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Genetics of Recurrent and Spontaneous Miscarriage

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ABSTRACT

The aim was to find out the genetic basis of recurrent spontaneous abortion (RSA) from the past pregnancies and ensure a more favourable outcome in the current or future pregnancy. Pregnancy loss has always been a devastating experience for the mothers and the clinician of concern. One out of four pregnancies ends in miscarriage. It is estimated that 50-60% of all first trimester pregnancy losses are the cause of chromosomal abnormality.

8 couples were selected with the history of Recurrent Spontaneous fetal loss and were suggested ultrasound scan while no such abnormalities were found, hence further we asked for cytogenetic procedure for detection of chromosomal abnormalities by the method karyotyping.

We discovered 45;X/46;XX, 45;X/46;XY and 46;XX/46;XY in female partners and 46;XX/46;XY, 46;XY/47;XXY mosaicism in male partners. Two unique balanced translocations in females such as 46;XX,t(5q35:8q24) and46;XX,t(14q:21q) and a single balanced translocation in male partner 46;XY,t(6q:8p) with reproductive failure. A case of Robertsonian translocation carrier in female partner with karyotype of 45,XX,rob(14q.21q).Single case of 45,X/46,XY in male partner. We also observed three cases with deletion in long arm of chromosome Y.

INTRODUCTION

Pregnancy loss was always a devastating experience for the parents and the clinician of concern. Previously we have come through different names for miscarriages as recurrent primary or secondary infertility, absent or irregular ovulation, irregular menses, a family history of miscarriage, advancing age, a known history of uterine fibroids, a family history of miscarriage, medical history and a prior history of pregnancy complications.

Normal miscarriage is also known as spontaneous miscarriage because the miscarriage takes place without any reason or past records of Genetical or Anatomical defects. The main non genetic reasons for the miscarriages are diabetes mellitus, tobacco smoking, drug or alcohol consumption and obesity. The miscarriage takes place within 20 weeks of pregnancy leading to blood clotting, still births etc. Well over 45% of pregnancy loss is due to the aged 40 while the risk begins to increase from the age of 30.Other conditions that can cause same symptoms are ectopic pregnancy, implantation bleeding, Human chorionic gonadotropin (HCG) and ultrasound.

Though the pregnancy loss is based on many factors Anatomic Anomalies, Endocrine/Hormonal Abnormalities, Genetic/Chromosomal Abnormalities, Endocrine Factors Infection, Rh Isoimmunisation, Blood Coagulation , Protein/Platelet Defects, Pre-Eclampsia, Obesity, Smoking, Drinking, Diabetes Mellitus etc. many of these can be easily diagnosed.

In this paper the purpose we have covered on topics related to RSA while major spotlight was on the Genetic/Chromosomal Abnormalities which takes place due to patient's hereditary transformations often known as Bad Obstetrics History.

In the past few years it has become a main issue for concern among 2013 more than 39 lacks of live births 23,000 belongs to infant death, nearly 4,778 are responsible for birth defects, low birth weight and pre-maturity are 4,213, maternal complications are 1,597, Sudden infant death syndrome are 1,561, accidents are nearly

1,150. Roughly 1 in 4 pregnancies lead to miscarriage. According to the National prevalence estimation of selected major Birth defects of 2004-2006 the rate of chromosomal defects has been twice the record in 2004.

FACTORS RESPONSIBLE FOR PREGNANCY LOSS

Anatomic Anomalies

Congenital uterine malformations

Anatomical causes responsible for fetal loss are responsible for the different shapes of uterine malformations. It has been considered that it cause about 15% recurrent miscarriage. Diagnoses are made by MRI or combined laparoscopy hysteroscopy of the uterus as shown **Figure 1**.

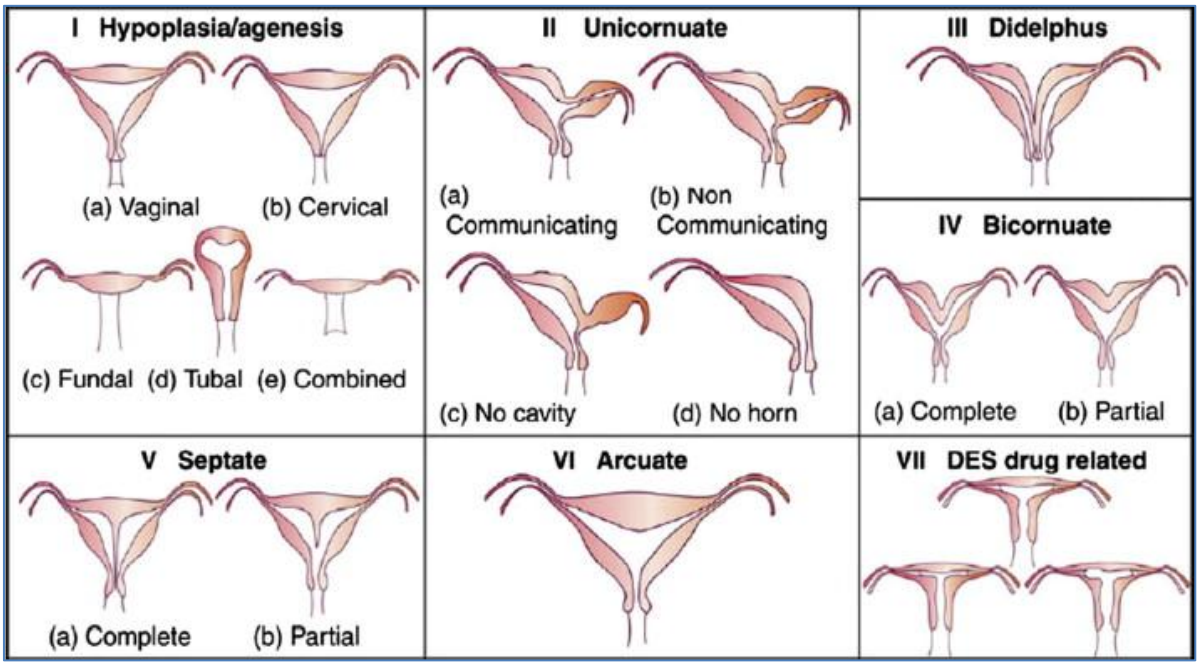

Figure 1. Showing different types of uterine anomalies.

Cervical weakness

Cervical weakness is caused in the second trimester miscarriage; the real cause for this abnormality is unknown. There is no certain diagnosis for cervical weakness.

Endocrine/hormonal abnormalities

Patients with Hypo or Hyper -thyroidism or diabetes mellitus are referred to specialist physicians. They are advised to receive detailed examination and expect pregnancy after treatment of the underlying condition. Cooperation with specialist physicians is also recommended in management of the condition during pregnancy.

Rh isoimmunization

It's also known as Rhesus isoimmunization categorized under the hemolytic Disease of newborn. The disease ranges from mild to severe, and typically occurs only in some second or subsequent pregnancies of Rh negative women where the fetus's father is Rh+, leading to a Rh+ pregnancy. During birth, the mother may be exposed to the infant's blood, and this causes development of antibodies, which affects the health of subsequent Rh+ pregnancies.

Blood Coagulation

Blood clots in pregnant women tend to form deep veins of the legs or in the pelvic area. This condition is known as Deep Vein Thrombosis. Pulmonary Embolism is a life-threatening event that occurs when a DVT breaks off and travels to the blood vessels of the lungs. DVT and PE, collectively known as venous thromboembolism, are highly preventable.

Pre-Eclampsia

Pre-eclampsia is a disorder of pregnancy characterized by the onset of high blood pressure and often a significant amount of protein in urine. The condition begins after 1st trimester of pregnancy. In severe disease there may be red blood cell breakdown, a low blood platelet count, impaired liver function, kidney dysfunction, shortness, swelling of breath due to fluid in lungs, or visual disturbances.

Genetic/Chromosomal Abnormalities

Parental chromosomal rearrangements

Chromosomal abnormalities accounts for over 50% of fetal loss in first trimester, and 29-37% in second trimester.

There are mainly two types of genetically factors for fetal loss Parental chromosomal rearrangement or balanced chromosomal rearrangement and Embryonic aneuploidy and polyploidy as described in the **Figure 2** given below.

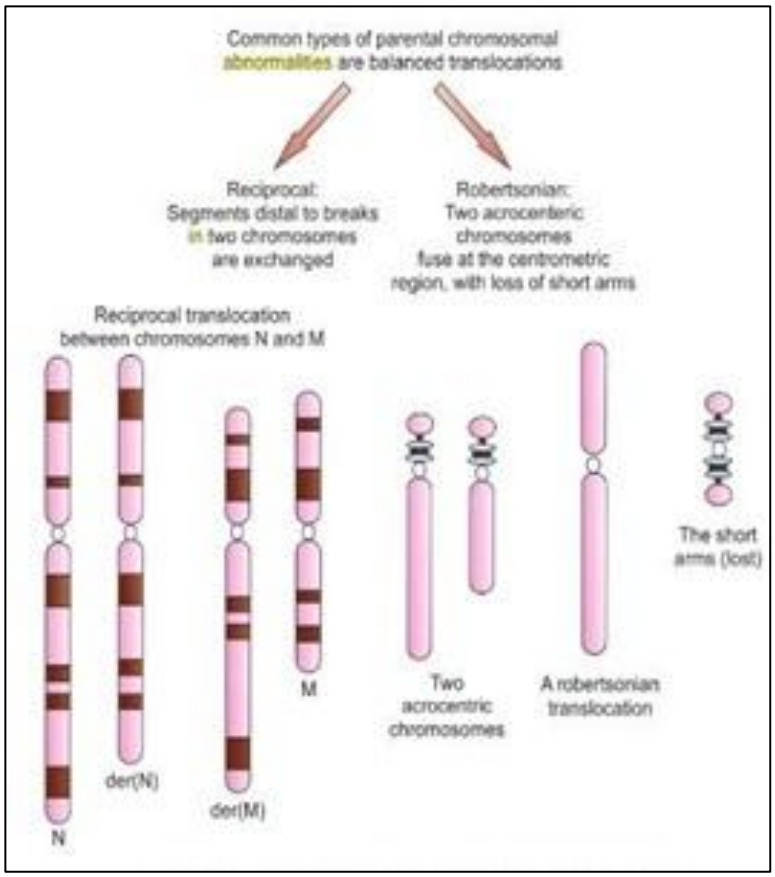

Figure 2. Common types of parental chromosomal abnormalities.

Embryonic chromosomal abnormalities

Couples with recurrent miscarriages account for over 30-57% of future miscarriages. It mainly relates with the advancement of maternal age. Number of pregnancy loss is directly proportional to risk related to euploidy pregnancy loss.

MATERIALS AND METHODS

Cytogenetic analysis procedures were carried out based on by the standard procedure described in [1], of both the male couples and the female partner. Lymphocyte culturing and GTG-banding were performed based standard protocols as described by the AGT cytogenetic laboratory manual. Karyotypes were described according to ISCN 2005 [2]. Chromosome profiling (loss and gain analysis) was done by the Cytovision Software.

RESULTS

The results of the couples were hence observed and noted down. **Table 1** and **Table 2** are the description of different types of abnormalities present in male and the female individuals while **Figure 3** and **Figure 4** are the karyotypes showing the chromosomal aberrations responsible for recurrent spontaneous aberrations (RSA).

Table 1. Showing different types of chromosomal abnormalities observed in female individuals.

Sl.no	Chromosomal Aberration type	Karyotype	Affected Females	% Abnormality
1	Numerical	45;X	3	7.14%
2	Numerical	45;X/46;XX	5	11.90%
3	Numerical	45;X/46;XY	1	2.38%
4	Structural	46;X,del(Xq)	2	4.76%
5	Structural	46;X,del(Xp)	1	2.38%
6	Structural	45;XX,t(14q:21q)	1	2.38%
7	Structural	46;XX,t(5q35:8q24)	1	2.38%
8	Structural	46;XX,t(4q:13q)	1	2.38%

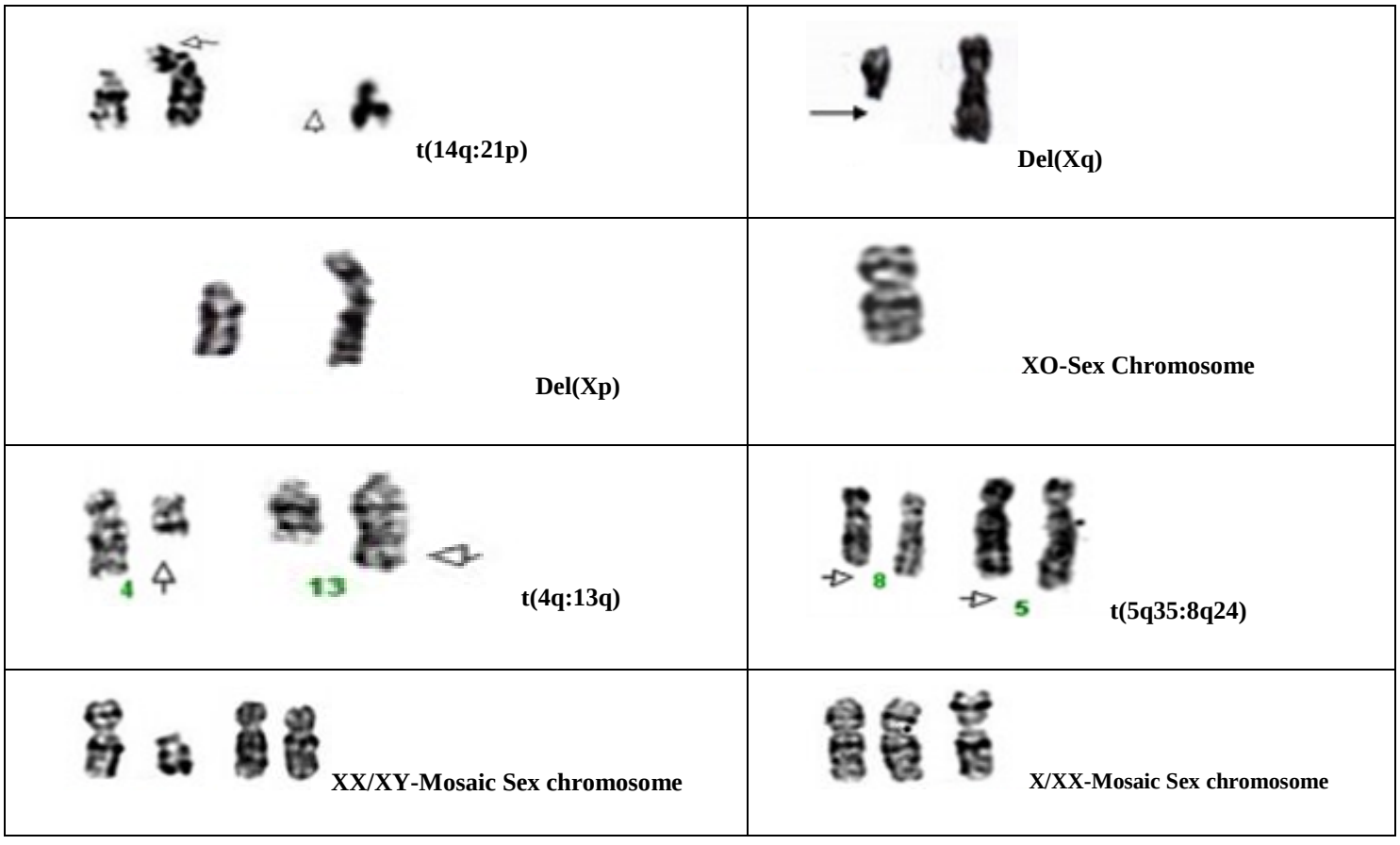

Figure 3. Showing different types of chromosomal abnormalities observed in female individuals.

Table 2. Showing different types of chromosomal abnormalities observed in male individuals.

Sl.no	Chromosomal Aberration type	Karyotype	Affected Females	% Abnormality
1	Numerical	47;XXY	2	4.76%
2	Numerical	47;XYY	1	2.38%
3	Numerical	46;XX/46;XY	1	2.38%
4	Numerical	45;X/46;XY	1	2.38%
5	Numerical	46;XY/47;XXY	1	2.38
6	Numerical	46;XY,del(Yq)	2	4.76%
7	Structural	46;XY,der(9q)	1	2.38%
8	Structural	46;XY,t(6q:8p)	1	2.38%

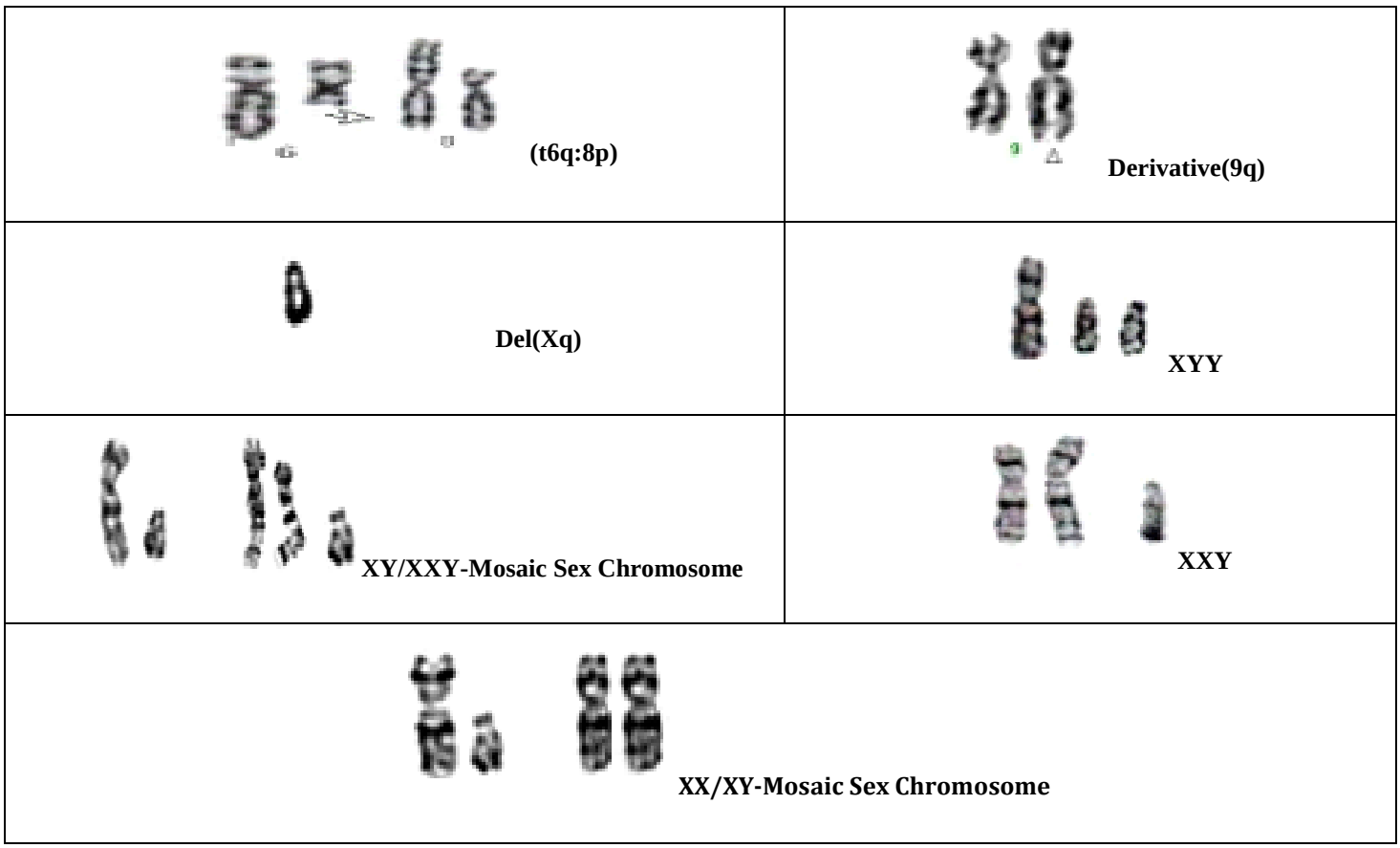

Figure 3. Showing different types of chromosomal abnormalities observed in male individuals

DISCUSSION

The first pregnancy for couples and there failure is a huge massacre while unknown of the abnormalities that are responsible for Recurrent pregnancy loss (RPL). One out of four pregnancies ends in miscarriage. The miscarriage takes place within 20 weeks of pregnancy leading to blood clotting, still births etc. Well over 45% of pregnancy loss is due to the aged 40 while the risk begins to increase from the age of 30 [2-15].

Most of the cases of recurrent pregnancy loss are related with lifestyle/non-genetical or physical challenges such as smoking, drinking alcohol, obesity, etc [15-36].

In this study we have randomly selected 8 couples with the history of recurrent spontaneous abortion and there cases were studied, while all these cases has gone through screening test to confirm any types anatomical abnormalities like ultrasound testing, and no such abnormalities were listed so we moved forward for cytogenetic lab testing leading to karyotyping of the couples blood sample [36-49].

Several types of numerical cellular mosaicism, along with the classical aneuploids, were observed 45;X/46;XX, 45;X/46;XY and 46;XX/46;XY in female partners and 46;XX/46;XY, 46;XY/47;XXY mosaicism in male partners. Two unique balanced translocations in females such as 46;XX,t(5q35:8q24) and46;XX,t(14q:21q) and a single balanced translocation in male partner 46;XY,t(6q:8p) with reproductive failure. A case of Robertsonian translocation carrier in female partner with karyotype of 45,XX,rob(14q.21q).Single case of 45,X/46,XY in male partner. We also observed three cases with deletion in long arm of chromosome Y.

CONCLUSION

The evaluation of patients with a history of repeated spontaneous abortions requires consideration of potential genetic, anatomic, endocrine, infectious, and immunologic factors. The present study and literature review showed that infertility had a higher prevalence of chromosomal abnormalities, even though they did not show any phenotypical features of a particular genetic disease. Chromosomal abnormality affects in infertility significantly, among which female and male shows different ratios of anomalies. Therefore, our present study re-emphasized the need of chromosomal evaluation for a problem like infertility and evaluating couples who need assisted reproductive technologies for genetic counseling.

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