

Transferring Mosaic Embryos during ART Cycles: Increasing the Load of Genetic Diseases in Human Generations—A Critical Analysis

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ABSTRACT

“Mosaic” as an adjective describes any type of work or art which is produced by joining of many small pieces differing in size and color. Virtually all multicellular organisms are mosaics of cells with different forms and functions. Normal developmentally determined mosaicism involves permanent changes in the DNA of somatic cells giving rise to specialized cells of various organ systems of the body. Several mechanisms, such as cell cycle dysregulation, centrosome overduplication, and cancer formation, have been reported as end products of mosaicism, either chromosomal or germline, arisen prenatally or postnatally, in many cases. There is an extensive literature present which describes the presence of genetic mosaicism in human diseases. With the development of more advanced molecular genetic diagnostic techniques, it has been recognized that genetic mosaicism is involved in many monogenic and polygenic complex diseases. This review highlights the dilemma between the creation and transferring of the mosaic embryos detected by preimplantation genetic diagnosis aneuploidy testing during assisted reproductive technology cycles. The main question of concern is not only the implantation potential of the accepted mosaic embryos but also the well-being of future generations to follow from these phenotypically normal mosaic individuals.

Keywords: Genetic load, Intracytoplasmic sperm injection, Mosaicism, Mosaic embryos, Preimplantation genetic testing.

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WHAT IS MOSAICISM?

Mosaicism is the result of mitotic errors and it can be described as the presence of dissimilar cell populations with distinct genotypes in an individual. Its clinical repercussions are immense in practice of embryo transfer during assisted reproductive technology (ART) cycles as transference of genetic information is crucial to human growth and development.¹ Aneuploidies many times are an end product of aberrant chromosomal segregations occurring either during gametogenesis or somatic division. These types of aneuploidies are generally deleterious for cellular or organismal fitness. These anomalous mutations give rise to mosaicism within an organism and are an outcome of postzygotic mutational events. These kinds of mutations vary from being big structural variants or aneuploidies to single nucleotide polymorphisms (SNPs). As our insight on complexities of the human genome is increasing day by day, our understanding of involvement of mosaicism in various diseases is also increasing. Now scientists are realizing that phenotype or expression of a disease may vary depending on the type of mutation, location, and the number of affected cells by mosaicism in an organ.²

Almost 70% of cleavage-stage embryos and 90% embryos in the blastocyst stage were found to have genetic mosaicism in them during the ART cycles. So, we can say that mosaicism is not an exception but a rule in the ART industry. At the level of an organism, mosaicism can be classified into two types, i.e., somatic mosaicism and germline mosaicism. The most common inheritance patterns seen in the case of germline mosaicism are autosomal dominant and X-linked, though it can be observed in any inheritance pattern. As mosaic germline mutation can be passed on to next generation, it is the most significant type of mosaicism.³

In most cases, it is only after the birth of affected children that individual becomes aware about his/her germline mutation status.

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The progeny of an individual with mosaic germline mutation in its egg or sperm cell will have mosaicism in all its cells, and in further worse scenario if this mutation is autosomal dominant, the child will have a genetic disorder and not just be mosaic-like parents. In case of somatic mutation, the individual may or may not get the genetic disorder caused by that particular mutation, and individual phenotype will depend on the number and type of cells affected.⁴ An individual carrying somatic mosaicism who manifests a milder phenotype of a genetic syndrome may have only a small proportion of cells with mutation or the mutation is restricted to a small section of body cells. But in case somatic mutations take place in the initial development stages, they can affect the whole organ or organ system. The best example for somatic mosaicism includes mosaic Down syndrome and mosaic Klinefelter syndrome. Though all mutations are not deleterious to the tissue structure and function but as our knowledge is increasing about mosaicism, we now know that mosaicism in a clonally expanded form can kick in many detrimental effects in humans. It has been known for long

about the link of constitutional aneuploidy occurring during egg development as the main promoter for female fertility decline due to aging. Turning on or off of genes during cell differentiation is a very crucial phenomenon, as the outcome of a particular mutation on a tissue or life stage will directly depend on it. With every coming day, the overall understanding of the role of somatic mosaicism in human health is increasing. In diseases like cancer, developmental or neurological disorders, somatic mosaicism plays a very significant role as early developmental stage mosaicism has a profound effect on the prognosis of these diseases.⁵

HOW AND WHEN IT HAPPENS?

All life junctures are vulnerable to genetic mosaicism but the early stages of development are more susceptible to mosaicism because cellular proliferation rates are quite high, whereas DNA repair capabilities diminish in the later stages of life.⁶ During an embryonic stage, some mutations are proven fatal during initial developmental periods, especially during the period of organogenesis, increasing the probability of clonal expansion and the detrimental effect on phenotype.⁷ In genetic mosaicism, mutations can affect a single base to large DNA rearrangements, which can involve a few or thousands of bases to the whole of the chromosome. A nondisjunction event during an early embryonic division can lead to an aneuploidy mosaicism, though with a milder phenotype because of the absence of mutations in all cells.⁸ In some cases, reversion of anomalous genotypes can also lead to mosaicism in an individual.⁹

Special Forms of Mosaicism

In gonadal mosaicism, a few gametes carry mutations but the rest are normal and can be transmitted to next generation as *de novo* germline mutations. These mutations happen prior to the process of spermatogenesis or oogenesis during the origination of primordial germ cells in parents. The whole of progeny will not be affected by these mutations as these mutations may present only in a few stem cells. Many studies have shown that early stages of development like early embryogenesis and differentiation of primordial germ cells are more critical and have higher capabilities to instigate mutations than succeeding stages like postpubertal spermatogenesis because the rate of mutation per cell division is much higher in these life stages.^{10,11} In confined placental mosaicism, mutations can be spotted in the chorionic villi, whereas the fetal cells show no abnormality pre or postnatally.¹² In this type of mosaicism, most of the times the fetus experiences no complication at all, and it develops into a perfectly normal child but sometimes prenatal or perinatal complications do arise. The development of placenta and the placental function may get affected by mosaicism of the placental cells without affecting the fetal cells.¹³

Clinical Implications of Mosaicism

Mosaic mutations have been linked to complex diseases like neurological disorders and cancers. These diseases are the coalescence of numerous gene mutations and epigenetic factors. The biggest factor for genomic instability in various cancers is the genetic heterogeneity of tumors. In literature, this is a well-documented fact that widespread somatic mosaicism is caused by developmental mutations in the hematopoietic system. These developmental mutations are the sole reason for childhood leukemia in many cases. The childhood cancers are

usually attributed to inheritance that is when mutation occurs prior to the very first zygotic cell division. However, a few research studies have indicated that early childhood cancers may originate from developmental mutations. In case the developmental mutations occur in the initial rounds of postzygotic cell division, then numerous stem cells begin life with mutation, and this way developmental mutations behave the same as the inherited mutations and metamorphose a fraction of cells causing mosaicism. In case a disease which is manifested is derived from mutated cells which are in a very small number, then it may be regulated by developmental mutations. Best example for this phenomenon is the cancer progression. In cancer, initially one or very few cells get affected but ultimately it embraces a large number of cells of a tissue. This way the developmental mutations seed abnormality in many stem cells and increase the risk of those predisposed cells to cancer.¹⁴

Mostly disorder caused by mosaicism is present in a milder form in its carrier than their offspring and in many cases symptoms present are so different that they can be considered as different syndromes altogether. For example, a woman had mosaicism for COL2A1 mutation and she was suffering from Stickler syndrome, but she gave birth to a child with Kniest dysplasia as her child carried this mutation in all of its cells.¹⁵ Amyotrophic lateral sclerosis (ALS), a neurodegenerative disease, also shows much of the same process. The highest risk and the earliest age of onset is for those with inherited predisposition due to mutation in every single cell as it happens in germline mosaicism.¹⁶ In somatic mosaicism, a mutation in early developmental stage has only a slightly reduced risk and outbreak of disease at a later stage, as compared to the inherited cases.¹⁷

Major psychiatric disorders and autoimmune diseases have higher incidences of chromosomal mosaicism. The degree of mosaicism in various disorders is like 16% in schizophrenia and autism, 3–5% in mental retardation, more than 10% in Alzheimer's disease, and 4% in autoimmune thyroid disease.¹⁸

Mosaicism in Embryos

An embryo with two or more cell populations with different genotypes is defined as a mosaic embryo. Embryonic mosaicism results from mitotic errors happening after fertilization. This most commonly occurs during second or third cleavage but sometimes happens during the first cleavage stage too. In case of diploid-aneuploid mosaics, one cell line is euploid and the second is aneuploid, but in aneuploid mosaics two or more aneuploid cell lines exist with 100% of abnormal cells.¹⁹

Clinical Implications of Transferring Mosaic Embryos

The pervasiveness and the outcomes of mosaicism are much more conspicuous when it is detected in the course of the cleavage stage than during the blastocyst stage, thus indicating a selection mechanism at odds with mosaicism in the later stages of development. So, clinical outcomes of mosaicism depend upon a range of factors like time when the error occurs or after its occurrence it keeps on propagating or not.²⁰ The validity of a diagnosis of mosaicism and potential of these mosaic embryos is now under scanner more because in next-generation sequencing (NGS) detection, the rate of mosaicism is much higher as compared to comparative genomic hybridization (CGH). A fear of abnormal pregnancies due to the transfer of mosaic embryos creates many apprehensions about transferring mosaic embryos during ART cycles.²¹

A study by Greco and Minasi supported the idea that mosaic embryos can self-correct themselves because in many cases mosaic embryo transfer resulted in either healthy live births with normal karyotyping or biochemical pregnancies. Another explanation for this phenomenon can be false-negative testing, i.e., the embryos which were labeled mosaic were actually euploid.²² In another study during retrospective reanalysis of whole genome of 76 blastocysts by means of NGS, which were marked as euploid by CGH, 6 of 38 blastocysts which resulted in live births were found to be mosaics. The rest of 38 resulted in miscarriages, and out of these 12 were found to be mosaics.²³ Though some mosaic embryos result in live births but the risk of early pregnancy loss is quite high in such embryos. The degree of implantation in mosaic embryos is far less than the euploid embryos. The mosaicism frequency in live births, children, and adults is not studied well because normally chromosomal analysis in live births is not very sought-after and done only when there is a clinical symptom or a compelling speculation of a chromosomal disorder.²⁴

Since the human karyotyping is introduced, cytogenetic abnormalities are the well-known reasons for the condition of being infertile. Infertility has been linked to the cytogenetic abnormalities in germ cells of individuals with infertility and who are having normal constitutional karyotypes. Determined by particular translocation, the risk of an unbalanced karyotype occurrence in a spermatozoon due to Robertsonian translocation is between 3 and 27%. A pregnancy which is an outcome of such spermatozoon could end with spontaneous abortion or a chromosomally abnormal offspring, subject to the lethality of the chromosome involved. Most of these unbalanced chromosomal constitutions are nonviable. Even though the low-risk abnormalities should be disclosed to parents, the long-term effects of abnormal pregnancy are devastating. A disomy 13 or nullisomy 13 spermatozoon can be an end product of a Robertsonian translocation between the same chromosome 13. As all spermatozoa carry this abnormality, intracytoplasmic sperm injection (ICSI) cannot be an option for such individual as all embryos would be monosomy 13 or trisomy 13 and will not survive.²⁵

There are a few kinds of translocations which have higher possibility of survival but progeny suffers from the serious outcomes including abnormal physical and mental conditions. A number of embryos with unbalanced segregations of reciprocal translocations have already been documented after ICSI.²⁶

Infertile Men with Normal Karyotypes

It is a well-known fact that individuals with somatic chromosomal abnormalities face reproductive difficulties. But in recent times, infertility in individuals with normal constitutional karyotypes but having some kind of cytogenetic abnormalities in germ cells is becoming very common. In both kinds of abnormalities, there is an enhanced risk of miscarriage and birth of mentally or physically disabled children.²⁷ Some studies have been done on sperm chromosome complements in men with normal karyotypes with a condition of infertility. The main focus of these studies was to find whether meiosis in these infertile individuals is susceptible to errors of nondisjunction which can end as an aneuploidy. It was seen that there was a marked rise in the frequency of disomy for chromosome 1, X and Y. If a spermatozoon with any disomy fertilizes a normal oocyte, this will produce an embryo with trisomy, which would in all likelihood be lost prior to implantation because this trisomy is a lethal condition for the

survival of the fetus.^{28,29} Aneuploid spermatozoa specifically for sex chromosome have been reported in infertile patients with abnormal semen parameters. Men with abnormal semen parameters like low sperm count, low percentage of motile sperms, and high follicle-stimulating hormone (FSH) have been seen carrying sex chromosome mosaicism.³⁰ Some reports about ICSI pregnancies where prenatal diagnoses have been done show an increased risk of sex chromosomal aberration, mostly with paternal origin.³¹ Familial aggregation which affects multiple individuals and generations could be linked to the germline mosaicism and this can help in finding an explanation for the reappearance of rare mutations in a single pedigree.^{32,33} Many molecular mechanisms, such as defective chromatid cohesion, cell cycle dysregulation, and centrosome overduplication, which play a crucial role in cancer formation in the body, are also seen to promote chromosomal mosaicism in human embryos.³⁴

PGDIS Guidelines

According to preimplantation genetic diagnosis international society (PGDIS) guidelines, during ART embryo transfers mosaic trisomies 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 17, 19, 20, 22, X, and Y should be favored over mosaic trisomies 2, 7, 13, 14, 15, 16, 18, and 21. This is may be because the latter group of trisomies carries the known risks of syndromes like Patau syndrome and Down syndrome. But mosaicism of other chromosomes increases the risk of intrauterine growth retardation (IUGR) and uniparental disomy. The preferred trisomies according to the PGDIS guidelines have been seen to carry abnormal phenotypes which are most probably dependent upon the fraction of the affected tissue types and abnormal cells.³⁵

Critical Analysis of the Situation

Even if there are live births out of the mosaic embryos, there have been a number of studies which propose that somatic mutations of the germ line may be existing in the phenotypically normal individuals.³⁶ Various disorders like ornithine transcarbamylase deficiency, pseudoachondroplasia, Crouzon syndrome, hemophilia A, Apert syndrome, osteogenesis imperfecta type II, Duchenne muscular dystrophy, tuberous sclerosis, achondroplasia, aniridia, and dominantly inherited ectrodactyly have all been reported in families in which parents are phenotypically normal by all known tests but in which more than one of their children has been affected with dominantly inherited or X-linked recessive disorders.^{37,38} Potential explanations that have been put forward comprise germline mosaicism in one of the phenotypically normal parents, genetic heterogeneity, or epistasis.^{39,40}

Then what is the future of any type of mosaic embryos being transferred in an *in vitro* fertilization preimplantation genetic diagnosis-aneuploidy testing (IVF-PGD-A) cycle? Both embryonic viability and reproductive end product are critically dependent on the function of the spermatozoa. Dominant genetic disorders, childhood cancers, or other complex monogenic or polygenic disorders in offspring are directly linked to the damaged or defective spermatozoa.⁴¹ Genetics is becoming more important following the development of IVF and ICSI as these lead to more genetic abnormalities in offspring. The use of ICSI has raised major concerns about the safety of the offspring since it bypasses the physiological protective mechanisms related to normal fertilization. Natural selection prevents the transmission of mutations causing infertility, while this protective mechanism is overcome by ART.^{42,43}

CRITICS VIEW: A DILEMMA IN THE PRESENT SCENARIO

Geneticists and molecular biologists are working hard on a very advanced technology. Attaining that knowledge is good and fully justified. But application to a person in the society is fully mismatched, as it cannot be so easily swallowed by an affected person. Preimplantation genetic diagnosis (PGD) has its own limitations and has ethical concerns. The question is: Are we ready for accepting genetically affected individuals in the society knowingly or unknowingly through IVF/ICSI technology? It may be a bliss or a boon for the future. In this situation, we cannot say “no” to advancement, but we also cannot say “yes” to the genetically suffering generation.

So, with transferring mosaic embryos which can be aneuploid mosaic/diploid-aneuploid mosaic/ploidy mosaic/chaotic mosaic, we normal humans in charge of doing PGD-aneuploidy are putting at risk the future of two generations and others to come, deliberately increasing the load of genetic disorders in the human population. The situation remains unanswered today and is critically under appraisal.

REFERENCES

- Forsberg LA, Gisselsson D, Dumanski JP. Mosaicism in health and disease—clones picking up speed. *Nat Rev Genet* 2017;18(2):128–142. DOI: 10.1038/nrg.2016.145.
- Lichtenstein AV. Genetic mosaicism and cancer: cause and effect. *Cancer Res* 2018;78(6):1375–1378. DOI: 10.1158/0008-5472.CAN-17-2769.
- Taylor TH, Gitlin SA, Patrick JL, et al. The origin mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. *Hum Reprod Update* 2014;20(4):571–581. DOI: 10.1093/humupd/dmu016.
- Yousoufian H, Pyeritz RE. Mechanisms and consequences of somatic mosaicism in humans. *Nat Rev Genet* 2002;3(10):748–758. DOI: 10.1038/nrg906.
- Machiela MJ, Chanock SJ. Detectable clonal mosaicism in the human genome. *Semin Hematol* 2013;50(4):348–359. DOI: 10.1053/j.seminhematol.2013.09.001.
- Rasouli M, Mc Daniel K, Awadalla M, et al. Mosaic turner syndrome presenting with a 46,XY karyotype. *Case Rep Obstet Gynecol* 2019;3719178:1–3. DOI: 10.1155/2019/3719178.
- Godschalk RW, Yauk CL, Benthem JV, et al. In utero exposure to genotoxicants leading to genetic mosaicism: an overlooked window of susceptibility in genetic toxicology testing? *Environ Mol Mutagen* 2020;61(1):55–65. DOI: 10.1002/em.22347.
- Acuna-Hidalgo R, Bo T, Kwint MP, et al. Post-zygotic point mutations are an underrecognised source of de novo genomic variation. *Am J Hum Genet* 2015;97(1):67–74. DOI: 10.1016/j.ajhg.2015.05.008.
- Biesecker LG, Spinner NB. A genomic view of mosaicism and human disease. *Nat Rev Genet* 2013;14(5):307–320. DOI: 10.1038/nrg3424.
- Rahbari R, Wuster A, Lindsay SJ, et al. Timings, rates and spectra of human germline mutation. *Nat Genet* 2016;48(2):126–133. DOI: 10.1038/ng.3469.
- Sasani TA, Pedersen BS, Gao Z, et al. Large, three-generation human families reveal post-zygotic mosaicism and variability in germline mutation accumulation. *Elife* 2019;8:e46922. DOI: 10.7554/elifesciences.46922.
- Kalousek DK, Dill FJ. Chromosomal mosaicism confined to the placenta in human conceptions. *Science* 1983;221(4611):665–667. DOI: 10.1126/science.6867735.
- Kalousek DK, Vekemans M. Confined placental mosaicism. *J Med Genet* 1996;33(7):529–533. DOI: 10.1136/jmg.33.7.529.
- Meza R, Luebeck EG, Moolgavkar SH. Gestational mutations and carcinogenesis. *Math Biosci* 2005;197(2):188–210. DOI: 10.1016/j.mbs.2005.06.003.
- Zlotogora J. Germ line mosaicism. *Hum Genet* 1998;102(4):381–386. DOI: 10.1007/s004390050708.
- Nicolas G, Veltman JA. The role of de novo mutations in adult-onset neurodegenerative disorders. *Acta Neuropathol* 2019;137(2):183–207. DOI: 10.1007/s00401-018-1939-3.
- Frank SA. Somatic mosaicism and disease. *Curr Biol* 2014;24(12):R577–R581. DOI: 10.1016/j.cub.2014.05.021.
- Rodriguez MV, Rubio C. Assessing the true incidence of mosaicism in preimplantation embryos. *Fertil Steril* 2017;107(5):1107–1112. DOI: 10.1016/j.fertnstert.2017.03.019.
- Delhanty JDA. Inherited aneuploidy: germline mosaicism. *Cytogenet Genome Res* 2011;133(2–4):136–140. DOI: 10.1159/000323606.
- Sachdev NM, Maxwell SM, Besser AG, et al. Diagnosis and clinical management of embryonic mosaicism. *Fertil Steril* 2017;107(1):6–11. DOI: 10.1016/j.fertnstert.2016.10.006.
- Lledo B, Morales R, Ortiz JA, et al. Implantation potential of mosaic embryos. *Syst Biol Reprod Med* 2017;63(3):206–208. DOI: 10.1080/19396368.2017.1296045.
- Greco E, Minasi MG. Healthy babies after intrauterine transfer of mosaic aneuploid blastocysts. *N Engl J Med* 2015;373(21):2089–2090. DOI: 10.1056/NEJMc1500421.
- Kushnir AV, Darmon SK, Barad DH, et al. Degree of mosaicism in trophoctoderm does not predict pregnancy potential: a corrected analysis of pregnancy outcomes following transfer of mosaic embryos. *Reprod Biol Endocrinol* 2018;16(1):6. DOI: 10.1186/s12958-0183-0322-5.
- Fragouli E, Alfarwati S, Spath K, et al. The developmental potential of mosaic embryos. *Fertil Steril* 2015;104:e96. DOI: 10.1016/j.fertnstert.2015.07.297.
- Shi Q, Martin RH. Aneuploidy in human spermatozoa: FISH analysis in men with constitutional chromosomal abnormalities and in infertile men. *Reproduction* 2001;121(5):655–666. DOI: 10.1530/rep.0.1210655.
- Liebars I, Bonduelle M, Van Assche E, et al. Sex chromosome abnormalities after intracytoplasmic sperm injection. *Lancet* 1995;346(8982):1095–1096.
- Guttenbach M, Martinez-Exposito MJ, Michelmann HW, et al. Incidence of disomic sperm nuclei in 45 infertile men. *Hum Reprod* 1997;12(3):468–473. DOI: 10.1093/humrep/12.3.468.
- Schiff JD, Luna M, Evans MI, et al. Sex chromosome micromosaicism in infertile men with normal karyotypes. *Fertil Steril* 2010;93(6):1903–1906. DOI: 10.1016/j.fertnstert.2007.11.094.
- Campbell IM, Yuan B, Robberecht C, et al. Parental somatic mosaicism is underrecognised and influences recurrence risk of genomic disorders. *Am J Hum Genet* 2014;95(2):173–182. DOI: 10.1016/j.ajhg.2014.07.003.
- Greaves M. In utero origins of childhood leukemia. *Early Hum Dev* 2005;81(1):123–129. DOI: 10.1016/j.earlhumdev.2004.10.004.
- Martin RH. The risk of chromosomal abnormalities following ICSI. *Hum Reprod* 1996 May;11(5):924–925. DOI: 10.1093/oxfordjournals.humrep.a019319.
- Vegetti W, Van Assche E, Frias A, et al. Correlation between semen parameters and sperm aneuploidy rates investigated by fluorescence in situ hybridisation in infertile men. *Hum Reprod* 2000;15(2):351–365. DOI: 10.1093/humrep/15.2.351.
- Shi Q, Martin RH. Aneuploidy in human sperm: a review of the frequency and distribution of aneuploidy, effects of donor age and lifestyle factors. *Cytogenet Cell Genet* 2000;90(3–4):219–226. DOI: 10.1159/000056773.
- Frank SA. Somatic evolutionary genomics: mutations during development cause highly variable genetic mosaicism with risk of cancer and neurodegeneration. *Proc Natl Acad Sci U S A* 2010;107(Suppl 1):1725–1730. DOI: 10.1073/pnas.0909343106.
- PGDIS position statement on chromosome mosaicism and preimplantation aneuploidy testing at the blastocyst stage. *PGDIS Newsletter* July 2016 www.pgdis.org/docs/newsletter-071816.html.

36. McCoy RC. Mosaicism in preimplantation human embryos: when chromosomal abnormalities are the norm. *Trends Genet* 2017;33(7):448–463. DOI: 10.1016/j.tig.2017.04.001.
37. Allanson J. Germline mosaicism in Apert Syndrome. *Clin Genet* 1986;29:429–433. DOI: 10.1111/j.1399-0004.1986.tb00516.x.
38. David TJ. Dominant electrodactyly and possible germinal mosaicism. *J Med Genet* 1972;9(3):316–320. DOI: 10.1136/jmg.9.3.316.
39. Hirschhorn R. Genetic mosaicism: what Gregor Mendel didn't know. *J Clin Invest* 1995;95(2):443–444. DOI: 10.1172/JCI117682.
40. Hall JG. Review and hypothesis: somatic mosaicism: observations related to clinical genetics. *Am J Hum Genet* 1988;43(4):355–363.
41. Lewis S, Kumar K. The paternal genome and the health of the assisted reproductive technology child. *Asian J Androl* 2015;17(4):616–622. DOI: 10.4103/1008-682X.153301.
42. Halder A. Reproductive genetic counselling in genomic era. *EC Gynaecology* 2015;2(1):132–148.
43. Faddy M, Silber S, Gosden RG. Intra-cytoplasmic sperm injection and infertility. *Nat Genet* 2001;29(2):131. DOI: 10.1038/ng1001-131.