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Keywords: *karyotype, products of conception, FISH, chromosome abnormality, maternal age.*

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Dr. Yamini Jadhav [α], Vidya Bhairi [σ], Ajinkya Jadhav [ρ], Bhagyashree Gedam [ω], Vedant Patole [¥], Shweta Parab [§] & Dr. Jayaram Kandandale [χ]

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Conclusions: Pregnancy loss is high in women with advanced maternal age group. The study of products of conception helps the couple to recognize the cause of miscarriage. These results help the couple to cope up with the emotional burden of miscarriage and in the future pregnancy management.

Keywords: karyotype, products of conception, FISH, chromosome abnormality, maternal age.

I. Introduction

Advanced maternal age is defined as a pregnancy in women at 35 years of age or more regardless of parity, whether the conception is first or not. Reproductive health is a state of complete mental, physical, and social well-being related to all stages of reproductive processes [1]. Delayed motherhood due to carrier opportunities and changes in marriage pattern, use of contraception, social support, and other possible factors such as stress, pollutants, and smoking habits are responsible for the increase in the rate of pregnancy loss or miscarriage. The trend of delaying pregnancy has been observed worldwide.

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Miscarriage is one of the most recognizable difficulties during pregnancy. The rate of miscarriage in known pregnancies is 15-20% [2]. Most pregnancy losses occurred during the first trimester. The frequency of pregnancy loss due to the presence of aneuploidy or unbalance chromosomal abnormality is about 50-60% [2-4].

Fetal chromosomal abnormalities may result due to abnormal gametogenesis during the process of fertilization or during the first cellular division of the zygote. Many pregnancies fail in the early-stage and hence may not be clinically recognized. Approximately 30% of pregnancies end with live birth. After three pregnancy failures, the risk of miscarriages increases to 35% [5].

It is necessary to carry out laboratory testing of the products of conception to help to recognize the cause of miscarriage. These results help the couple to cope up with the emotional burden of miscarriage and in the future pregnancy management [6, 7].

A systematic study of abnormalities detected in products of conception (POC) is necessary; hence we present here the results of karyotype and FISH studies of POC specimens and studied the effect of maternal age on pregnancy loss. With this study, we hope to provide updated and add-on perspective to the current knowledge of chromosomal abnormalities.

II. Material and Methods

a) Study Specimens

The retrospective study was performed on the products of conception samples received at the clinical cytogenetics department. Proper collection and transport guidelines for POC sample collection are circulated and explained to the centers sending the samples. For all first-trimester pregnancy losses, the abortus material was collected in a sterile container with transport media under aseptic precautions.

The results were archived from the laboratory database, and in addition to maternal age, no personal information from the patients was included. As the laboratory receives material from different medical facilities with limited information, clinical data such as gestational age at the time of abortion and clinical

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history of the parents were not available for all the samples received. A total of 513 results from POC analysis were performed.

Our study has been performed in two groups. Group I consists of cases with maternal age 18 to 34 years, and Group II consists of cases with advanced maternal age group (Age 35 years and above).

b) Cytogenetic and FISH analysis

All the POC specimens received were cleaned to remove decidual tissues as well as bloodstains. Then the tissue samples were digested using trypsin and collagenase. After tissue digestion, it was divided for the culture set up for karyotype and the FISH study. The karyotype, as well as FISH, was done using the standard protocol. The FISH study was performed for aneuploidy detection which includes chromosomes 13, 18, 21 and sex chromosomes. For each probe mix, 50 interphase cells were studied.

The GTG banding was done for the karyotype study, and for each case a minimum of 20 metaphases was analyzed. Karyotype nomenclature was designated as per an international system for human cytogenomic nomenclature (ISCN 2016) [8].

III. Results

Out of 513 cases 416 cases showed normal results for Group I and II and 97 cases showed chromosomal abnormalities (Table 1). The rate of abnormality in the overall study was 18.91 % (97/513).

Table 1: Distribution of studied cases

	n	Age Group	
		18-34 Years	35 Years and above
NORMAL	416	361 (83%)	55 (71%)
ABNORMAL	97	75 (17%)	22 (29%)
TOTAL	513	436	77

Out of the 97 abnormal cases trisomy was seen in 45.36% (n=44) cases followed by monosomy and triploidy in 25.77% (n=25) and 27.84% (n=27) each. Monosomy X was seen in 23.71% of cases followed by Trisomy 18 in 18.56%, Trisomy 21 in 13.4% and Trisomy 13 in 9.28% cases (Table 2).

Table 2: Distribution of chromosomal abnormality based on age group

Chromosome anomaly	Age Group		Total Abnormal Cases (%)
	18-34 Years	35 Years and above	
Trisomy 6	1	0	1 (1.03%)
Trisomy 7	0	1	1 (1.03%)
Trisomy 10	0	1	1 (1.03%)
Trisomy 13*	7	2	9 (9.28%)
Trisomy 16	1	0	1 (1.03%)
Trisomy 18	12	6	18 (18.56%)
Trisomy 21**	8	5	13 (13.40%)
Monosomy X	20	3	23 (23.71%)
Monosomy 18	1	0	1 (1.03%)
Monosomy 21	0	1	1 (1.03%)
Triploidy	24	3	27 (27.84%)
Tetraploidy	1	0	1 (1.03%)
Total	**75**	**22**	**97**

**46, der(15)t(13;15)(q10;q10),+13 and 46,t(8;12), rob(13;14),+13 were counted in Trisomy 13 group.*

***46, der(14;21)(q10;q10),+21 was counted in Trisomy 21 group.*

In terms of abnormality, we found that, the highest frequency was Trisomy followed by Monosomy X and Trisomy 18.

In the age group below 35 years, 83% had normal results, whereas abnormalities were found in 17% of cases. For the advanced maternal age group (Age 35 years and above), normal results were found in 71% of cases and abnormal results in 29% of cases. The rates of abnormal results were significantly higher for the advanced maternal age group when compared to the younger maternal age group (Figure 1).

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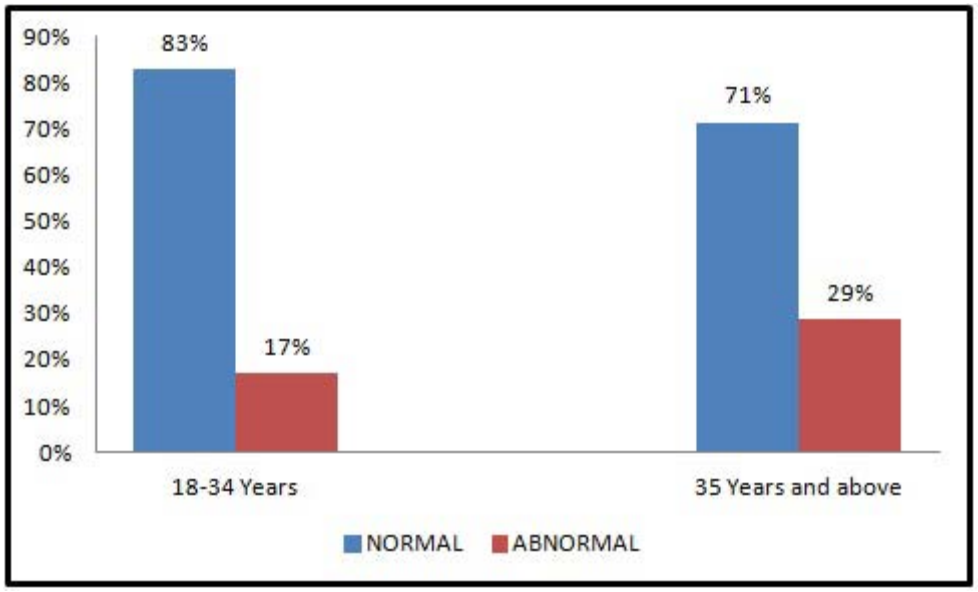


Figure 1: The relationship between maternal age and chromosomal abnormality.

IV. Discussion

The etiology of pregnancy loss is heterogeneous which involves association among maternal, paternal and placental or fetal risk factors in pathways associated with conception and, fetal growth. The maternal risk factor includes infection, endocrine, anatomic, immunological and genetic abnormalities whereas embryonic defects such as chromosomal abnormality reduces embryonic development. The rate of miscarriage is higher after the age of 30 -35 years due to declined potential fertility.

For couples with a history of recurrent miscarriages, it is ideal to study the POC specimen where couples karyotype study shows normal karyotype results. Hence to know the genetic etiology behind the pregnancy loss and it is recommended to study POC specimen, where fetal chromosomal abnormality can be ruled out (if any).

Different types of chromosomal abnormalities are linked with different clinical states. The occurrence of trisomy increases with increasing maternal age, which is due to the meiotic non-disjunction that occurred during gametogenesis. In the present study, the most frequent trisomy type is trisomy 18, followed by trisomy 21 and trisomy 13. Aneuploidies account for the largest amongst the abnormalities detected in POC, same as Menasha et al. [3].

The most commonly observed chromosomal abnormality is Trisomy followed by triploidy which is resulted due to abnormal fertilization. The presence of autosomal monosomy is very rare in pregnancy loss. In the present study we have found one case with monosomy 21 and monosomy 18 each. Monosomy X is most frequently observed amongst pregnancy losses. Twenty-three cases of monosomy X were found in our study. The structural abnormalities found in pregnancy loss are mainly translocations and inversions. In our study, the structural abnormalities were observed in 3 cases along with trisomy. One case of trisomy 21 along with translocation involving chromosome 14 and 21, karyotype result: 46, der(14;21)(q10;q10),+21. One case of trisomy 13 along with translocation involving chromosome 13 and 15, karyotype result: 46, der(15)t(13;15)(q10;q10),+13 and one case of trisomy 13 along with double translocation, karyotype result: 46, t(8;12), rob(13;14),+13 was seen in the study.

Presence of chromosomal abnormality in one of the parents results in a structural abnormality in the fetus. About 2-5% of couples with translocations experience repeated pregnancy losses [9-12].

The frequency of translocation amongst the couples with recurrent pregnancy losses is 40% for Robertsonian translocation and 60% for reciprocal translocations [13]. As compared to male partners, the balance chromosomal abnormalities are found twice in female partners. This is due to the fact that, the chromosomal abnormalities that are compatible with female fertility may result in male sterility.

In our study we have found higher abnormality rate (29%) in advanced maternal age group as compare to younger population studied (17%). The present findings consistent with the studies that reported the increased incidence of chromosomal abnormality with increasing maternal age [14-16]. Various studies have concluded that the women's with advanced maternal age have a higher incidence of unfavourable reproductive outcomes such as complications during pregnancy, spontaneous pregnancy loss, infertility or congenital anomalies in foetus as compared to the younger women which is consistent with the present study [17-22].

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Study of products of conception using karyotype technique is highly suggested as it studies structural as well as numerical abnormalities. It has some drawback such as longer time, for reporting, laborious processing, and culture failure. Since we receive products of conception samples from various locations for testing, the FISH method plays an important role for aneuploidy detection of chromosome 13, 18, 21, X and Y. Advances in new techniques, help to improve the detection of abnormalities and subsequently increases the diagnostic abilities. The use of interphase FISH has allowed cytogenetic setups to study POC samples that have failed to grow hence failed to report the results.

V. Conclusion

Pregnancy loss is high in women with advanced maternal age group and should be taken into consideration during pregnancy planning. Irrespective of previous pregnancy outcomes, maternal age at the time of conception is an independent and strong risk factor for fetal demise.

For the cost-effective management of the couple with a history of recurrent pregnancy losses, genetic evaluation for chromosomal abnormalities, if any, in POC samples plays an important role in avoiding the expensive non-genetic work up and also to understand the etiology behind pregnancy losses.

Genetic counseling is important in the clinical management of pregnancy losses to identify the recurrent risk in future pregnancy influenced by karyotype results. Hence finding this information in an accurate, fast and, reliable manner is critical. Other molecular testing methods such as array CGH and sequencing are useful in the detection of numerical aberrations such as monosomy or trisomy. Structural chromosomal aberrations, tetraploidy, polymorphism may be difficult to identify depending on the method used for detection. Hence the possible algorithm for assessing products of conception could be conventional karyotype study followed by FISH testing, which can identify the common trisomy, tetrasomy, or polyploidy.

New technologies such as Microarray, NGS studies of POC are still not commonly used due to high cost, the difficulty of CNV interpretation, inability to detect balanced chromosomal translocation, and limitation of ploidy change detection in some microarray platforms. However, both these techniques enable fast genetic testing and atomization; we believe that these testing will be implemented in wide practice soon.

The limitation of present study is small sample size and unavailability of maternal cell contamination data hence, further study is necessary to address these problems.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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