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Original Research Article

Do karyotypic abnormalities exist in young infertile women with diminished ovarian reserve?

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ABSTRACT

Background: Women are endowed with a finite number of oocytes, which decrease in number and quality over time. Environmental factors, hormonal influence, iatrogenic and genetic factors impact the ovarian reserve. Diminished ovarian reserve indicating a reduction in the quantity and quality of ovarian follicular pool in women of reproductive age affects 10% women seeking fertility treatment. Objective was to find out karyotypic abnormalities in young infertile women with diminished ovarian reserve.
Methods: This retrospective study was carried out over a period of one year at the Assisted Reproductive Technology Centre of a tertiary care public sector hospital. Medical records including the infertility data of 784 couples who underwent In vitro fertilization cycle during the study period was analysed. A total of 104 women with diminished ovarian reserve as evidenced by anti-Mullerian hormone (AMH) value less than 1.1 ng/ml were included in the study.
Results: Out of 104 women with DOR, only 5 women (5 %) had slight variation in karyotype like 46XX 1qh+, 46XX 15ps+, 46XX 16qh+ which are normal polymorphic variations seen in general population. Remaining 99 (95%) women had normal female karyotype (46 XX).
Conclusions: Women with diminished ovarian reserve mostly have a normal female karyotype.

Keywords: Diminished ovarian reserve, IVF, Karyotype

INTRODUCTION

Ovarian reserve is defined as the size and quality of the remaining ovarian follicular pool. The total number of oocytes in any given woman is genetically determined. Human oocytes peak in number during fetal life and are maximum at 20 weeks of intrauterine gestation. As there is an inevitable decline throughout life, from approximately 1-2 million at birth, to about 3 lakhs at puberty it further dwindles to 25,000 at the age of 40, and lesser than 1,000 at menopause.[1] Although female fertility decreases with advancing age but it is difficult to predict the rate of decline of reproductive capability in a particular woman. It has been postulated that the decrease in female fertility begins after the age of 31 years which accelerates after the age of 37 years leading to sterility at the age of 41 years.[2] The terminology of diminished ovarian reserve is generally used to describe women of reproductive age with regular ovulatory cycles, whose response to ovarian stimulation is lesser as compared to women of same age group. It is different from premature ovarian failure (POF) or premature menopause where cycles are anovulatory and irregular eventually leading to cessation of menses before the age of 40 years and an increase in the levels of follicle stimulating hormone (FSH) levels which is >40 IU/l.

AMH is a glycoprotein produced by granulosa cells of the preantral and small antral follicles and is a marker of ovarian reserve.[3] Low AMH levels indicate diminished ovarian reserve and ovarian senescence.

DOR has multiple aetiologies like advanced age, iatrogenic, autoimmune, genetic and idiopathic.[4] Ovarian surgery, chemotherapy and radiation are iatrogenic causes of DOR causing direct destruction of ovarian tissue. Uterine artery embolization for fibroid, uterine artery ligation, salpingectomy for ectopic pregnancy or hydrosalpinx also compromise the vascular supply of ovary and subsequently lead to DOR. Endometriosis like a moth eats away the healthy ovarian tissue and causes permanent depletion of ovarian follicles. Smokers experience menopause 1-4 years earlier than women who are non-smokers.[5] Endocrinopathies like insulin dependent diabetes mellitus, parathyroid disease and myasthenia gravis also cause DOR.[6] In many cases, the etiology is idiopathic. Physiologic DOR is due to advanced maternal age whereas other causes are said to be pathologic.[7] Whatever the reason may be, DOR is associated with poor response to ovarian stimulation, higher cycle cancellation rates and lower pregnancy rates during in vitro fertilization. Identification of pathologic DOR prior to undergoing ovarian stimulation in IVF cycle would allow for proper counselling of such women.

It is possible that an undetermined percentage of pathologic DOR has an underlying genetic cause, as in those women with a family history of premature menopause.[8] Whereas many genetic causes of POF are well established, literature does not quote much about definitive gene mutations associated with DOR. One of the known genetic causes of POF, a mutation in the FMR1 gene causing Fragile X syndrome, has been implicated as a significant cause of DOR.[9]

Karyotypic abnormalities are changes in the number or structure of chromosomes. Chromosomes carry genetic information and any alteration can impact various bodily functions, including reproductive health. The precise mechanisms underlying the association between karyotypic abnormalities and DOR are complex and multifaceted. Several potential pathways have been proposed like karyotypic abnormalities cause accelerated follicular atresia leading to premature exhaustion of the follicle reserve. They interfere with normal ovarian morphogenesis, leading to reduced follicle numbers and impaired ovarian function. They impact the hypothalamic-pituitary-ovarian axis, leading to hormonal imbalances that further compromise ovarian function. Genetic instability caused by chromosomal aberrations may increase oxidative stress, contributing to follicle damage and depletion. As there is paucity of literature documenting the prevalence of karyotypic changes in DOR women, we conducted a study with an aim to find out if karyotypic abnormalities exist in young infertile women with DOR.

METHODS

This retrospective study was conducted in the Assisted Reproductive Technology Centre (ART) of a tertiary care public sector hospital over a period of one year from July 2023 to June 2024. Approval of institutional ethical committee was taken. Registration records of OPD, OT register and lab documentation data was scrutinized to search for cases of DOR. A total of 784 women underwent IVF cycle during the study period out of which 104 cases were of DOR. Inclusion criteria were women who attended ART centre for infertility treatment in the age group 21-35 years and had AMH level <1.1 ng/ml. Exclusion criteria included women more than 35 years, women with known genetic disorder, those who had undergone ovarian or tubal surgery or were on chemotherapy or radiotherapy treatment. Medical data of these 104 DOR patients were also analysed to study the demographic profile in the form of age of woman, duration of infertility, type of infertility, cause of infertility. Karyotype report and basal hormonal profile (FSH, LH, AMH, TSH, prolactin) was also checked. Clinical data was collected about their IVF stimulation protocol and outcome in form of number of oocytes retrieved, embryo transfer and pregnancy (Figure 1). As an institutional protocol, we had done karyotype test for all DOR patients as a part of the infertility evaluation and work up.

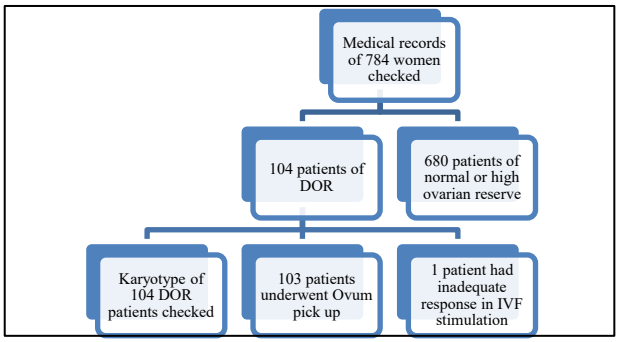

Figure 1: Schematic representation of study population.

The following stimulation protocols were used in our study population- (i) antagonist protocol: patients were started on injection FSH; recombinant follitropin beta (Organon USA Inc) 200 to 300 IU/day subcutaneously (individually tailored dose) from day 2/3 of menses. Injection Cetrorelix (Intas Pharmaceticals) 0.25 mg subcutaneous was administered from day 6/7 of menses based on transvaginal findings of follicle size ≥13 mm. Injection human menopausal gonadotropin (Menotropin) 225/300 IU/day intramuscular was started in later part of menstrual cycle for adequate follicular growth. (ii) Flair antagonist protocol: similar to antagonist protocol, but initial 3 doses of FSH were supplemented with GnRH agonist injection triptorelin (Decapeptyl) 0.1 mg subcutaneously to provide flare effect. In both the stimulation protocols, whenever more than two follicles of size 18 mm were obtained, ovulation trigger was given with injection human chorionic gonadotropin 2000 IU (Coral Pharmaceuticals) intramuscular plus injection recombinant human chorionic gonadotropin (Ovitrelle) 250 microgram subcutaneously and ovum pick up (OPU) was done 34-36 hours later. Oocyte retrieval was done under total intravenous

anaesthesia by transvaginal ultrasonographic guidance using 17-gauge OPU needle. Semen preparation in all cases was done using double density gradient (80%; 40%) media and swim up technique. Insemination or Intracytoplasmic sperm injection (ICSI) was done based on male seminal parameters and fertilization failure in previous IVF cycle. Fresh or frozen embryo transfer was done based on endometrial thickness, serum progesterone report (done on the day of ovulation trigger) and other associated factors. Luteal phase support was provided with parenteral and oral progesterone. Pregnancy was confirmed by blood test (beta hCG) on day 18 and transvaginal ultrasound was done on day 21 for pregnancy localisation. Beta hCG level >25 mIU/ml was considered positive for pregnancy.

Statistical analysis

The data was entered in Microsoft Excel worksheet and analysed. Numerical continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as count/ percentage.

RESULTS

In our study group, patients belonged to age group 22 to 35 years, the mean age being 29.7±0.70 years. Age distribution of patients is depicted in Figure 2 below.

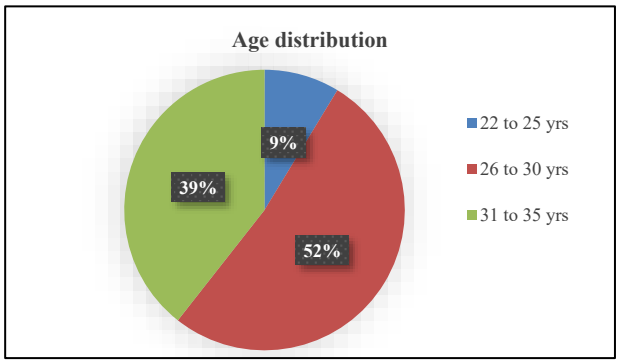

Figure 2: Distribution of patients as per age group.

Table 1: Cause of infertility of DOR patients.

Cause of infertility	Total % (n=104)
DOR only	51
DOR and bilateral tubal block	7
DOR and unilateral tubal block	8
DOR and male factor (azoospermia, oligospermia, asthenospermia)	14
DOR and hypothyroidism	15
DOR and endometriosis	2
DOR and fibroid uterus	2
DOR and uterine septum (resection done)	1

The mean duration of infertility was 4.55±1.41 years with 64% patients being in the 1-5 years group, 26% in the 6-10 years group and 10% in the 11-15 years group. In our study population, 67% were cases of primary infertility and 33% were secondary infertility who had previously conceived but had a pregnancy loss. Causes attributing to infertility of our patients is depicted in Table 1.

Table 2: Hormonal profile of study population.

Hormone (measurement unit)	Mean	Std. deviation
Day 2 Follicle stimulating hormone (FSH) (IU/l)	10.81	2.27
Day 2 Luteinising hormone (LH) (IU/l)	4.56	0.17
Anti Mullerian hormone (AMH) (ng/ml)	0.63	0.29
Thyroid stimulating hormone (TSH) (mIU/l)	2.70	1.08
Serum Prolactin (ng/ml)	15.73	0.16

As part of initial infertility evaluation, all patients had got their hormonal profile done as shown in Table 2.

The lowest AMH value in our study population was 0.07 ng/ml and highest value was 1.08 ng/ml and mean level was 0.63 ng/ml. The mean FSH level was 10.81 IU/l suggesting these patients had accelerated ovarian aging.

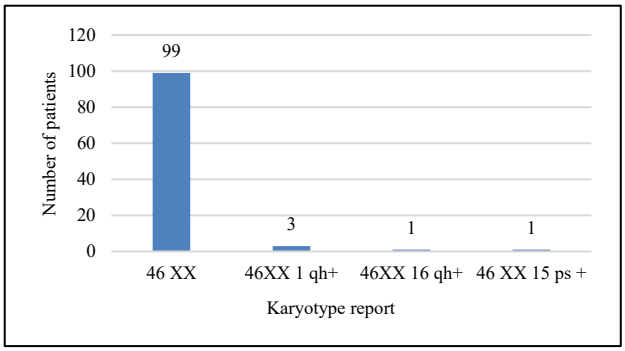

Figure 3: Karyotype report of study population.

Karyotype was done for all patients with DOR as a part of the infertility evaluation. The test was done through blood to study the chromosomal content of patients. Out of the 104 patients, 5 (5%) had a slight variation in karyotype. 3 patients had a report of 46 XX 1 qh+ which was increase in length of heterochromatic region on the long arm of chromosome 1 and was reported to be normal polymorphic variation seen in general population. One patient had a report of 46 XX 16 qh+ and another patient had 46 XX 15 ps+ which was increase in length of heterochromatic region on long arm of chromosome 16 and short arm of chromosome 15 respectively; both of which were again normal variants. Rest 99 (95%) patients had a normal female karyotype 46 XX as shown in Figure 3.

Out of 104 patients, 99% underwent IVF cycle at our centre. One patient had inadequate response despite high

dose of gonadotropins being given for 10 days and hence patient was counselled and cycle was abandoned. The antagonist protocol or the flare protocol was used for ovarian stimulation as described in methodology and dosage was individualised as per patient's clinical characteristics. During OPU, oocytes were retrieved in 98 (95%) patients; 5 (5%) patients had no retrieval of oocytes.

Out of 98 patients where oocytes were retrieved, 12 patients (12%) had fertilization failure. Total 71 patients underwent embryo transfer out of which 40 patients (41%) had fresh embryo transfer and 31 patients (32%) underwent frozen embryo transfer. Embryos of remaining 15 patients (15%) were vitrified at our centre and FET is yet to be done for them. Out of the 71 patients who underwent embryo transfer, 14 patients conceived in their first IVF cycle accounting to a pregnancy rate of 19.7%. One DOR patient conceived spontaneously after two consecutive IVF failures.

DISCUSSION

Treating infertile women with DOR has always been an overriding concern and big challenge for ART Clinicians. While ovarian follicular attrition normally progresses with advancing age, invariably many young women also have DOR which could be multifactorial. It was postulated that there was an exaggerated loss of ovarian follicular pool at an advanced maternal age of 37-38 years when it reaches below a critical level of 25,000 oocytes; however the mean age of women with DOR in our study population was much lesser being 29.7 years.[10] DOR has to be differentiated from POI where there is secondary amenorrhoea and FSH value greater than 40 IU/l. Genetic origins, specifically chromosomal abnormalities, have long been recognised as a frequent cause of POF with a higher prevalence among women with primary amenorrhoea.[11] Overall, the prevalence of chromosomal abnormalities in POF varies among reports from different populations, ranging from as low as 2.5-32%, with an average rate of 15%.[12] A large series of cytogenetic studies performed on Iranian women with POF revealed the prevalence of chromosomal abnormalities to be 10.05%.[13] However, the arena of genetic and specifically karyotypic abnormalities implicated in causing DOR has not been studied much in literature and still needs to be discovered.

Few chromosomal abnormalities have been attributed to cause pathological DOR as per review of literature. DOR and an acceleration of the loss of ovarian function has long been described in women with Turner's syndrome (45,X).[14] The initial case report of Turner's syndrome by Jacobs et al in 1959 described a woman who presented at 19 years of age with secondary amenorrhoea.[15] In Mosaic Turner's syndrome (45,X/46,XX) some cells have 45,X while others have normal 46,XX karyotype. Reciprocal translocations (exchange of segments between non-homologous chromosomes) and Robertsonian translocations (fusion of two acrocentric chromosomes) can disrupt genes critical for ovarian development and function. Kummer reported a case of diminished ovarian reserve in a 33-year-old Caucasian woman with a balanced 13;21 translocation.[16] X chromosome deletions, duplications or inversions are structural alterations which also influence ovarian function negatively. Bui et al reported rapid decline in AMH from 10 ng/ml to 0.5 ng/ml and cycle day 3 antral follicle count from 58 to 4 total follicles during 18 months follow up in a 35 year old woman with 46 XX, Inv(9)(p11q13) karyotype.[17] Women with trisomy X (47,XXX) have high risk of ovarian dysfunction and DOR. Singhal et al reported premature ovarian failure related to Trisomy X (47,XXX karyotype) in two patients with primary infertility.[18] Tang et al reported a case of diminished ovarian reserve in a woman at age of 30 who had 45, X/47,XXX mosaicism.[19]

Greene et al in their systematic review of literature, highlighted the genetic associations with DOR, but there is no extensive study giving insight into karyotypic abnormalities in infertile DOR patients. There are only few case reports mentioning abnormal karyotype in DOR women like those by Kummer et al, Bui et al and Tang et al. Since such association has not been much cited in literature, the objective of our study was to explore if at all such abnormalities exist.[16,17,19] In our study we found slight karyotypic aberrations in 5 (5%) women, although they were normal variants in general population and do not have a negative connotation. Remaining 99 (95%) had normal female karyotype (46 XX). Identifying karyotypic abnormalities in women with DOR can aid in prognostication and counselling regarding reproductive options. Depending on the severity of ovarian dysfunction and the specific karyotype, various options like IVF with self or donor oocytes can be considered. Women with significant chromosomal abnormalities should be offered choices like oocyte donation IVF-ET or preimplantation genetic testing to enhance the chances of a successful pregnancy. Even emphasis can be laid on adoption as a way of parenthood in such women.

DOR patients generally respond poorly to ovarian stimulation during an IVF cycle. As per study by Belgin et al, the incidence of empty follicle syndrome was estimated to be 0.6% to 7%; in our study no oocytes were retrieved in 5% patients which is in congruence to the study.[20] In a study by Yun et al clinical pregnancy rate in DOR patients undergoing IVF was 11.5% per cycle, and the total cancellation rate was 34.4%.[21] In our study the findings are corroborating with a pregnancy rate of 19.7 % per first IVF cycle.

The major limitation of our study was its small sample size with limited duration of study and inability to do further genetic testing to find out specific genetic variations leading to DOR, hence our results cannot be representative of the general infertile clientele with DOR. Additional rigorous research is needed to delve deeper into the relationship between karyotypic abnormalities and DOR. However, ours is the first study of its kind which intended

to explore presence of karyotypic abnormalities in young infertile women with DOR.

CONCLUSION

Women with DOR generally have a poor reproductive prognosis due to reduction in quantity and quality of oocytes. Karyotypic abnormalities are a crucial factor in the fertility management of young women with DOR. Understanding these underlying chromosomal factors can help in tailoring appropriate treatment plans and managing expectations. Early detection and proper management through genetic counselling and individualised fertility treatment can help improve outcomes for these women.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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