Recurrent Spontaneous Abortion: An Overview of Genetic Backgrounds and Impact of Male Factors: A Review

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ABSTRACT
Genetic factors in the form of maternal or fetal single gene disorders, chromosomal abnormalities, inherited thrombophilia and other genes involved are the main causes of recurrent abortion (RA). The risk of miscarriage is highest among couples where the woman is >35 years of age and the man >40 years of age. In about 50–70% of miscarriage, a chromosomal abnormality is identified in the products of conception, this chromosomal abnormality derived from one parent or the recurrence of a numerical abnormality. In about 3-5% of couples with two or three spontaneous pregnancy losses, a balanced chromosome rearrangement was found in one member of the couple. Also man’s factors have an important role in RA since the man gamete contributes one-half of the genomic content to the embryo. Moreover the paternally expressed genes may have an impact on implantation, placental proliferation, and placenta quality. So any situation which leads damage of sperms DNA (e.g. varicocele) will be associated with a reduction in some fertility indices.

INTRODUCTION
Spontaneous abortion is defined as the spontaneous loss of pregnancy before 24 weeks of gestation, and sometimes it is considered before 20 weeks due to advances in neonatal care(Speroff and Fritz 2005; Jauniaux et al. 2006; Branch et al. 2010). Recurrent abortion is referred to the miscarriage of two or more consecutive pregnancies in the first or early second trimester of gestation (Carp et al. 2002).

Among all factors the only undisputed causes of recurrent pregnancy loss are genetic factors, anatomic or immunologic, even after a comprehensive evaluation recurrent pregnancy loss remains unexplained in well more than half of affected couples (Branch et al. 2010).

GENETIC FACTORS OF RA

Single Gene Disorders

Certain genetic mutations thought to be involved with implantation may predispose a patient to infertility or even miscarriage (Harper 2010). An example of a single gene disorder associated with recurrent pregnancy loss of maternal origin is myotonic dystrophy. The cause of the abortion is unknown, but it may be related to abnormal gene interactions combined with disordered uterine function (Harper 2010). So diagnosis of myotonic dystrophy should be considered for a woman with recurrent miscarriage who has a family history of myotonia, and progressive muscle weakness especially in the setting of early onset cataracts (Gupta and Kabra 2011). Other maternal diseases associated with increased fetal wastage includes connective tissue disorders (for example, Marfan and Ehlers-Danlos syndromes) (Bick 2003; Yudaeva 2009), and hematologic abnormalities like sickle cell anemia due to increased risk of placental vessels microinfarcts (Hsu et al. 2007). Fetal causes of RA include autosomal dominant lethal skeletal dysplasias (for example, thanatophoric dysplasia and type II osteogenesis imperfecta) (Senat et al. 2007), autosomal recessive disorders (for example, Alpha thalassemia major) (Chui and Waye 1998), and X-linked disorders that are lethal in males may cause recurrent pregnancy loss (Allison and Schust 2009). So when loss of multiple male fetuses is noted in the family pedigree, lethal X-linked dominant disorders should be considered (for example, incontinentia pigmenti) (Gupta and Kabra 2011).

Inherited Thrombophilias

Inherited predisposition to thrombophilia is one of the main causes of RPL (recurrent preg-
nancy loss), in particular if several diseases potentially responsible of RPL have been already excluded (Carp et al. 2002; Di Micco et al. 2007). Several gene variants are associated with an increased risk of venous thrombosis; these are designated as genetic thrombophilias. The two most common inherited thrombophilias, factor V Leiden and prothombin G20210A, are associated with an increased risk of first-trimester and later pregnancy loss. Another rare thrombophilia, protein S deficiency, is also associated with RPL (Rey et al. 2003; Kovalevsky et al. 2004). This is together with the fact that pregnancy is a hypercoagulable state secondary to both an increase in the levels of factors V, VII, VIII, X and fibrinogen decreased levels of protein increased resistance to activated protein c, higher concentrations of plasminogen activator inhibitors (PAI), and an increased tendency to platelet aggregation, all promoting thrombosis (Kutteh and Triplett 2006).

**MTHFR Gene**

Methylenetetrahydrofolate reductase (MTHFR) defect is a rare genetic abnormality that leads to complications in pregnancy (Altomare et al. 2007). MTHFR gene produces an enzyme called methylene tetrahydrofolate reductase and mutation in the gene inhibits the production of this enzyme, result in hyperhomocysteinemia, this disorder has been linked to a variety of pregnancy complications such as congenital malformations. Elevated levels of homocysteine have been associated with placental disease, preeclampsia and RPL (Foka et al. 2000)

**Chromosomal Abnormalities**

A chromosomal abnormality derived from one parent or the recurrence of a numerical abnormality may cause recurrent abortion. In about 50–70% of abortion, a chromosomal abnormality is identified in the products of conception (POC) (Hogge et al. 2003; Shawky and Kamal 2012). Percentage of prenatal loss of chromosomally abnormal fetus is different according to type of aberration, it was estimated to be 100% loss for autosomal monosomy and tetraploid, autosomal trisomy 96.5% while structural rearrangement 53.4% (Pflueger 1999).

**Aneuploidy**

A majority of miscarriages that occur before 10 weeks’ gestation are due to chromosomal aneuploidies arising from noninherited nondisjunctional events (Sierra and Stephenson 2006). The rate of miscarriage increases with a maternal age of less than 18 years or an age of 35 years or more and a paternal age of more than 40 (de La Rochebrochard and Thonneau 2002). The sharp increase in the rate of miscarriage in women 35 years of age or older is due in part to increasing rates of aneuploidy in association with older oocytes (Andersen et al. 2004; Sierra and Stephenson 2006). Also aneuploid embryos can result from lengthening of the interval between ovulation and fertilization, so it has been suggested that this could account for the relationship between maternal age and the incidence of trisomy, as with increasing age intercourse is likely to occur less frequently with delayed fertilization therefore being more likely (Turnpenny 2011).

It was noted that the couples who have had a previous miscarriage with an aneuploid POC were at an increased risk in the subsequent pregnancy for a recurrent trisomy which may be responsible for both recurrent and sporadic losses (Gupta and Kabra 2011). Some couples are genuinely predisposed toward chromosomally abnormal conceptions and they might logically be at increase risk not only for aneuploid abortuses but also for aneuploid liveborn infants (Simpson and Elias 2003). In some species non-disjunction is under genetic control, this could account for those occasional families that seem to be prone to recurrent non disjunction (Turnpenny 2011). Cryptic gonadal mosaicism in one parent is another explanation for recurrence of aneuploidy (Simpson and Elias 2003; Gupta and Kabra 2011). Also the risk of spontaneous miscarriage is reported to be high in women with mosaic Turner syndrome or have very distal Xp deletions (Sybert and McCauley 2004).

The trisomies distribution in spontaneous abortions quite different from that seen at term (Di Micco et al. 2007; Pflueger 1999). The most common trisomy observed in spontaneous abortuses is trisomy 16, followed by trisomy 22, while trisomy 21 is third most frequent. Identification of trisomic conceptuses is of clinical importance because of the question of possible increased risk for aneuploidy in subsequent pregnancies (Di Micco et al. 2007).
responsible for preclinical abortion (Mark 2000; Stephenson et al. 2002; Shawky and Kamal 2012) except of monosomy 21 which has been found and occasionally compatible with survival to term in the mosaic state (Munné 2005). Monosomy X (Turner syndrome) is the single most common chromosomal abnormality among spontaneous abortions accounting for 20-25% of cytogenetically abnormal abortuses (Munné 2005; Stephenson et al. 2002), the single X chromosome is maternally derived in 80% of patients (Kovalevsky et al. 2004).

**Polyploidy**

It accounts for 30% of chromosomally abnormal spontaneous abortions. Some triploid conceptuses present as a partial mole, characterized by a large gestational sac and cystic degeneration of the placenta. Tetraploidy rarely progresses beyond 4 or 5 weeks of gestation (Stephenson et al. 2002).

**Morphologic Correlations**

Attempts have been made, with arguable success, to correlate morphologic abnormalities with specific trisomies reported that empty gestational sacs characterize trisomies 2, 4, 7, 9, 14, 15, 20 and 22; discernible embryonic tissue was found in mono-somy X and in abortuses trisomic for 12, 13, 15, 8, 20, and 22. Trisomies incompatible with life predictably show slower growth than trisomies compatible with life, moreover trisomies can have wide range of pathologic presentations, ranging from late abortions with a well developed fetus to an empty gestational sac (Keagle and Gersen 2005; Schmidt-Sarosi et al. 1998), while triploidy which results from the presence of additional set of paternal chromosome, the placenta is usually swollen with what are known as hydatiform changes (Partial hydatidiform mole). In contrast, when triploidy results from additional set of maternal chromosomes, the placenta is usually small (Mark 2000).

**Structural Chromosomal Abnormalities**

In about 3-5% of couples with two or three spontaneous pregnancy losses, a balanced chromosome rearrangement is found in one member of the couple (Allison and Schust 2009). Although individuals who carry balanced rearrangement (for example, translocation and inversion) are unlikely to be at risk for health problems, they have a higher risk for conceiving a fetus with an unbalanced anomaly which can lead either to a pregnancy loss or a liveborn child with multiple abnormalities due to the unbalanced chromosomal status (Allison and Schust 2009).

When a parent carries a balanced chromosomal rearrangement, the chance of having a live birth with an unbalanced chromosome anomaly is usually about 1% to 15% and the chance of spontaneous abortion is usually 25% to 50%. The exact risk depends on the specific chromosomes involved, size of the segment(s) involved in the rearrangement (Daniel et al. 1989; Harper 2004).

**The Impact of Men Factor**

It would make sense that recurrent pregnancy loss may have a male factor since the male gamete contributes one-half of the genomic content to the embryo (Puscheck and Jeyendran 2007). The structural chromosomal problems in men not only leads to low sperm concentrations, abnormal sperms or male infertility (Puscheck and Jeyendran 2007), but also higher miscarriage rates especially men with reciprocal translocations who had a higher rate of abortion compared with men with Robertsonian translocations who are complaining mainly of infertility and finally those with inversions. This has been explained as that reciprocal translocations do not affect sperm production and sperm parameters which occur in Robertsonian translocations and in turn lead to men infertility (Gualandi et al. 2000; Sugiuara-Ogasawara et al. 2004). Also there is an increased rate of sperms’ aneuploidy for chromosomes 13, 18, 21, X, and Y detected by fluorescence in situ hybridization in the sperms of men who had history of unexplained recurrent miscarriage especially with increase paternal age (Borini et al. 2006). As men age, not only there is accumulation and increased chance for mutation or aneuploidy during the maturation of male germ cells, but also there is a decrease in sperm quality (particularly motility), a decrease in conception rate, an increase in miscarriage rate, an increase in autosomal dominant diseases in the offspring as paternally expressed genes may have an im-
pact on implantation, placentation, proliferation, and placenta quality (Aitken and Baker 2006; Puscheck and Jeyendran 2007). These placentomal effects may also play a role in recurrent pregnancy loss in old men (Puscheck and Jeyendran 2007), as the amount of DNA damage in sperm of men aged 36–57 is three times that of men 35 years (Aitken and Baker 2006). The DNA damage can also occur in men with varicocele due to excessive sperm oxidative DNA damage (Agarwal et al. 2009; Iselin et al. 2010; Wang et al. 2012), which is associated with a reduction in some fertility indices, but the risk of child loss decreased significantly with varicocelectomy (Wang et al. 2012).

CONCLUSION

Genetic factors play an important role in recurrent abortion and also men factors. Chromosomal study for POC is important to identify the type of abnormality so that genetic counseling can be helpful in providing information about the risk of future miscarriage or liveborn offspring with an unbalanced karyotype which varies with the size and location of the chromosomal rearrangement. Awareness about men factors is important as normal men somatic chromosomal study does not exclude structure or aneuploid chromosomal aberration of sperms or sperms’ DNA damage which can also occurs as a complication of varicocele. Sperm cytogenetic study and DNA damage assessment may be valuable among tests for couples with unexplained recurrent abortion. Moreover varicocelectomy can change the likelihood bad reproduction outcome. Also IVF with prenatal genetic diagnosis (PGD), may be helpful in case of recurrent aneuploidy or a known balanced carrier parent.

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