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Genitourinary Diseases Prior Spontaneous Abortion as a Risk Factor for Recurrent Pregnancy Loss

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A B S T R A C T

The etiology of recurrent spontaneous abortion (RSA) is still unexplained. Many couples do not find the cause of their RSA at all. The purpose of this research was to evaluate the association between recurrent pregnancy loss and previous (cured prior to pregnancy) acute/chronic genitourinary infections in both parents. Couples (226) having two or more (up to six) spontaneous abortions were analyzed in this retrospective case-control study. The control group consisted of 124 couples with neither miscarriages nor complicated pregnancies in their past. The data (serum immunological markers, karyotype, flow cytometry data, PHD) were collected from their medical charts. It was found that there was no statistically significant difference in average weeks of pregnancy in which the second, third and fourth abortion occurred. There was a statistically significant difference in previously experienced genitourinary infections between women from the RSA group and the control group, as well as for men from the RSA group and the control group. It can be concluded that past infections of the maternal and/or paternal genitourinary system may be the causal factor for recurrent pregnancy loss and can also pre-determine women that are of greater susceptibility to preterm pregnancy. Therefore the genetic counseling of couples should include thorough medical and family history of both partners and their first- and second-degree relatives in conjunction with typical medical examination.

Key words: *recurrent spontaneous pregnancy loss, infectious diseases, genitourinary system, risk factor*

Introduction

Pregnancy loss syndrome (also known as fetal wastage syndrome) is characterized by recurrent spontaneous abortions (RSA). Historically, 50% of spontaneously expelled abortuses have been thought to be chromosomally abnormal. The majority (95%) of chromosomal anomalies are numerical. About 60% are trisomies and 20% are monosomies. Another 15% have ploidy, especially triploidy. In cases of a numerical chromosomal anomaly in spontaneous abortions, the parental chromosomes are usually normal.

The incidence of miscarriage increases with age, from 15% under 25 years of age to 35% after age 38. Actually, the largest increase in occurrence of miscarriage comes after 1 miscarriage, increasing from 13% with no previous miscarriage, to 23% after 1 miscarriage, to 29% after 2 miscarriages, and to 33% after 4 miscarriages[1,2]. However, the etiology of a large proportion of miscarriages, as well as the etiology of recurrent miscarriages, remains unexplained. Previous studies of such cases have suggested many risk factors, such as: history of prior fetal losses, abortions and previous deliveries, caffeine, alcohol, tobacco and drug use, uterine anatomic defects, endocrine disorders, deregulation of a component of the immune system, etc[3–5].

Maternal genitourinary infections during the first 22 weeks of gestation, as well as during the perinatal period,

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caused by many different microorganisms (virus, protozoa and bacteria), have also been linked to pregnancy loss, as well as to stillbirths or a congenital anomaly of predilected organ.

Furthermore, infections that have activated the maternal immune system (during pregnancy) are linked to a greater expression of γ-interferon and the tumor necrosis factor (TNF) in the endometrial cells. These cytokines, and their gene polymorphisms in women, are also known to increase the risk of spontaneous abortion. However, recurrent spontaneous abortions are quite frequent in mothers with no indications of any well known risk factors, including the absence of laboratory/clinical signs of a present infection. Therefore, the question that springs to mind, related to the connection between a mother's infectious diseases and pregnancy loss, is whether acute or chronic inflammatory illness of the genitourinary system that was overcome prior to pregnancy, could play a part as a risk factor for recurrent spontaneous abortion. It is also possible that recurrent infectious diseases in a mother's relatives, for several generations, are also an indication of whether a miscarriage will occur.

Current evidence relating to the effects of paternal factors in terms of the risk of spontaneous abortion is obscure, dealing mostly with paternal age, occupation, alcohol drinking and smoking[6–9]. Nothing is known about a possible connection between paternal genitourinary infections (either previous or present at the time of conception) and the occurrence of spontaneous abortions, although there is some evidence that an infection by *Chlamydia trachomatis* and *Mycoplasma,* and the presence of sexually transmissible pathogens in sperm, decrease men's fertility potential and may cause miscarriage[10,11].

Therefore, the aim of this study was to evaluate the association between recurrent spontaneous abortion and 1) previous (overcome prior to pregnancy) acute or chronic genitourinary infections in both parents, and 2) medical history factors of other diseases in both parents.

Patients and Methods

Two hundred twenty-six couples, representing the Genetic Counseling Unit, Pediatric Clinic, Clinical Hospital Center Split, Croatia, who suffered two or more (up to six) spontaneous abortions in the period from 1985 to 2001, were included in this retrospective case-control study. All together, the couples suffered from 528 miscarriages which happened at or prior to the 16th week of gestation. The control group consisted of 124 couples who were matched by ethnic origin, with neither miscarriages nor complicated pregnancies in their medical history, and with healthy and chromosomally normal offspring (control group).

All couples were of European Caucasian origin. No women had either abnormal karyotypes, or coagulation disorders, or polycystic ovary syndrome or any other known risk factor for RSA.

A pedigree analysis was done for each couple. The participants were questioned about age, profession, smoking and alcohol habits, previous and current medical treatments, previous spontaneous abortions, stillborns, other illnesses, and about illnesses in their relatives (family members and other siblings). Clinical data, such as serum immunological markers, karyotyping, flow cytometry for aneuploidy, and pathohistological findings in aborted material were collected from each mother's medical chart that was completed at the Genetic Counseling Outpatient Unit and cytogenetic laboratory.

The study received approval by the Ethics Committee of the Clinical Hospital Split.

Statistical analysis

Statistical analysis of the data was done using the analytical systems SPSS and PAST. The data obtained by counting are shown as absolute numbers and relative frequencies. The data obtained by measuring (age) are shown by a method of five points: minimum, first quartile, median, third quartile and maximum.

Categorical data obtained by counting were compared by χ^2-test or Fischer's exact test. Continuous data were compared by the use of one-way analysis of variance (ANOVA) followed by Tukey's HSD test. All tests were two-dimensional. The results were considered significant when $p<0.05$[12,13].

Results

The total number of spontaneous abortions (SA) found in 226 couples was 528 (Table 1). The majority of couples (N=165) experienced two SA (all together 330), followed by couples who experienced three (49 couples, 147 miscarriages) and four or more SA (12 couples, 51 miscarriages).

The average age of both partners at the time of pregnancy loss is shown in Table 2. The mean average age of control women was 28.3 and control men 32.6 years. There was no statistically significant difference between maternal and paternal age and corresponding control individuals ($\chi^2 = 5.919$, df = 5, p = 0.2080 for women and $\chi^2 = 2.8702$, df = 5, p = 0.7200 for men). There was also no statistically significant difference (Contingency Table Test, p = 0.549) between the average age of females and males (bolded rows) in any group of couples based on the number of experienced SA. Most females (N=177; 78%)

TABLE 1
NUMBER OF RPL PER COUPLE

Number of abortions per couple	Number of couples (%)	Number of abortions
2	165 (73)	330
3	49 (22)	147
4 and more	12 (5)	51
Total	226 (100)	528

TABLE 2
MATERNAL AND PATERNAL AGE IN RELATION TO THE NUMBER OF EXPERIENCED PREGNANCY LOSS

Groups	Age (females)	Number of spontaneous abortion			Total
		2	3	4	
		Number of females			
1.	19–22	13	3	0	16
2.	23–27	59	15	5	79
3.	28–35	73	21	4	98
4.	36–40	15	9	3	27
5.	41–43	5	1	0	6
	Number (females)	165	49	12	226
	Average age – females	29.4	29.7	29.2	29.4
	Average age – males	32.1	33.4	31.5	32.3

– the average age of control women was 28.3 and control men 32.6 years

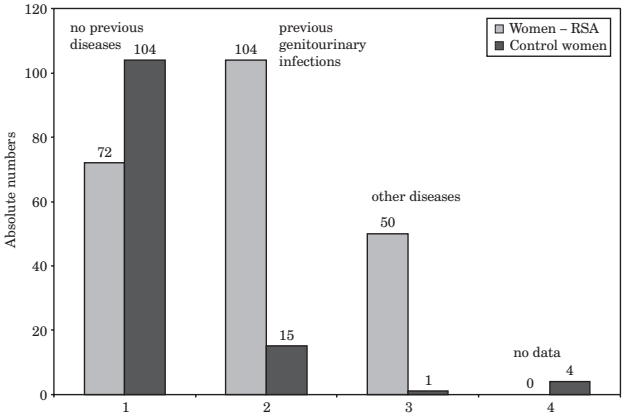

Fig. 2. The kind of diseases female participants suffered before SA (women – RSA) in comparison to the diseases experienced by women from control group (control women). 1 – no previous (to RSA) diseases; 2 – previous genitourinary infections; 3 – respiratory infections, diseases of other systems, sterile or infertile marriage; 4 – the data were not available.

were between age 23 and 35, irrespective of the number of experienced SA.

Figure 1 shows the number of abortions in relation to the gestational period when it occurred. Of the total 528 abortions, 465 happened before or shortly after the 16th week of pregnancy. The largest number of abortions occurred between the 8th and 10th week of pregnancy (the second, third and fourth abortions were analyzed). ANOVA variance analysis and corresponding F-test revealed that there was no statistically significant difference in average weeks of pregnancy in which the first, second, third and fourth abortion occurred.

Figures 2 and 3 show the kind of diseases female and male participants suffered from prior to SA. Seventy two women (32%) and 96 men (42%) had no previous history of diseases. For 12 men, the data were not available. The rest of the 154 females and 118 men suffered from one or more different diseases. Among these women, there were 104 (68%) of them that suffered from previous infections of the genitourinary tract. The rest of the women (N=50) suffered from either diseases of the respiratory system or diseases of other organ systems, or experienced sterile or infertile marriages. Among the 124 women in the control group, 104 (84%) had no prior diseases, for four of them the data were not available, and 15 women experienced infectious diseases (one woman had HPV and one had *Chlamydia trachomatis* infection, two had streptococcus agalactie of the cervix, and 11 women had E. coli in the urine culture). Based on these data, the statistical analysis showed (contingency table test, p=0.0329) a significant difference in previously experienced genitourinary infections between women who suffered from recurrent SA and the control group.

Among the 118 men in the RSA group, 52% (61 men) previously suffered from genitourinary infections and

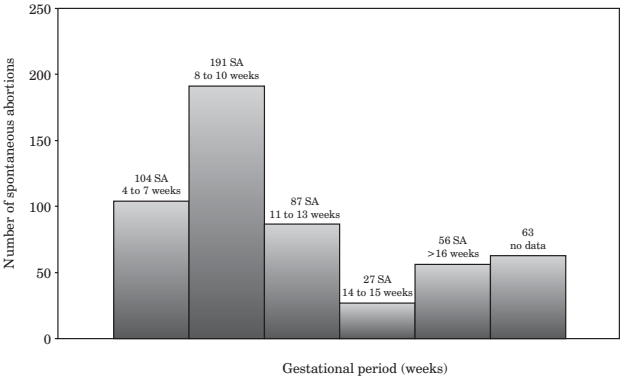

Fig. 1. Total number of spontaneous abortions (SA) in relation to the gestational period (weeks).

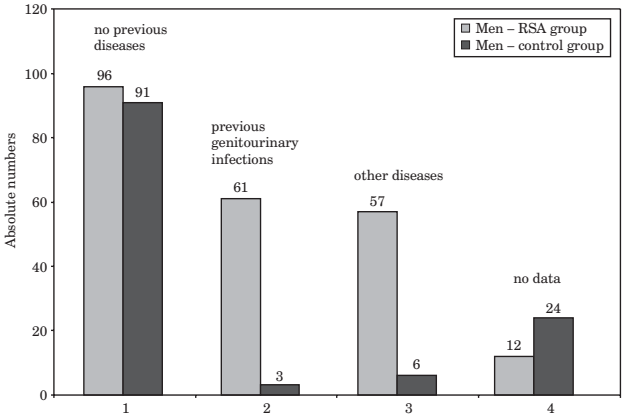

Fig. 3. The kind of diseases male participants suffered before SA (men – RSA group) in comparison to the diseases experienced by men from control group. 1 – no previous (to RSA) diseases; 2 – previous genitourinary infections; 3 – respiratory infections, diseases of other systems, sterile or infertile marriage; 4 – the data were not available.

48% (57 men) from various diseases of other organ systems. Among the men in the control group, 91 had no prior diseases, for 24 of them the data were not available, only 3 men (3%) suffered from previous genitourinary infections, and 6 men suffered from diseases of other organ systems (Figure 3). Based on these data, the statistical analysis showed a significant difference ($p=0.035$) in previously experienced genitourinary infections between men from the RSA group and the control group.

Discussion

Recurrent miscarriage or pregnancy loss (RPL) syndrome is characterized by repeated spontaneous abortions (RSA). For a long time, RPL has been defined as three or more consecutive pregnancy losses prior to the 20th week of gestation. However, it is now recognized that the definition of RPL includes two or more consecutive spontaneous miscarriages[1]. So, this principle has been accepted in our Clinic as well. In this respect, the majority of couples (226) included in our study suffered from RSA because they went through two (165 couples), three (49 couples) and four or more (12 couples) consecutive abortions.

Recurrent miscarriage (RM) can have deep emotional and psychological effects on both partners. Therefore, genetic counseling is indispensable in helping such couples overcome emotional and psychosocial problems and, in their best interest, make mutual decisions about their life and pregnancy planning. The first and most important part of genetic counseling is to take a thorough medical and family history of both partners, as well as their first and second relatives in conjunction with typical medical examinations[1]. This is exactly how it was done in our study.

The variety of risk factors (mentioned in the Introduction), including maternal infection, have been suggested as the underlying causes of RSA occurrence[1–5,14,15]. However, many couples do not find the cause of their RSA at all, in part due to the possibility of having different causes for each miscarriage. In such cases, it may not be possible to discover a pattern for a woman's miscarriages. A similar situation was shown by Patriarca and coworkers[16] who evaluated the causes of RSA in relation to the period of abortion and number of embryo losses. Forty-six percent of patients turned out to be *sine causa*.

However, despite which risk factors underlie RSA, so far there is no corresponding way to estimate the total risk for RSA in a longer period of pregnancy, such as from soon after conception to 27 weeks of gestation[17]. Therefore, the attention should be put on searching for risk factors in shorter periods of preterm pregnancy. For this reason, the couples included in our study were all those who experienced SA up to the 16th week of gestation.

As mentioned above, various maternal infections have been reported as a cause of sporadic spontaneous abortion. However, evidence linking infection and RSA are only anecdotal. The majority of data are related to the second trimester of pregnancy, but the role of infection in a first trimester RSA is still controversial[18]. Only few well documented studies on this topic have been conducted, and the results are inconsistent. For instance, while Witkin and coworkers found that high-titer IgG antibodies to *C. trachomatis* were associated with RSA[19,20], Paukku and coworkers found just the opposite[21]. On the other hand, genital mycoplasma and ureaplasma species are frequently found in women with recurrent miscarriages[22]. Later on, no evidence suggests that either *Listeria* or *Treponema pallidum* organisms play a role in patients with a history of recurrent pregnancy loss[23]. CMV is associated with random miscarriage but not recurrent miscarriage[24,25]. Similar, contradictory results were also found for HPV and AAV[26–28]. Probably the most obvious risk situation in RSA is chronic infection that can spread to the placenta in a patient who is immunocompromised.

So, what could be the cause of recurrent miscarriage in couples/mothers that lack any well known risk factors, including absence of laboratory/clinical signs of present infection? It is now becoming evident that inappropriate activation of the mother's immune system may cause early first trimester miscarriages. Current theory suggests that during a normal pregnancy, the fetus, which carries the father's foreign genes, can nevertheless survive in the mother's uterus because of special protection from the mother's immune system. For certain couples, this protective response does not occur, and the maternal immune system rejects the father's foreign material in the fetus, resulting in miscarriage.

In this respect, is it possible that acute or chronic inflammatory illnesses of the genitourinary system in both parents, that were overcome prior to pregnancy, can play a part as a risk factor for recurrent spontaneous abortion? By analyzing 226 couples with RSA we have shown (based on statistical analysis) that the hypothesis on the relationship between genitourinary infections cured before one's next pregnancy and one's next RSA is correct, for both mothers and fathers. Even 68% of women and 52% of men suffered before the next preterm pregnancy from some kind of genitourinary infection.

However, how can we explain these findings? Our assumption is that changed activity of the immunological system during the infection persists, in some parts, even after the infection is cured, and in this respect may cause next preterm pregnancy. Namely, to avoid the rejection of the embryo, the mother's immune response should be suppressed in a physiological manner. It seems that the major component of this suppression is the reduction of the synthesis of pro-inflammatory cytokines caused by a Th1/Th2 balance shift, as well as the normal activity of specific subsets of NK and T cells[29,30]. If this doesn't happen, the embryo is rejected. But why wouldn't this happen? As we said above, it is possible that changed activity of the immune system during the infection persists in some parts, even after the infection is cured, and in this respect may cause next preterm pregnancy. In line with this hypothesis are the following findings. The percentage of endometrial suppressor T lymphocytes was decreased in recurrent aborters, their CD4:CD8 (helper to

suppressor) ratio was increased, and a CD16-CD56 bright NK cell subset, predominant in normal deciduas, was decreased, indicating that endometrial lymphocytes of RSA aborters harbor a distinct immunophenotypic profile[31].

Later on, successful pregnancy depends on an adequate fine modulation between the levels of pro-inflammatory and anti-inflammatory cytokines. It is generally believed that the presence or increase of Th-1 related pro-inflammatory cytokines are associated with pregnancies that end in miscarriage, whilst the production of Th-2 related anti-inflammatory cytokines are associated with ongoing successful pregnancies[32–34]. The exact immune dysfunction was also found in patients with a history of RSA: the proinflammatory cytokines (IL-2, IL-12, IFN-γ) and IL-2 receptors expression/level were increased in peripheral blood mononuclear cells and serum, and the level of anti-inflammatory cytokines IL-10 and IL-18 were decreased in non-pregnant women with a history of RSA when compared to non-pregnant women with no history of RSA [30,32,35–40].

Increased numbers of activated leukocytes have also been found in the deciduas of women with a history of unexplained pregnancy loss[41] suggesting that an activated immune system might be a factor involved in RSA. However, the question is: why is the immune system activated when an infection is not present. One possibility is that the mother's immune system has not returned to normal after miscarriage. We did not measure immunological status of women with a history of RSA. However, even if we did, such a possibility would have been rejected, since at the time the women included in our study group attended our Clinic, it had been at least 6 months since they had suffered from last miscarriage. Therefore, there must be some other factor which is responsible for RAS in such cases. In our opinion and based on the presented data, past infections of the genitourinary system in women with a history of RSA, may induce an alteration of the immune system. If a next pregnancy happens when the immune system is still in an activated state, there is a great probability of early pregnancy miscarriage. Therefore, we suggest that past genitourinary infections in women with a history of RSA might predispose them to another unsuccessful outcome in the next pregnancy.

The explanation of why RSA happens when infection is not present may also involve endometrial damage from a past infection, as was shown for chlamidial infections, or an immune response to an epitope shared by an infectious agent (shown for *Chlamydia*) and a fetal antigen. Neither of the mentioned possibilities was presented in our study.

Another question that springs to mind is, why in some women, the immune system is still activated even after the prolonged period after the last RSA or past (cured) infection of the genito-urinary system. One of the possible explanations is the presence of specific polymorphisms (which modulate gene expression) in the genes responsible for synthesis of the components of the immune system. One such polymorphism found in intron 2 of the gene for IL-1 receptor antagonist (IL-1RA) is a changed number of tandem repeats[42]. The most common allele possesses in a second intron four 86 bp long tandem repeats (IL-1RA^4) and is associated with the normal activity of the gene. Contrary to this, polymorphic allele with only 2 tandem repeats (IL-1RA^2) is associated with decreased gene activity. IL-1RA is a competitive inhibitor of major pro-inflammatory cytokine, IL-1. Therefore, the relative levels of IL-1RA and IL-1 determine whether the immune response will persist or will be terminated. When the ratio level between IL-1RA and IL-1 is decreased, as seen in homozygotes and heterozygotes for 2 tandem repeats polymorphism (IL-1RA^2/IL-1RA^2 and IL-1RA^2/IL-1RA^4), the inflammatory reaction is prolonged or persistent even in the absence of specific antigen[42,43]. So, several studies have demonstrated an association between IL-1RA2 and recurrent miscarriage[42–45]. However, the results of some other study groups indicated no significant difference in the distribution of IL-1R alleles in recurrent miscarriage women and control fertile women[42,46].

As shown recently by the »omics« methods, the expression level of several other immunosuppression, angiogenesis and apoptosis-related genes is associated with RPL[47]. However, eventhough immunological abnormalities have been demonstrated to underlie, at least in part, unexplained RSA, additional, more comprehensive studies at the molecular level are required to understand the exact mechanisms of RSA occurrence.

There have been multiple studies which look at the maternal factors leading to spontaneous abortion; however, there are limited studies identifying the male factors. Several studies have suggested that paternal age may play a role. It is known that advanced paternal age is associated with abnormalities in sperm, certain chromosome defects, and numerous birth defects associated with autosomal dominant mutations. Increasing paternal age is significantly associated with spontaneous abortion, independent of maternal age and multiple other factors[48].

Given the current lack of effective predictors of further miscarriage in recurrent cases, and based on the data that past infections of maternal and paternal genital and urinary systems are in positive correlation with the occurrence of next RSA, we hypothesize here that such infections may be the causal factor for RSA and can also pre-determine women who are at greater susceptibility for next preterm pregnancy outcome.

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GENITOURINARNE BOLESTI PRIJE SPONTANOG POBAČAJA – ČIMBENIK RIZIKA OPETOVANIH POBAČAJA

SAŽETAK

Etiologija brojnih slučajeva spontanih opetovanih pobačaja (RSA) još je uvijek nepoznata. Većina bračnih parova nikada ne sazna uzrok RSA. Stoga je svrha ovog istraživanja bila vidjeti postoji li povezanost između RSA i ranije preboljenih (izlječenih prije slijedeće trudnoće) akutnih i kroničnih genitourinarnih infekcija u oba roditelja. Ovom retrospektivnom, kontroliranom, studijom obuhvaćeno je 226 parova koji su iskusili dva ili više (do šest) spontanih pobačaja. Kontrolnu grupu sačinjavalo je 124 parova koji nisu iskusili niti pobačaj niti nikakve druge kompikacije trudnoće. Podaci o imunološkim biljezima u serumu, kariotipu i PHD-statusu preuzeti su iz medicinske dokumentacije parova. Nađeno je da se drugi, treći i četvrti pobačaj događaju otprilike u istom tjednu trudnoće. Međutim, nađena je statistički značajna razlika u povezanosti preboljenih (prije pobačaja) genitourinarnih infekcija i opetovanih pobačaja u skupini RSA a u odnosu na kontrolnu skupinu, i u žena i u muškaraca. Stoga se može zaključiti da su infekcije genitourinarnog sustava preboljene prije pobačaja, i u žena i u muškaraca, jedan od uzročnih čimbenika opetovanih pobačaja. Ovaj nalaz može poslužiti za predviđanje žena s većom podložnošćut razvitku spontanog pobačaja. Stoga bi genetsko savjetovanje parova s problemom spontanih pobačaja trebalo uključivi pažljivo ispitivanje medicinske i obiteljske anamneze oba partnera, ali i njihovih srodnika u prvom i drugom koljenu, kao i tipične kliničke pretrage.