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Original Research Paper

Parental Karyotyping in Recurrent pregnancy loss in tertiary care hospital

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ABSTRACT:

Introduction: Recurrent pregnancy loss is a devastating outcome for patients and their clinicians and it continues to be clinical dilemma. **Aims and objectives:** To know the role of chromosomal abnormalities and cytogenetic evaluation in the couples with RPL and to determine the prevalence and types of chromosomal anomalies in couples with RPL. Materials and methods: The couples with recurrent first trimester abortions visiting the Department of OBG King George Hospital, Vishakhapatnam. It is Hospital based observational study for one year from December 2020 to November 2021. In this study detailed clinical evaluation, laboratory investigations and cytogenetic analysis were done. Inclusion criteria: Couples with prior history of two or more abortions and age between 18 -35 years. Exclusion criteria Couples with recurrent second and third trimester loses, congenital female genital tract abnormalities and couples who have not given consent. **Methodology:** At enrollment, after informed consent is taken, information on demographic characteristics, any medical history , family history and clinical data are collected along with a three generation pedigree and recorded as per proforma .All couples are subjected to basic laboratory investigations.After basic clinical and laboratory work up , couples are subjected to cytogenetic analysis.A Peripheral blood sample of about 3 ml is collected and lymphocytes are cultured in presence of a mitogen.After an optimum time of culture mitotic inhibitor colchicine is added to the culture and mitosis is arrested in metaphase as colchicine block the formation of spindle fibres. Peripheral blood lymphocyte cultures are set up according to modified method of Moorhead et al for detection of karyotyping abnormalities using G banding. **Results:** Primary RPL is more common than secondary RPL. The majority belonging to age group 21 to 25 and the majority of males belonging to the age group of 26 to 30 yrs. 42.9% of the couples had a total of 3 abortions. Most common chromosomal anomaly detected were Balanced reciprocal translocations detected in 3 cases(42.8%) and 2 were in females and 1 was in male .Robertsonian translocations were detected in 2 cases(28.57%) , one in male and one in female. Chromosomal inversion was detected in one female (14.2%) and Mosaicism was in 1 female (14.2%). **Conclusion:** Recurrent pregnancy loss is a challenging problem for Obstetricians. Cytogenetic analysis is an essential investigation for couples, in whom genetic counseling and proper management can be planned accurately.

Key words: recurrent pregnancy loss, cytogenic, karyotype

INTRODUCTION:

Recurrent pregnancy loss is a devastating outcome for patients and their clinicians and it continues to be clinical dilemma. According to ACOG early pregnancy recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more pregnancy losses confirmed by ultrasound or histopathology of products of conception.[1]. According to RCOG, Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive. It has been estimated that 1–2% of second-trimester pregnancies miscarry before 24 weeks of gestation.[2] The European Society for Human Reproduction and Embryology(ESHRE) special interest group for early pregnancy defines recurrent miscarriage as three early consecutive losses or two late pregnancy losses.[3] The current definition does not include women with ectopic, biochemical pregnancies and pregnancy of uncertain location .Each of these conditions is known to be associated with poor obstetric outcome and can be recurrent. The chromosomal abnormalities can be divided in two basic groups: numerical and structural abnormalities. These abnormalities can involve one or more autosomal chromosomes, sexual chromosomes and both simultaneously [3]. They are most commonly found as balanced rearrangements, i.e. abnormalities cause no clinical symptoms in carriers but possibly induce the production of abnormal reproductive cells containing abnormal amounts of genetic material[2].

Apart from the genetic reasons many other reasons contribute to the recurrent abortions and these include the uterine anatomical factors, hormonal factors, immunological and non-immunological mechanisms.

Even environmental factors, stress and occupational factors do seem to be related in few cases though there is no strong evidence .Apart from these known etiologies, recurrent pregnancy losses were found to be due to unknown reasons in majority of the patient The risk of miscarriage increases with increasing maternal age and the subsequent pregnancies and the loss of a pregnancy at any stage is a devastating experience to the woman as the chances of a next successful pregnancy outcome decrease. Hence early diagnosis and treatment should be initiated to provide a healthy baby to the mother.

Primary vs Secondary RPL:

Primary recurrent miscarriage**:** It is defined as two or more losses with no pregnancy progressing beyond 20 weeks.

Secondary recurrent miscarriages: It is defined as two or more losses after a pregnancy that has progressed beyond 20 weeks which might have resulted in a live or still birth.

Epidemiology

Based on the incidence of spontaneous pregnancy loss , the incidence of recurrent pregnancy loss is approximately 1 in 300 pregnancies[6] .However epidemiological studies have revealed that about 1 -5 % of couples attempting childbirth. Although a clear data is not published , the best available data suggest that risk of miscarriage in subsequent pregnancy after 2 losses is 30 % compared with 33 % after 3 loses. Among the patients without a history of live birth .Hence , it strongly suggests a role of evaluation after just 2 miscarriages in patients with no prior live births .Chromosomal anomalies of parents with recurrent pregnancy losses are observed in about 2 % to 8% of the couples.

Indian scenario:

Among the studies done in India, the prevalence of chromosomal abnormalities varied between 7 and 18%.(8)Genetic causes Approximately 2 to 4% of RPL is associated with a parental chromosomal abnormalitie They include: balanced structural chromosomal rearrangement. Most commonly balanced reciprocal or robertsonian translocations. 2) Chromosomal inversions 3) Mosaicisms.4) Inversions. Types of inversions 1.Peri-centric 2.Para-centric 5)Mendelian disorders.6)Sex chromosome aneuploidies.7) Single nucleotide variants 8) Epigenetic aberrations Under current recommendations, the clinical management of RPL couples includes parental karyotyping as first line genetic test. Karyotyping of both the parents is included in a standard clinical evaluation of the couples with recurrent pregnancy loss. According to Christiansen et al. there is two- to sevenfold increased prevalence of recurrent miscarriages among first-degree relatives compared to the background population[5], and further studies showed that overall frequency of miscarriage among the siblings of patients with idiopathic RPL is approximately doubled compared to that in the general population[6]. Consanguineous marriages also significantly increase the incidence of inherited recessive disorders and cause some reproductive and developmental health problems and also promote recurrent loss of pregnancies. Genetic and genomic studies of RPL potentially have the benefit of understanding the mechanism underlying the cause of RPL, producing a risk estimation for the couple in the future and may suggest a treatment.

AIMS AND OBJECTIVES:

To know the role of chromosomal abnormalities and cytogenetic evaluation in the couples with Recurrent pregnancy loses. 2) To determine the prevalence and types of chromosomal anomalies in couples with recurrent miscarriages.

MATERIAL AND METHODS:

Study population: The couples with recurrent first trimester abortions visiting the Department of Obstetrics and Gynaecology of King George Hospital , Vishakhapatnam. This study is Hospital based observational study done for one year December 2020 to November 2021. The study was done in 2 parts. In first 10 months Couples were recruited from OBG department and a detailed clinical evaluation, laboratory investigations and cytogenetic analysis were done .in last two months Data analysis was done. Sample size: 70

Inclusion criteria:

1. Couples with prior history of two or more abortions.
2. Aged between18 -35 years, after obtaining informed consent.

Exclusion criteria:

1.Couples with recurrent second and third trimester loses

2.Congenital female genital tract abnormalities.

3.Couples who have not given consent.

METHODOLOGY:

At enrollment, after informed consent is taken, information on demographic characteristics, any medical history , family history and clinical data are collected along with a three generation pedigree and recorded as per proforma .All the couples are then subjected to basic laboratory investigations , which includes a Complete blood picture , HIV , HbSAg, VDRL , HCV , Blood grouping and typing , Thyroid profile , Fasting and Post prandial blood sugars ,Bleeding and Clotting time. Apart from the routine investigations Semen analysis is done in male partners and Ultrasonography of the pelvis , TORCH and APLA profile are done in the female partners .After basic clinical and laboratory work up , couples are subjected to cytogenetic analysis .in this Peripheral blood sample of about 3 ml is collected and lymphocytes are cultured in the presence of a mitogen.After an optimum time of culture (i.e. 72 hrs for adult sample) , mitotic inhibitor colchicine is added

to the culture and mitosis is arrested in metaphase as colchicine block the formation of spindle fibres.Peripheral blood lymphocyte cultures are set up according to modified method of Moorhead et al (1960) for detection of karyotyping abnormalities using G banding.G banding is carried out by modified method of Seabright (1971) A total of 25 intact spread metaphases are screened for each individual with microscope and metaphases will be karyotyped using Cyto vision software.International system for human chromosome nomenclature (ISCN 2016) is followed for the analysis and reporting of the karyotype.Data analysis: Case report forms (Data sheets) will be used for data collection and it will be tabulated in Microsoft excel. Data analysis will be done using SPS.

RESULTS:

Table 1.Types of RPLS with respect to female age groups

			AGE GROUP				Total
			18-20	21-25	26-30	31-35	
Primary VS secondary	Primary	Count	3	28	23	4	58
		%	100.0%	90.3%	74.2%	80.0%	82.9%
	Secondary	Count	0	3	8	1	12
		%	0.0%	9.7%	25.8%	20.0%	17.1%
Total		Count	3	31	31	5	70
		%	100.0%	100.0%	100.0%	100.0%	100.0%

CHI SQUARE = 3.504, P VALUE = 0.32

In the present study, majority of the couples (n=58 , 82.8%) had a non consanguineous marriage .It was followed by third degree consanguineous marriage (n=8 , 11.5%) and second degree consanguineous marriage (n=4, 5.7%).

figure 2: Pie diagram showing the distribution based on degree of consanguinity

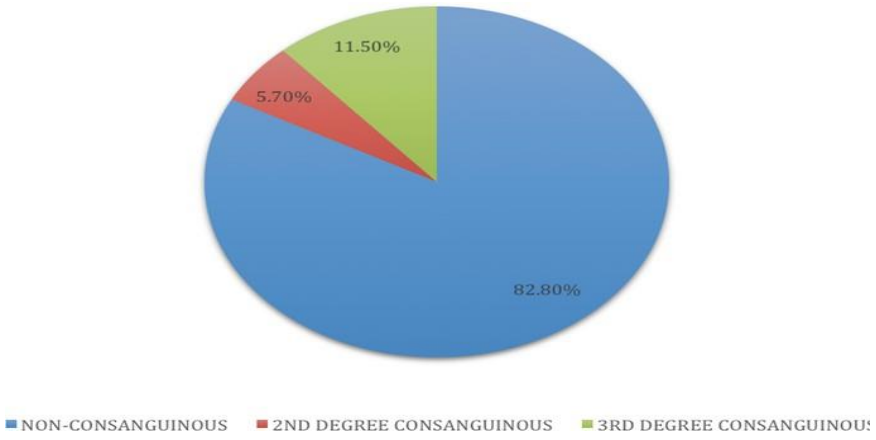


Table 2: Types of recurrent pregnancy loss

	Frequency	**Percent**
Primary	58	82.9
Secondary	12	17.1
Total	70	100.0

Table 3: No of Abortions

No. of abortions	**Frequency**	**Percent**
2	21	30.0
3	30	42.9
4	13	18.6
5	6	8.6
Total	**70**	**100.0**

Table 4 : Types of Chromosomal Anamalies

Balanced reciprocal translocations are the most common chromosomal aberration recorded in the

	FEMALE	**MALE**
BALANCED RECIPROCAL TRANSLOCATION	2	1
BALANCED ROBERTSONIAN	1	1
INVERSION	1	0
NUMERICAL ABNORMALITIES	1	0
TOTAL	5	2

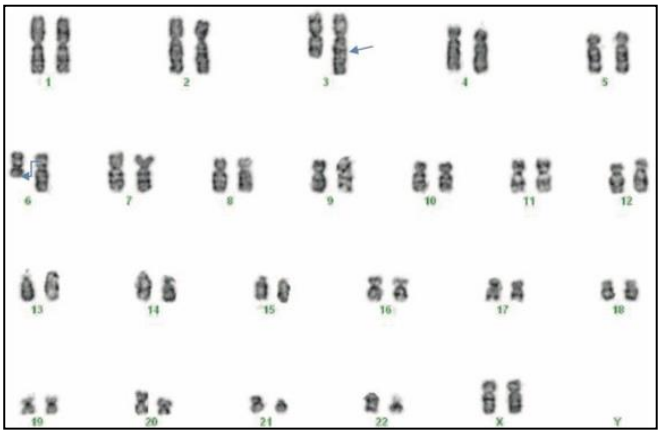
Present study (n=3 ,42.4%). 2 were observed in females and 1 was in male partner. It was followed by balanced robertsonian translocation, which are observed in 2 cases (n=2,28.5%).1 was observed in female partner and 1 in male partner. Inversion and numerical mosaicism were observed in one case each(14.2% +14.2%), both of them are female carriers. Female to male carrier ratio in our study is 2.5 :1

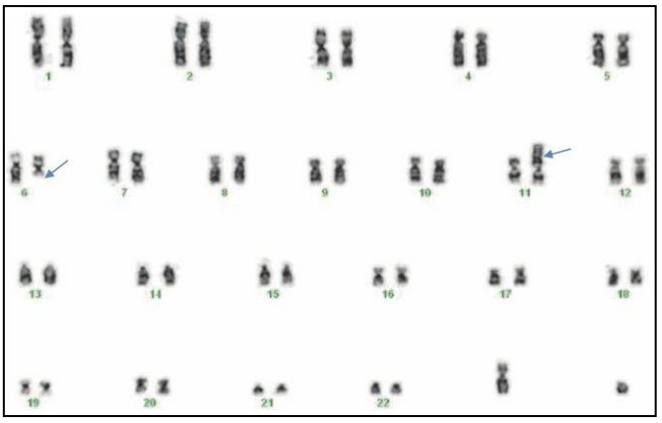
Table 5. Abnormal Karyotype With Respect to Age and Sex

	Female	**Male**
Hypothyroid	5	2
Hyperthyroid	3	2
Diabetes	3	3
Tuberculosis	1	2
Hiv	1	1
bronchial asthma	1	2
anemia (sickle cell trait)	1	0
heart disease	1	1

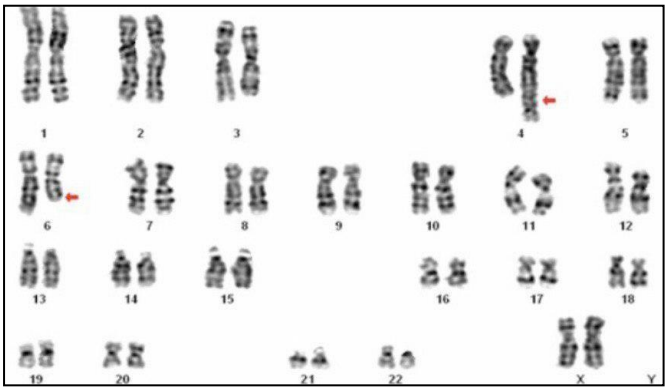
Table 6: Associated Medical Condition With Respect to Sex.

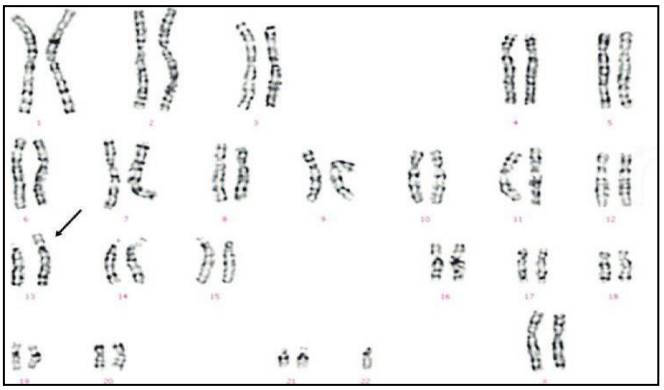
Case	Type of chromosomal Anomaly	Karyotype	Age	Sex	No of abortions
1	Balanced reciprocal Translocation	46,XX, t(3;6),(q29;q14)	22yrs	Female	3
2	Balanced reciprocal Translocation	46,XY,t(6;11),(q14,p15)	28yrs	Male	3
3	Balanced reciprocal Translocation	46,XX,t(4:6)(q35;q22)	24 yrs	Female	2
4	Robertsonian Translocation	45,XX,rob(13;22) (q10;q10)	26yrs	Female	4
5	Robertsonian Translocation	45,XY,rob(14;22) (q10,q10)	29yrs	Male	4
6	Inversion	46,XX,inv(9),(p12q21)	24 yrs	Female	3
7	Numerical mosaicism	mos46XX[22]/45X[3]	32yrs	Female	3



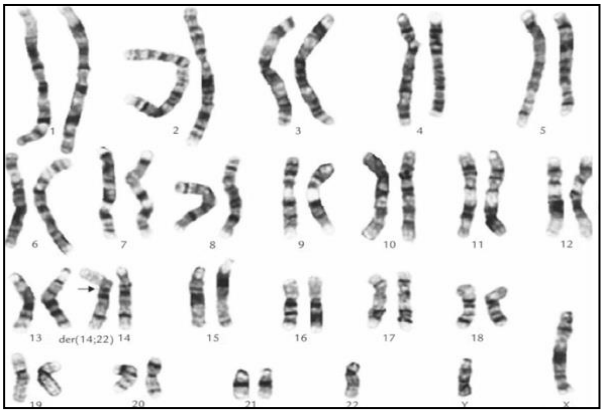


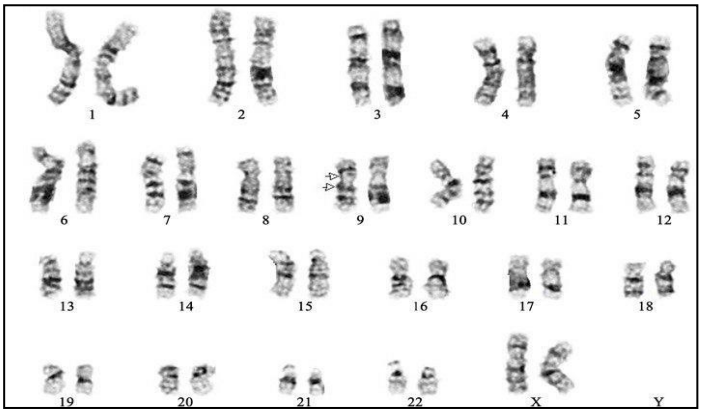
46,XX,t(3;6),(q29;q14). 46,XY,T(6;11),(Q14,P15)





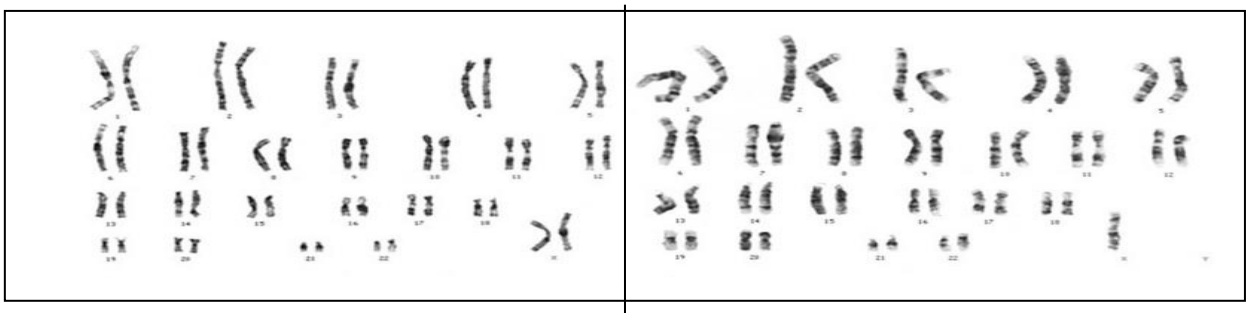
46,XX,t(4;6)(q35;q22). 45,XX,rob(13;22),(q10,q10)





45,XY,ROB(14;22)(Q10;Q10)

46,XX,inv(9),(p12q21) mos46XX[22]/45X[3]



DISCUSSSION:

Incidence of RPL is variable all around the world, and is dependent on various factors. Various studies regarding the associated the association of genetic component have been done.

AGE DISTRIBUTION:

In the present study, mean age of the female partners is 25.9 yrs . Majority of the cases in the study belonged to the age group 21 -25 yrs & 26-30 yrs .Mean age of the male partners in the study is 28.87 yrs with majority of the cases between the ages 26 and 30 yrs.

Table-8 Comparison of Mean Ages of Males and Females in Various Studies

Study	Female mean age	Male mean age
Present study	25.9yrs	28.87 yrs
Neha Sudhir et al	27.9yrs	32.4 yrs
Rim Frikha et al	28 yrs	33 yrs
Wiem Ayed et al	31.9yrs	36.6yrs
Reza Alibakshi et al	29.33 yrs	33.74yrs
Vishali Kalotra et al	31.1 yrs	33.9 yrs

Gender Distribution of Abnormal Karyotype

In the present study, out of the 7 cases with abnormal karyotype 5 were detected in females and 2 were detected in males. female predominance is observed with male to female ratio being 1:2.5.

Table -9 Comparison of Male to Female Carrier Ratio

Study	Male carriers	Female carriers	Ratio
Present study	2	5	1 : 2.5
Frenny J Sheth et al	49	121	1 :2.1
Vishali Kalotra et al	7	10	1: 1.43
Mau et al	18	9	2:1
Pritti K Priya	3	2	1.5:1

Comparison of chromosomal anomalies in our study to previous studies: In the present study

TYPE OF ABERRATION	CASES	%
Balanced reciprocal translocations	3	42.8%
Robertsonian translocation	2	28.57%
Inversion	1	14.2%
Mosaicism	1	14.2%

In the present study the incidence of chromosomal anomalies is 10 % of the couples who were showing Recurrent preganacy loss and 5% of the individuals of the affected couples.

Chromosomal anomalies in various studies:

Ashoke K paul etal[7] (2018)

Total no of couples taken in study were 172.

Out of which 17 were found to have chromosomal anomalies.

Balanced reciprocal	8	47%
Robertsonian	2	11.7%
Inversion	5	29.4%
Aneuploidy	1	5.8%
Mosaic	1	5.8%

Zouhair Elkarhat et al [51](2019)

Total no. of couples taken in the study were 627. Karyotype analysis showed abnormalities in 69 %.

Inversion	27	39.1%
Reciprocal translocation	17	24.6%
Robertsonian translocation	9	13%
Aneuploidy	1	1.4%
Mosaicism	4	5.7%
Polymorphic variants	8	11.5%
Miscellaneous	3	4.3%

IN THE PRESENT STUDY:

In our study 7 individuals had a chromosomal abnormality , out of which 3 (42.8%) were carriers of balanced reciprocal translocation , 2 (28.5%) were carriers of Robertsonian translocations , 1(14.2%) was a carrier of inversion and 1 (14.2%) was a numerical mosaic . These results are comparable to Asoke K Pal et al[7] , in which 4.94 % of the individuals and 88% of the couples with RPL had chromosomal anomalies. Several studies reported different types of structural and numerical chromosomal anomalies in RPL and the percentage of affected couples varied from 4 to 9% .

Table-17: Comparison of Incidence of Chromosomal Anomalies in Different Studies on Recurrent Pregnancy Loss.

Study	No. of couples	Affected couples	%
Present study	70	7	10%
Asoke K pal et al(2017)	172	17	9.88%
Tusi et al	512	51	9.96%
Nazmy et al (2008)	376	34	9.04%
Pal et al (2009)	56	5	8.92%
Gonclaves et al (2014)	151	11	7.28%

Balanced reciprocal translocations

They are the most common structural chromosomal aberrations associated with recurrent loss of pregnancy in many studies.in the Present Study, balanced reciprocal translocations were recorded in 3 cases, accounting for 42.8% of the total chromosomal anomalies .It is comparable to the above mentioned studies

Robertsonian translocations

Some studies show a higher frequency of Robertsonian translocations. In the study conducted by Pal S et al[12] , Robertsonian translocations were observed in 20% of the cases with chromosoamal anomalies .In the study conducted by Ashalatha et al [13] Robertsonian translocations were observed in 27.27% of the cases with chromosomal anomalies. They are comparable to the present study. In the present study, Robertsonian translocation was identifies in two case out of the seven cases with chromosomal anomalies. It accounts for 28.57% of the cases with chromosomal anomalies,1.4% of the individuals and 2.8% of the couples with recurrent pregnancy loss.

INVERSIONS:

In the present study, chromosomal inversions were observed in 1 cases out of the 7 cases with chromosomal anomalies , accounting for 14.2% . Among the couples with RPL , they account for 1.4% and among the individuals they account for 0.7% . They are second most common anomalies observed after balanced reciprocal translocations. The results in our study are comparable to the study conducted by Wiem Ayed et al [9] .

MOSAICISM:

In the present study , one case was observed out of 7 cases with chromosomal anomalies accounting for 14.2%.Out of the 70 couples taken into the study .Mosaicism accounts for1.4% , and 0.71% of the individuals of the study. The present study is comparable to study done by Rim Frikha et al[10] in 2020 . In it Mosaicism was observed in 2 cases out of 12 cases with chromosomal anomalies accounting it for 16.6%. In the study done by Khalid A Awatarni [11], 14 cases of mosaicism were detected which accounts for 18.18% . The results of the study are comparable to the present study.

LIMITATIONS

The sample size was small. As the present study was a hospital based study , and the patients attending the OPD do not represent a random sample of the population ,the study sample cannot represent whole population

SUMMARY:

A hospital based observational study of Parental karyotyping in recurrent pregnancy loss was undertaken during the period of December 2020 to November 2021 , at the Department of Obstetrics and Gynaecology ,Andhra Medical College , Visakhapatnam. The objectives of the study are : 1).To determine the prevalence of chromosomal anomalies in couples with RPL 2) To know the cause of the RPL and plan for further management like Genetic counseling , ART, PGD etc. With due consideration to the inclusion and exclusion criteria, 70 couples with history of 2 or more pregnancy losses have been recruited in the study . Primary RPL is more common compared to secondary RPL.The mean age of females in the study was 25.59 yrs with majority belonging to age group 21 to 25 and 26 to 30 yrs. The mean of males in the study was 28.87 yrs with majority belonging to the age group of 26 to 30 yrs. Majority of the couples had a total of 3 abortions accounting upto 42.9% of the couples in the study. Most common chromosomal anomaly detected were Balanced reciprocal translocations , which were detected in 3 cases(42.8%) . 2 were females and 1 was detected in

male . 1) 46,XX, t(3;6),(q29;q14) 2) 46,XY,t(6;11),(q14,p15) 3) 45,XX,t(4;6)(q35;q22) Robertsonian translocations were detected in 2 cases(28.57%) , one was detected in female and one was detected in male .1) 45,XX,rob(13;12)(q10;q10) 2) 45,XY,rob(4;22)(q10,q10) Chromosomal inversion was detected in one female (14.2%). 46,XX,inv(9),(p12q21) Mosaicism was detected in 1 female (14.2%). 46,XX[22]/45,X[3].

CONCLUSION:

In the present study, Cytogenetic analysis was done in 70 couples with recurrent pregnancy loss. Abnormal karyotype was observed in 7 cases out of 140 individuals who underwent karyotyping. Translocations are the predominant chromosomal anomalies detected in our present study, followed by Chromosomal inversions and mosaicism. Among the Translocations , Balanced reciprocal were predominant than Robertsonian translocation. Recurrent pregnancy loss is a challenging problem for Obstetricians .Cytogenetic analysis is an essential investigation for couples , in whom genetic counseling and proper management can be planned accurately. Determining the presence of such a rearrangement in a parent is useful because it provides : a)An explanation for the miscarriages b) Information about the risk for a live – born child with potentially serious anomalies, as well as the risk for future miscarriages c) Availability of prenatal diagnosis in a future pregnancy D) Information for members of extended family who may be at risk and may wish to undergo chromosome testing In those cases with abnormal karyotype in one of the partner, the "healthy couple may produce unbalanced gametes resulting in abnormal embryos leading to an abortion. Also embryos with aneuploidies. In these cases ,for further pregnancies pre implantation genetic testing (PGT) can be performed after IVF with trophectoderm biopsy at blastocyst stage to test chromosome content of embryos before replacing back them in uterus. With this approach , the risk of further miscarriage and unbalanced offspring decrease to a percentage similar to that of general population. Some patients with apparently normal karyotypes may require molecular studies for assessment of recurrent risk of miscarriages due to genetic anomalies. Despite the absence of any obvious reasons for RPL, the overall chance of pregnancy is good (>50%). No intervention is required in most of the couples.

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