

# Genetics of Recurrent Spontaneous Abortion

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## Abstract

Recurrent Spontaneous Abortion (RSA) is defined as the loss of 3 or more consecutive pregnancies before the 24th week of gestation. RSA is a complex multifactorial problem associated with endocrine dysfunction, autoimmune disorders, advanced maternal and paternal age, infectious processes, environmental toxins and congenital or uterine anomalies apart from genetic abnormalities reflected by inherited disorders. It has been reported that about 15-20 % of all pregnancies end in spontaneous miscarriages and the contribution of chromosomal abnormalities among such cases is as high as 70 %. The contribution of chromosomal abnormalities and the frequency of chromosome inversions and novel chromosome insertion have reported 11.25 % of chromosomal abnormalities. The other causes associated with RSA and genetic abnormalities can be classified into three categories, namely the maternal age, prevalence of consanguineous marriage, distribution of number of abortions and the gestational age of the abortion. The influence of maternal characteristics especially risk of fetal death with increased maternal age has been reported in many studies. Women of 30 years or older continue to have higher risk of fetal death compared to their younger counterparts. Advanced maternal age continues to be a risk factor for fetal death. Studies conducted 'hitherto' have shown no significant correlation between recurrent miscarriage and consanguinity. Therefore consanguineous marriage is not an important etiologic factor in relation to recurrent miscarriage. It has been reported that the rate of pregnancy losses increases with increased risk of subsequent abortion. Studies have concluded that even a single pregnancy loss doubles the risk of abortion in the next pregnancy. History of one or more first trimester abortion was related to an increased risk of abortion for the following pregnancy. Studies have suggested that women with second trimester loss are significantly more likely to have recurrent second trimester loss in subsequent pregnancy than women with preterm or full term births.

**Keywords:** Recurrent Spontaneous Abortion, Cytogenetics, Chromosomal Abnormalities, and Genetic Factors.

## Introduction

The most common complication of pregnancy is spontaneous abortion, which is estimated to occur in 10-15 % of pregnancies and about 80 % of these abortion occur within 2 to 3 months of gestation (1). By definition, a complete abortion is the expulsion of all products of conception before the 20th week of gestation (2).

Spontaneous abortion is one of the least understood pathological processes. The classic definition of RSA is the loss of 3 or more clinically recognized pregnancies spontaneously during early gestation (3,4,5). The modern definition, however, is the spontaneous loss of 2 or more consecutive pregnancies before 20 weeks of gestation, which takes into consideration that a woman over 35 is at greater risk for pregnancy loss

than a 25 year-old woman (6). The World Health Organization (WHO) has defined a miscarriage as the loss of a fetus or embryo weighing = 500g, which would normally be at 20-22 complete weeks of gestation (WHO 1977)(7,8).

## Etiology

It is estimated that fetal viability is achieved only in 30 % of all human conceptions, 50 % of which are lost prior to the first missed menses (9)) Patients with a systemic problem will comprise an increasingly larger fraction of all RSA patients with an increased number of previous pregnancy losses (8).

In the early weeks, death of the fetus often precedes the expulsive action of the uterus and seems to be the precipitating factor for abortion. Some of the later abortions begin by rupture of the membranes allowing the liquor amnii to escape. Recognition of these two groups is of practical value in narrowing the search for the cause of abortion.(10). Pathophysiology of a spontaneous abortion may be suggested by the timing of miscarriage.

Potential causes of pregnancy loss include Pathologic (blighted) ovum-anembryonic gestation, Embryonic anomalies, Chromosomal anomalies, Increased maternal age, Uterine anomalies, Intra uterine device, Teratogen, Mutagen, Maternal disease, Placental anomalies and Extensive maternal trauma.

Chromosomal defects commonly are seen in spontaneous abortions, especially those that occur during 4-8 weeks' gestation. The contribution of chromosomal abnormalities is as high as 70 % (1). Genetic etiologies are

common in early first-trimester loss but may be seen throughout gestation. Trisomy chromosomes are the most common chromosomal anomaly.

Insufficient or excessive hormonal levels usually result in spontaneous abortion before 10 weeks' gestation. Infectious, immunologic, and environmental factors generally are seen in first-trimester pregnancy loss. Anatomic factors usually are associated with second-trimester loss. Factor XIII deficiency and a complete or partial deficiency of fibrinogen are associated with recurrent spontaneous abortions. (11).

## Non Genetic Factors

### Anatomical Factors

Anatomic abnormalities include uterine abnormalities like double uterus, or uterine adhesions as in the case of Asherman's syndrome; presence of endometrial polyps, sub mucous fibroids and mullerian duct defect (8). Congenital or acquired anatomic factors reportedly are present in 10-15 % of women who have recurrent spontaneous abortions.

Acquired lesions are intrauterine adhesions (i.e., synechiae), leiomyomas, and possibly, adhesions due to endometriosis (11) (Figure 1).

### Endocrine Factors

Endocrine factors potentially contribute to recurrent abortion in 10-20 % of cases.

The most common abnormality contributing to spontaneous abortion is luteal phase insufficiency, which occurs when abnormal corpus luteum function results in insufficient

progesterone production. A deficiency or an imbalance of oestrogen and progesterone in circulation to produce oestrogen dominance is a theoretical cause of abortion. Hypothyroidism, hypoprolactinemia, poor diabetic control, and polycystic ovarian syndrome contribute to pregnancy loss (11). Poly Cystic Ovary Syndrome and type I Diabetes Mellitus has also been found to be associated with RSA (12).

### Infectious Factors

Presumed infectious etiology may be found in 5 % of cases. Bacterial, viral, parasitic, fungal, and zoonotic infections are associated with recurrent spontaneous abortion (11). Herpes Simplex Virus has been linked to Spontaneous Abortion and Chronic HSV is a possible cause of RSA (8).

### Nutritional Causes

The deficiency of vitamin A is a cause of increased infant mortality (13). A metabolic effect of folate deficiency is an elevation of blood homocysteine. The presence of maternal homocysteine concentrations have been associated both with increased habitual spontaneous abortion and pregnancy complications (8).

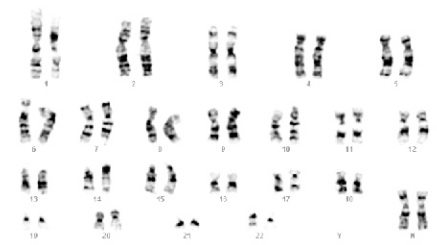
### Immunological Factors

Immunologic factors may contribute in up to 60% of recurrent spontaneous abortions. Both the developing embryo and the trophoblast may be considered immunologically foreign to the maternal immune system. Antiphospholipid antibody syndrome generally is responsible for more second-trimester pregnancy losses than for first-trimester losses (11).

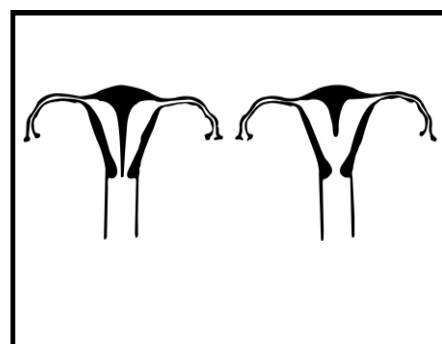
### Miscellaneous Factors

Miscellaneous factors may account for as many as 3 % of recurrent spontaneous abortions. Other contributing factors implicated in sporadic and recurrent spontaneous abortions include environment, drugs, placental abnormalities, medical illnesses, and male-related causes (11).

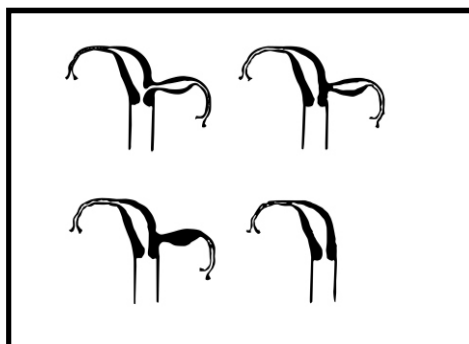
### Maternal Factors



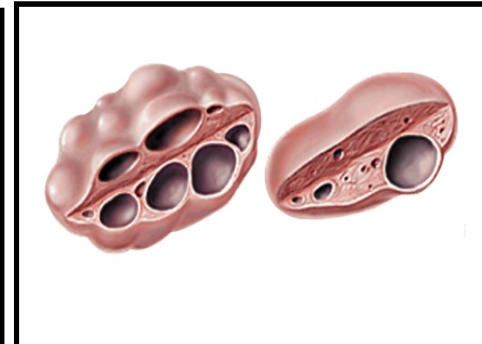
Age and increased parity affect a woman's risk of a miscarriage. In women younger than 20 years, miscarriage occurs in an estimated 12 % of pregnancies; in women older than 20 years, miscarriage occurs in an estimated 26 % of pregnancies. Age primarily affects the oocyte. Women in the advanced reproductive age who have a reduced ovarian reserve are prone to higher risk of repeated miscarriages. Such miscarriages are due to decreased egg quality.



Complete Partial Uterine Septate



Mullerian Defect

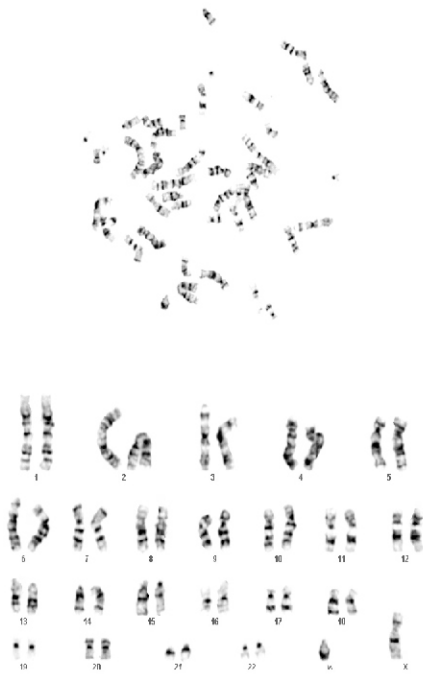


Polycystic Ovary

Normal Ovary

Figure 1 : Various anatomical factors associated with RSA

**Male Factors**



Male fertility may gradually decline with advancing age because morphological changes in the ageing testis, such as an increase of atypical spermatogonia, malformed spermatids, fibrosis of the tubular membrane and increased desquamation of immature germ cells are observed (14). In addition, in ageing men, the weight of the testis, the germinal tissue: total testis tissue ratio, and daily sperm production are significantly reduced (15).

Oligozoospermia are more frequent in spermatozoa from patients whose partner had an early RSA compared with those who had a late spontaneous abortion or a premature birth. A positive correlation exists between the percentage instability of the sperm nucleus and the percentage of abnormal forms (16). The alteration in the nuclear chromatin is probably one of the causes of the morphological aberrations in sperm head.

**Genetic Factors**

Balanced chromosome rearrangements have been found with an increased frequency in couple with recurrent early pregnancy wastage. When balanced rearrangement is present the chromosomes have difficulty in pairing up and dividing evenly during meiosis. As a result, gametes frequently

Table 1: A summary of different structural and numerical chromosomal abnormalities associated with RSA reported in various studies conducted 'hitherto'

Abnormal karyotype	No. of miscarriages	Age
<b>RECIPROCAL TRANSLOCATION</b>		
46,XX, t(1;5)(p33;q35)		30
46,XX, t(2;11)(q21;q24)		22
46,XX, t(3;11)(q26;11pter)		28
46,XX, t(3;17)(p22;p13)		26
46,XX, t(6;X)(q32;q22)		27
46,XX, t(6;12;13)(q22;q21;q23;q12)		25
46,XX, t(6;18)(q27;q21)		22
46,XY, t(7;8)(q11;p11)		25(Male)
46,XY, t(7;13)(pter;q13)		32(Male)
46,XX, t(8;15)(q12;p11)		35
46,XY, t(8;18)(q23;p23)		30(Male)
46,XX, t(8;19)(p22;p13.3)		35
46,XX, t(11;12)(p15;q22)		27
46,XX, t(15;8)(p13;q22)		26
46,XX, t(16;X)(q28;q24)		30
<b>ROBERTSONIAN TRANSLOCATION</b>		
46,XX, t(13;14)	Abortions range from 2-9	22
46,XX, t(21;22)		30
46,XX, t(22;22)		25
<b>INVERSION</b>		
46,XY, inv(4)(p15;q13)		22(Male)
46,XX, inv(9)(p13;q12)	3,3,4,3,5	25,22,28,26,32
46,XX, inv(12)(p11.2;p13)	3,4	27,30
46,XX, inv(13)(q12;q32)	5,4,4	35,31,33
46,XX, add(15)(p13)	3	20
46,XX, ins(12;6)(q24.2;q23q25)	4	32
<b>DELETION + MARKER</b>		
46,XY del(10)(pter q22) + marker	Abortion range from 2-9	30 (Male)
46,XY del(3)(pter q25) + marker		36 (Male)
<b>NUMERICAL CHROMOSOMAL ABNORMALITIES</b>		
47,XXX : 46,XX		35,25
47,XXY : 46,XY		36
47,XXX : 46,XX :45,X0	Abortion range from 2-9	24,30
46,XX : 45,X0		27,30,28
<b>POLYMORPHIC CHROMOSOMAL VARIANTS</b>		
9qh+, Pericentric inversion (9), 22p+, Fragile sites, 16qh+, 15p+, Yq+, Yq		

possess unbalanced set of chromosomal materials. The clinical consequences of such imbalances usually are lethal to the developing embryo, causing spontaneous abortions.

1. Major chromosome abnormalities have been found in 4.8 to 5.5 %.

Other abnormalities usually encountered include:

2. Sex chromosome mosaicism,
3. Chromosome inversions, and
4. Ring chromosomes. Besides spontaneous

abortions, these abnormalities are associated with a high risk of malformations and mental retardation.

5. **Translocation:** Robertsonian translocation, Reciprocal translocation. Multiple translocations.

A summary of different structural and numerical chromosomal abnormalities associated with RSA reported in various studies conducted 'hitherto' have been compiled in Table 2.

### Skewed X Chromosome Inactivation (XCI)

An increase in extremely skewed XCI of 90 % has been reported among women who experience RSA (17,18). A significant excess of trisomic losses was observed among the women who had RSA with skewed XCI versus those without skewed XCI. X linked mutations (deletions, translocations etc) have been clearly associated with skewed XCI and RSA in some families (19).

### Premature Centromeric Division

At metaphase, the two chromatids of each replicated chromosome are largely held together by a single centromere that also attaches the chromosome to the spindle equator. The centromere then divides and leads the separated chromatids to the spindle poles, ensuring a truly equational division of the chromosome complement.

Rarely, at metaphase, the chromatids of a single chromosome are separated at the centromere. The chromatids of this single chromosome have been interpreted as having separated precociously and the phenomenon has been termed premature centromere division (PCD). The term premature centromere division (PCD) has been used to describe the premature division of the X chromosome centromere (PCD, X) as compared with the centromeres of other chromosomes in the same metaphase (20) Metaphase chromosomes in PCD have separated rodlike straight chromatids. Premature division of the X-chromosome centromere (PCD, X) is a relatively common finding in a small proportion of cells in phenotypically normal women. It is positively associated with the age-related X-chromosome aneuploidy in lymphocytes (21)

### Present study

A study was conducted to evaluate the chromosomal abnormalities associated with recurrent spontaneous abortion (during I and II trimester of pregnancy) in 15 couples of South Indian origin. The medical history of the subjects was classified into three categories, namely the maternal age, prevalence of consanguineous marriage, distribution of number of abortions and the gestational age of the abortion.

The maternal age of the subjects were classified into three categories, namely 18-24 years, 25-29 years and 30-34 years. The distribution of the subjects in the three said categories was found to be 33 %, 47 % and 20 % respectively. The prevalence of consanguineous marriage was also recorded and 20 % of the subjects were positive for consanguineous marriage. However, studies conducted 'hitherto' have shown no significant correlation between recurrent miscarriage and consanguinity.

The distribution of number of abortions and its distribution in each trimester were recorded. The numbers of abortions in the subjects were two, three and four and their distribution was 40 %, 40 % and 20 % respectively. The number of abortions in 1<sup>st</sup> trimester was 64 % and in the II<sup>nd</sup> trimester was 36 %. The number of abortions recorded in the III<sup>rd</sup> trimester was insignificant.

The chromosomal analysis of the 15 couples did not show any numerical or structural abnormalities. The karyotypes of all the subjects were found to be normal. The results of chromosomal analysis did not show any numerical or structural abnormalities.

The karyotypes of all the subjects were found to be normal. The absence of any chromosomal abnormalities may be attributed to the small sample size and also the fact that RSA is a complex multifactorial problem associated with endocrine dysfunction, autoimmune disorders, advanced maternal and paternal age, infectious processes, environmental toxins and congenital or uterine anomalies apart from genetic abnormalities reflected by inherited disorders. A detailed medical history of the subjects which included obstetric

history, surgical history, menstrual history, general family history, coital and endocrine history was obtained from their previous medical records did not demonstrate significant abnormalities. However the use of alcohol, cigarettes, history of diabetes and hypertension has been reported in most couples. The influence of maternal characteristics especially risk of fetal death with increased maternal age has been reported in many studies. Women of 30 years or older continue to have higher risk of fetal death compared to their younger counterparts. Advanced maternal age continues to be a risk factor for fetal death. It has been reported that the rate of pregnancy losses increases with increased risk of subsequent abortion. Studies have concluded that even a single pregnancy loss doubles the risk of abortion in the next pregnancy. The frequency of abortion in the first trimester has been more prominent. History of one or more first trimester abortion was related to an increased risk of abortion for the following pregnancy. Studies have suggested that women with second trimester loss are significantly more likely to have recurrent second trimester loss in subsequent pregnancy than women with preterm or full term births.

### Conclusion

Worldwide studies showed considerable differences in the frequency of chromosomal aberrations, which ranged from 2.76 % to 18.75 %. The main possible reason for this could be the variation in the incidence of carriers with chromosome defects among different populations. It also reflects the contribution of the sample size, the basic criterion used for finding the cause, and the various cytogenetic methods employed for the analysis of defects in the studies reported so far.

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