that a considerable amount of research and progress has taken place in the field of reproductive medicine in the past few decades. Out of all human conceptions, fetal viability is attained in an estimated 30%, among which 50% are lost before the first missed menses. Within 7–14 days following the attachment to the uterine endometrium, the number of implanted embryos that are resorbed are estimated to be around 25%. The percentage of clinically recognized pregnancies that are lost before 20 weeks of gestation is 15%. Chromosomal abnormalities account for around 50–66% of all miscarriages, among which chromosomal aberrations occurring in the conceptus in the first trimester are around 50%, those occurring in the late pregnancy are around 5%, and 0.5% are occurring in live births. Balanced translocations (reciprocal and Robertsonian translocations) are common and have been recognized in around 4% of couples with RSA. It has been reported that the recurrence risk increases with each successive pregnancy loss. The pregnancy loss risk in women with at least one live born infant without any previous fetal loss is 12% for the next pregnancy, whereas the recurrence risk percentage for those with at least one to three prior losses is 24, 26, and 32% respectively. However, for the women without a live born infant and with two or more fetal losses, the risk percentage for the upcoming pregnancy increases up to 40–45%. Infertility is also a major problem in India and it affects approximately 10–14% of India population, with higher proportion in urban areas and nearly 27.5% couples actively trying to conceive suffer from infertility. In order to clearly understand the causes of reproductive issues in the Indian context, all the above factors need to be further investigated.

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