

Recurrent Spontaneous Abortions: An Overview of Genetic and Non-Genetic Backgrounds

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ABSTRACT Recurrent Spontaneous Abortion (RSA), Habitual Abortion or Habitual Miscarriage is the loss of 3 or more consecutive pregnancies before the 24th week of gestation. RSA occurs chiefly due to either a problem with the pregnancy or when there is a problem in the environment where it implants and further development occurs. 10-15 % of women with recurrent early pregnancy loss have congenital uterine abnormalities. The role of infections, hormonal imbalances, nutritional deficiencies, and grief has been studied but the results are contradictory from one study to the other suggesting a need of further study. Genetic basis of RSA is poorly understood. Single gene mutations, polygenic, and cytogenetic factors are all found to show association with RSA. In approximately 2-4% of couples with recurrent pregnancy loss, one partner will have a genetically balanced structural chromosome rearrangement. This review looks into the various factors associated with RSA in the West and in the work done in this area in India. It also emphasizes on the need for an appropriately designed framework to study the various aspects of RSA.

INTRODUCTION

'There are few subjects of such clinical importance as recurrent miscarriage so bedevilled by inconsistency, imprecision and unwarranted assumption. This applies particularly to the fundamental question of etiology in which physicians all too frequently confuse "association" with "cause".'

StiratGM, 1992.

Recurrent Spontaneous Abortions (RSA) of unknown etiology provides a fundamental insight into the processes of embryogenesis and implantation and is also a frustrating and emotionally charged clinical problem. Under the best of circumstances, the reproductive process in humans is quite inefficient, as approximately 70% of fertilized ova are lost. Spontaneous Abortion is one of the least understood pathological processes in spite of being one of the most common symptoms. In 50% or more of couples with RSA an evaluation including parental karyotypes, hysterosalpingography or hystero-scopy and antiphospholipid antibody testing will be negative. Therefore, a majority (approximately 50 – 75 %) of couples with RSA will have no certain

diagnosis. Facts regarding the frequency, familial distribution and relation to parity and parental age in this issue are either unknown or disputable due to the difficulty in obtaining reliable information.

WHAT IS RSA?

The classic definition of RSA is the loss of 3 or more clinically recognized pregnancies spontaneously during early gestation. 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 (<http://www.rba-online.com/recurrentloss.asp>). The World Health Organization (WHO) has defined a miscarriage as the loss of a fetus or embryo weighing $\leq 500g$, which would normally be at 20-22 complete weeks of gestation (WHO 1977). Recurrent Miscarriage, synonymously used with RSA, Habitual Abortion or Habitual Miscarriage is defined as the loss of 3 or more consecutive pregnancies before the 24th week of gestation (Reiss 1998).

How Common is RSA?

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 (Edmonds et al. 1982). In humans, approximately 25 % of implanted embryos are resorbed within

7-14 days after attachment to the uterine endometrium (Baines and Gendron 1993). The loss of clinically recognized pregnancies prior to the 20th week of gestation occurs at a frequency of 15 % (Alberman 1988; Warburton and Fraser 1963).

The physical, emotional and financial toll of pregnancy loss is large. The emotional issues surrounding pregnancy loss become magnified exponentially when miscarriage occurs on a repetitive basis. Studies suggest that, by statistical 'bad luck' alone, 4-6 % of all women attempting pregnancy will experience at least two miscarriages, and about 1-2 % will have 3 or more miscarriages (Feinberg 1997). Some studies suggest that clinical intrauterine pregnancy losses occur in 12-14 % of all pregnancies (Regan et al. 1989; Wilcox et al. 1988) and can be attributed to random factors (often fetal de novo chromosomal abnormalities). The number of women with RSA for non-recurrent reasons will decline exponentially with the number of previous miscarriages, because their risk of a new miscarriage in their fourth or fifth pregnancy is still only 14 % compared with the 35-50% risk in the whole group of RSA patients with a similar number of previous miscarriages (Cauchi et al. 1995). Patients with a systemic problem will comprise an increasingly larger fraction of all RSA patients with an increased number of previous pregnancy losses.

RSA and Major Causes

RSA is defined by repeated occurrence of miscarriage. There are 2 major reasons for RSA. Either there is something wrong with the pregnancy itself, such as chromosomal abnormality that prohibits the pregnancy from implanting/ growing properly or there is a problem within the environment in which the pregnancy grows.

Problems with the Pregnancy: Implantation usually occurs after 8-10 days of ovulation in most healthy pregnancies. The proportion ending in early loss increases when implantation is later than this period. Chromosomal abnormalities in the conceptus are usually the characteristic findings in cases of spontaneous abortions occurring due to problems with the pregnancy itself. Chromosomal abnormalities occur in about 50 % of all products of conception from first trimester miscarriages, 5 % of late pregnancy losses and 0.5 % of livebirths (www.haveababy.

com/rpl/causes.asp?site=rpl). Abortions due to trisomy have a high risk of repeating followed by monosomy and polyploidy. Biochemical or clinical abortion occurs in 30-40 % of women who achieve pregnancy after in vitro fertilization (IVF) and embryo transfer (ET). Structural rearrangements are found in 3 % of cytogenetically abnormal conceptions (Boue et al. 1975).

When embryonic or fetal tissue is available and the crown-rump length is at least 30 mm, morphologic examination can predict the karyotype in more than 98% of cases. Some 33% of all malformed fetuses and 66% of malformed embryos have chromosomal abnormalities (Stirat 1983). Studies suggest existence of paternal (sperm derived) effect on human embryo quality and pregnancy outcome that are not reflected as a chromosomal abnormality. Damaged sperm DNA can have a negative impact on fetal development and present clinically as occult or early clinical miscarriage (www.haveababy.com/rpl/causes.asp?site=rpl).

Problems with the Environment: Problems in the environment, in which the fetus grows after implantation, include chromosomal abnormalities, autoimmune disorders, endocrine anomalies, anatomic defects, defects in enzymes catalysing various metabolic pathways, endometriosis, hormonal imbalances and nutritional deficiencies in the mother. The problems involved are thus classified under the broad titles as anatomic, hormonal and metabolic, nutritional, psychological, infectious, genetic and immunologic/immunogenetic.

Anatomic Uterine Defects: Anatomical investigations are normally performed by hysterosalpingography, hysteroscopy or ultrasound scans. Mullerian duct fusion anomalies in the uterus have traditionally been considered responsible for cases of RSA and premature deliveries. Congenital uterine abnormalities have been associated most often with 2nd trimester pregnancy loss. However, 10-15 % of women with recurrent early pregnancy loss have congenital uterine abnormalities (<http://www.modem.com/search/article_display.cm?path=\\TANQUERAY\M.ContentItem&mstr=M_ContentItemZZZSJ24MUJC.html&soc=ACOG&srch_type+NAV_SERCH>). The most common malformations associated with RSA are variations of the double uterus (bicornuate, septate or didelphic) with septate uterus predominating. 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.

Some investigators believe that poor vascularisation of the uterine septum is a cause of spontaneous abortion, but studies provide mixed results. Uterine leiomyomata are usually asymptomatic during pregnancy, but circumstantial evidence suggests an association with an increase in threatened miscarriage and preterm labor. The mechanism of pregnancy loss may involve changes in blood flow and placental abruption is also common with submucous myomata.

Hysteroscopic myomectomy is advocated to remove pedunculated and small submucous fibroids. Women with a diagnosis of cervical insufficiency are often treated by a cervical cerclage (McDonald 1987). The efficacy of this intervention has been studied in three randomized control trials; none could demonstrate any significant effect with respect to decreasing perinatal mortality, in patients with at least three previous 2nd trimester miscarriages or stillbirths (Rush et al. 1984; Winisdoerffer et al. 1989). In a study carried out among 208 couples with Bad Obstetric History referred from hospitals in and around Bangalore (Srinivas and Rajangam 2001) anatomic causes were observed in 8 women. Most of the losses observed by this group were in the second trimester as seen in BOH patients with an anatomical defect.

Hormonal and Metabolic Disorders: Hormonal factors have been proposed to contribute to RSA in 10-20 % of patients (<http://www.haveababy.com/rpl/causes.asp?site=rpl>). Hormonal aberrations may result from problems with certain endocrine glands, such as the pituitary, thyroid, adrenal gland or ovaries. Ovulation problems resulting in deficient hormone levels may cause aberrant growth and support of the uterine lining resulting in a less-than-ideal "bed" for the embryo to implant in. Luteal Phase Defect (LPD) has been thought to be a cause of spontaneous abortions for decades, but the evidence linking LPD to recurrent abortion is subject to criticism. If a luteal phase endometrial biopsy is out of phase for >2 days or serum progesterone concentration measurements are below defined values, then it is often diagnosed as luteal phase defect or luteal insufficiency. LPD implicates poor follicular phase oocyte development, which

results in disordered estrogen secretion and subsequent dysfunction of either the corpus luteum or progesterone effect. The most popular therapy is progesterone supplementation. Poly Cystic Ovary Syndrome (PCOS) and type I Diabetes Mellitus (Dorman et al. 1999) has also been found to be associated with RSA. Poly Cystic Ovary Syndrome causes menstrual disorders ranging from amenorrhea to dysfunctional uterine bleeding, hirsutism and infertility. An elevated level of LH in PCOS is thought to be responsible for its role in RSA. Asymptomatic endocrinologic or metabolic disorders such as mild thyroid disease or glucose intolerance show little evidence towards an association with RSA.

Nutritional Causes: In a study conducted to explore the relationship between maternal health status and infant vitality, selected physical, nutritional, and biochemical parameters were measured in 157 pregnant women and 71 newborn infants at the Azimpur Maternity Center in India (Hussain et al. 1976). The third trimester hemoglobin levels in these women averaged 10.53 % during first pregnancy, 9.84 % in second pregnancy, 10.04 % in third and 10.36 % in fourth pregnancy. The average total protein and packed cell volume remained relatively constant with increases in parity. The prevalence of combined moderate and severe anemia was averaging within 41.2% to 48 % in these women during each of their pregnancies. Overall, 66% of the women had hemoglobin levels below 11 gm % and could be considered anemic. The increased incidence of anemia with increasing parity is attributed to the gradual drain on maternal nutritional reserves. Other than the rate of anemia the serum concentrations also are considered to play a major role. The deficiency of vitamin A is a cause of increased infant mortality (Sharma and Desai 1992). Low concentrations of dietary and circulating folate are associated with increased risks of preterm delivery, infant low birth weight, and fetal growth retardation. 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 (eg, placental abruption and preeclampsia), which increase the risk of poor pregnancy outcome and of decreased birth weight and gestation duration (Scholl and Johnson, 2000).

Based on their experience in cases of RSA,

some clinicians feel that the intake of fresh food like sprouts, fruits, raw vegetables is likely to improve the pregnancy outcome when compared with those taking processed food (personal communication with Dr. Sadaranga Andal). A study needs to be carried out to find out the reasons behind this.

Infections as a Cause: Clinicians suggest that if the uterine lining is infected or inflamed, then it would be a hostile environment for an embryo to implant and grow properly. Microorganisms like Toxoplasmosis, Listeria, Cytomegalovirus and parvovirus are known to cause sporadic pregnancy loss, but no infectious agent has been proven to cause RSA. Other infectious agents include Brucellosis, Mycoplasma, Ureaplasma, Chlamydia etc., though a proven relationship with recurrent abortion has not been established. Herpes Simplex Virus has been linked to Spontaneous Abortion and Chronic HSV is a possible cause of RSA. Fetal infection may lead to either fetal death or malformations incompatible with viability. Amnionitis in the first trimester may also cause pregnancy loss.

GENETIC CAUSES

i) Analysis of Couples

Genetic basis of RSA is poorly understood. Single gene mutations, polygenic, and cytogenetic factors are all found to show association with RSA. The analysis of single nucleotide polymorphisms in the genes coding for: 1) enzymes with regulatory role in crucial metabolic pathways (e.g. methylene tetra hydrofolate reductase), 2) clotting factors (Factor V Leiden and prothrombin), 3) hormones and hormone receptors (progesterone receptor) explain some cases of Spontaneous Abortions.

1) MethyleneTetraHydroFolate Reductase (MTHFR) and Transcobalamin: Polymorphisms in MTHFR (677 C→T and 1298 A→C) and Transcobalamin (776 C→G) genes lead to a defect in folate and vitamin B12 dependent homocysteine metabolism (Zetterberg 2004). These polymorphisms implicate as risk factors for several developmental disorders such as NTD, orofacial clefting and Down's syndrome. Vitamin B12 deficiency during pregnancy results in elevated homocysteine concentration in the embryo and increases the incidence of NTD. Hereditary deficiency of transcobalamin results

in profound neurological abnormalities and mental retardation. The molecular events that lead to NTD may include insufficient methylation of crucial metabolites in the developing embryo and abnormalities in neural cell proliferation, differentiation and apoptosis, which may be due to DNA nucleotide misincorporation that accompanies folate deficiency in proliferating decreased fetal viability.

2) Clotting Factor Mutations: Factor V Leiden and Prothrombin G 20210 A mutations found in approximately 8% and 3% respectively of Caucasian women in the US are associated with approximately 25% of isolated thrombotic events and approximately 50% of familial thrombosis. Other less common thrombophilias include deficiency of the anticoagulants Protein C, Protein S and antithrombin III. Some investigators have found one or more of these thrombophilic mutations associated with RSA.

3) Skewed X Chromosome Inactivation (XCI): An increase in extremely skewed XCI of $\geq 90\%$ has been reported among women who experience RSA (Sangha et al 1999; Lanasa et al 1999, 2001; Uehara et al 2001). Because there are many potential causes of skewed XCI, the reason for an association between RSA and skewed XCI is not clear and may be heterogeneous. 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 (Pegoraro et al 1997). Molecular study reveals a deletion on Xq28 as one of the causes of skewed XCI. One report indicated that highly skewed X-chromosome inactivation is associated with otherwise unexplained recurrent pregnancy loss. As yet, however, commercially available tests for this and other related molecular genetic abnormalities are not widely available.

4) Progesterone Receptor Gene: Progesterone is required for the maintenance of pregnancy and many times treatment with progesterone supplementation prevents abortions. Three linked single nucleotide polymorphisms were detected (Schweikert et al. 2004) in the progesterone receptor gene – exon 1: G 1031 C; Ser 344 Thr, exon 4: G 1978 T; Leu 660 Val, exon 5: C 2310 T; His 770 His.

Several other variations caused by single-gene mutations (Mendelian disorders) or muta-

tions at several loci (polygenic or multifactorial disorders) which cannot be detected by karyotype analysis are however, being identified with the aid of molecular biological techniques such as fluorescence in situ hybridization, polymerase chain reaction, restriction fragment length polymorphism's.

Work has only just begun on molecular mechanisms (e.g., structure and function of cell adhesion molecules, proteins involved in immune responses) that may be responsible for recurrent pregnancy loss. In anembryonic pregnancies, molecular genetic techniques using microsatellite and Y-specific probes can demonstrate both maternal and paternal contributions. Treatment of parental chromosome abnormalities is overcome by explanation after future risk assessment and by the use of donor eggs/sperm, or adoption. In approximately 2-4% of couples with recurrent pregnancy loss, one partner will have a genetically balanced structural chromosome rearrangement. A study by Bhasin et al (1973) reports that of the 27 women studied one showed a translocation and of the 16 husbands studied one showed a pericentric inversion. Balanced translocations account for the largest percentage of these karyotypic abnormalities. They can cause pregnancy loss because segregation during meiosis results in gametes with duplication or deficiency of chromosome segments. Other genetically balanced structural chromosome abnormalities, such as chromosome inversions, account for a small percentage of abnormal parental karyotypes among couples with recurrent pregnancy loss. Thus routine Cytogenetic testing fails to render a complete picture in 98 % of couples, who are cytogenetically normal (Thomas 1999; Patel et al. 2000). Damaged sperm DNA, genes predisposing to ovarian cancer; breast cancer; apoptotic genes like Caspase 3-12, CathespinH, FasL (Baek 2004) and tumor suppressor genes etc are also found to increase the incidence of RSA. Immunity and angiogenesis related genes like PP14, hCG, leukaemia inhibitory factor, integrin etc, involved in RSA have also been reported (Baek 2004).

ii) Recurrent Preembryonic or Embryonic Aneuploidy and Translocations

Analyses of karyotypes in consecutive abortions suggest that recurrent aneuploidy in the conceptus may be a cause of recurrent preg-

nancy loss. In one analysis of data, the karyotype of a second successive spontaneous abortion was abnormal in nearly 70% of cases when aneuploidy was found in the first abortus, but in only 20% of cases where the first abortus was chromosomally normal (Hassold 1980). The older age of the mothers is a possible reason to this finding (Warburton et al. 1987). More recently, two groups of investigators have shown using different techniques of analysis, that the next abortion in women with recurrent pregnancy loss was chromosomally abnormal in 48% or more of cases (Daniely et al. 1998; Stern et al. 1996), raising the possibility of recurrent aneuploidy despite normal parental karyotypes. Supportive evidence comes from studies of preimplantation genetic studies of women with recurrent pregnancy loss in which more than 50% of embryos were found to have aneuploidy (Vidal et al. 1998; Simon et al. 1998). Of the familial translocations, about 66% are maternally derived and the remaining are of paternal origin. Approximately 50% of all unbalanced translocations arise de novo during gametogenesis. The risk of delivering a live fetus with trisomy 21 is 10% to 15% if the mother carries the anomaly and 2% for a paternal carrier; approximately 50% of these concepti will be lost to spontaneous abortion. When the translocation involves chromosomes 13 and 14, the risk is 1% regardless of the parent involved. The birth of a trisomic infant increases the risk of a subsequent trisomic pregnancy by 1% (Boue et al. 1975).

Immunologic Causes: The main task of the immune system is to protect the individual from foreign microorganisms with the help of T- and B- lymphocytes, granulocytes, macrophages, monocytes and some non-cellular factors like Immunoglobulins, complement factors, and interleukins.

The immune factors associated with pregnancy loss are classified as autoimmune and allo-immune factors. The autoimmune factors include the synthesis of autoantibodies (anti-phospholipid antibodies, anti nuclear antibodies, anti thyroid antibodies). Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of significant levels of antiphospholipid antibodies and one or more clinical features, among which are recurrent pregnancy loss, fetal death, and thrombosis (Wilson et al. 1999). Alloimmune traits such as immunologic differences between individuals have been proposed as factors between reproductive partners

that cause otherwise unexplained recurrent pregnancy loss. The tendency for 1) partners with recurrent loss to share human leukocyte antigens, 2) the female partner to fail to produce serum "blocking factor," and 3) the female partner to produce antileukocytotoxic antibodies against paternal leukocytes have been described.

The HLA genes are the main genetic determinants of the repertoire of possible immune responses of an individual. Human Leukocyte antigens (HLA) play critical role throughout pregnancy by influencing gamete development, embryo cleavage, blastocyst and trophoblast formation, implantation, fetal development and survival (Choudhury and Knapp 2000, 2001). In couples with RSA, where no certain diagnosis has been possible, Human Leukocyte antigens (which play crucial role in transplantations) might be playing a role at the maternal-fetal interface. The fetus being semi-allogenic might face a rejection from the maternal antibodies if there is increased HLA sharing among the couple.

HLA complex or MHC contains over 150 loci spanning approximately 4 Mb of DNA on 6p21. The MHC is subdivided into 3 regions – Class- I, Class- II, and Class- III (Browning and McMichael 1996). HLA locus is a high gene density locus with a high frequency of gene rearrangements resulting in the formation of null alleles producing variant antigens or no antigen. HLA antigens play a major role in transplantation and are critical in pregnancy from gamete formation to completion of development. Class-I antigens express on the invasive trophoblast and play a role at the maternal-fetal interface. The results of studies in different populations in the west have revealed significant association of different alleles in each population. For example, studies by Pfeiffer et al (2001) suggest an increased frequency of HLA-G *01013 and HLA-G *0105N carriers in the RSA group compared to controls while a study by Aldrich et al (2001) suggests increased frequencies of the alleles HLA-G *0104 or *0105N. Another study reveals that RSA patients carry HLA-G *0106 allele which exhibits a 14 bp deletion in exon 8. This study reported that RSA women were homozygous for the 14 bp deletion but RSA men were low in frequency for the deletion (Hviid et al, 2002). In a case control study using the RFLP, the frequencies of the HLA- DRB1* 01 and HLA- DR* 03 allophenotypes were significantly increased among the patients with at least four previous miscarriages (Kruse et al

2004). Complement component C4 gene polymorphisms also are found to be associated with RSA. C4A null alleles increased in the primary abortions group wives and husbands compared to the controls and C4B null alleles show an increase in the secondary abortion wives and husbands compared to the controls. This study reports that 95 % of primary abortion couples and 83 % of secondary abortions couples had at least one C4A or C4B null in their phenotypes compared to 66 % among controls (Laitinen et al 1991). HLA-A, -B and -C loci were also studied but the results were not statistically significant. Thus, previous studies on association of HLA alleles (class-I, -II, and -III) and HLA sharing among couples have been contradictory leaving scope for further study. Moreover, to the best of our knowledge, no study has been conducted in India to reveal the association of HLA alleles with RSA.

Psychological Factors: Not much of research is done to find out the role of grief in spontaneous abortions. A few groups have studied the role of grief in women who undergo abortion in the first trimester of an unintended pregnancy. A study suggests no increase in anxiety or depressive reactions two weeks after a first trimester abortion when these patients were compared with non pregnant healthy working women in the age group of 19-39 years (Nielsen et al, 1996). In a different study conducted on 882 women undergoing abortion of unintended pregnancies 442 were followed up to 2 years. This group reports that 72 % of women felt they were benefited and 80 % were not depressed. 1 % reported posttraumatic stress disorder. This group opines that prepregnancy depression is a risk factor for depression, lower self esteem and negative abortion specific outcomes 2 years post abortion (Bergant et al, 1997; Major et al 2000). But a few groups also express a completely contrasting opinion. On the basis of their study in women undergoing spontaneous abortions, Hall et al (1987) report grief as a common response to the event. Patients often report prolonged distress following the episode of spontaneous abortions. Symptoms seen in these patients include shock, denial, anger, anxiety, grief and depression. Components of grief comprise high levels of guilt, the loss of part of self and a large impact upon personal identity.

A study funded by United States Department of Labor, carried out between 1976-1992 on 12,686 young girls in the age group of 14- 21, reports

that woman whose first pregnancy ended in abortion were 65 % more likely to score in the high risk range for clinical depression than women whose first pregnancies resulted in birth (Cougler et al. 2003). Hofberg and Ward (2003) suggest that depressive illness is often associated with postnatal mothers but it is equally common in pregnant women. Consequences of postnatal depression to the child, mother and the family include neglect of the child, family breakdown and suicide. Studies reveal that infants may develop emotional or behavioral problems or cognitive delays in childhood (Murray et al. 1999; Sinclair and Murray 1998). The depressive symptoms include a fear of pregnancy, fear of pain and symptoms like eating disorders (anorexia nervosa, bulimia nervosa) are common in the childbearing years. Anorexia is reported to be antagonistic to reproduction and pregnancy is rare in active anorexia nervosa except where ovulation is induced (Morgan 1999). A higher rate of stillbirths is reported in these patients. Yet another review concludes that miscarrying women are at increased risk for anxiety symptoms immediately following miscarriage and continuing until approximately 4 months post-loss (Geller et al 2000). Reports on effects after 4 months are inconsistent. Based on her long interaction with the RSA women Dr. Sadaranga Andal (personal communication) strongly believes that counseling these women to avoid stress symptoms results in successful pregnancy in a number of cases. From the foregoing analysis of the existing data on the role of grief no clear conclusions emerge, hence the need for further investigations into this aspect.

INDIAN SCENARIO

In Indian culture, having a baby is a life changing experience for the couple. There is no reliable estimate of the magnitude of abortions that take place in India but studies suggest that as women in India do not have control on their fertility and have poor health, there are very high chances that they experience abortions (either spontaneous or induced) more than once. It is difficult to attain a reliable estimate on abortion frequencies in the Indian context as the registration of marriages, births and deaths are usually not complete. As mentioned earlier recurrent abortions affect the couple psychologically, emotionally and are a traumatic experience

and many undergo treatment without actually knowing the cause. This is particularly true in Indian context. Child bearing in India is concentrated in the age group of 15-29, which contributes more than ¾ of total fertility. Current fertility is characterized by a substantial amount of early child bearing: 17 % of total fertility is accounted for by births to women in the age group of 15-19 (NFHS-I summary report). A study was carried out on the obstetric behaviour and outcome in teenage mothers (Pal et al. 1997). Anemia (27.5 %), intrauterine growth retardation (27.5 %) and hypertension (15 %) were mostly found as complications in the study group compared to controls (11.2%, 8.7%, and 8.7% respectively). The association of Vitamin A levels (Sharma and Desai 1992) and serum folic acid levels with RSA (Dutta 1977) is studied. A few research groups have been working to determine the extent of maternal infection with *Toxoplasma Gondii* responsible for reproductive disorders (Oumachigui et al. 1980; Pal and Agarwal 1979). Jalan (<http://jalanani.tripod.com/NIRMAN/id12.html>) suggests that in Indian situation we still do not have the abortus material available for chromosomal studies. Abortus studies would pickup chromosomal abnormalities in approximately 40 - 50 % of cases as against this we have parental karyotyping, where the pickup rate is not above 6 % in a couple. This study also quotes studies by Panthaki et al. (1999), which suggests a 2 % incidence of numerical aberrations among the couples.

Apart from these isolated studies restricted to certain parts of India there has not been much work in this area. Further, studies on spontaneous abortions in India have not been looked upon independently. In most of the studies patients with spontaneous as well as induced abortions have been combined together and the results therefore do not give a true picture of the causes and their frequency. Further, disruption of interacting factors, including interactions between HLA antigens, cytokines and natural killer (NK) cells are all expected to play crucial role in RSA. Excess sharing of HLA antigens between spouses has been considered by some to be a mechanism leading to maternal hyporesponsiveness to paternal antigens encountered in pregnancy and therefore subsequent miscarriage (Beer et al, 1981). Grief is also thought to be a potential abortogen. In order to attain a clear understanding of the causes of RSA in the

Indian context, all the above aspects, which are hitherto unexplored, need to be investigated using appropriate framework.

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