European Journal of Obstetrics & Gynecology and Reproductive Biology 161 (2012) 182–186

Contents lists available at SciVerse ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Positive reproductive family history for spontaneous abortion: predictor for recurrent miscarriage in young couples

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ARTICLE INFO

Article history:
Received 26 July 2011
Received in revised form 2 December 2011
Accepted 22 December 2011

Keywords:
Recurrent spontaneous abortion
Family history

ABSTRACT

Objective: The etiology of recurrent spontaneous abortions (RSA) in chromosomally normal parents is still unexplained. It is unclear whether or not some factors, such as spontaneous abortions (SA), which occur among extended family members can create a predisposition to RSA. Therefore, this study comprises two parts: (a) an epidemiological part, to evaluate the relationship between RSA in 567 couples and the frequency of SA among their first (I), second (II) and third (III) generation relatives, and (b) a genetic part, investigating whether parental and fetal chromosomal status may predispose to the occurrence of RSA.
Study design: Couples (567) having one or more SA were analyzed in this retrospective case-control study. The family reproductive history data was collected from their medical charts.
Results: The total number of SA found in 567 couples was 1174, and the largest number occurred at 8–10 weeks of gestation. The majority of spouses had normal karyotypes (88.5% and 91%). Of the remainder, 65% of females and 76% of males expressed constitutional chromosomal variation, mostly pericentric inversion of chromosome 9. Cytogenetic analysis of aborted material showed some type of change in 40% of cases. The family reproductive history data indicated that SA among the couples' I, II and III generation relatives happened with a frequency two to three times higher than that of the general population (55.5, 47.6 and 32.6% for female relatives, and 45.8, 44.1 and 15.1% for male relatives).
Conclusion: Positive reproductive family history for SA might be the causal factor for RSA and can also predetermine women that are of greater susceptibility to preterm pregnancy.

1. Introduction

Recurrent miscarriage syndrome is characterized by repeated spontaneous abortions (RSA). The etiology of RSA is still unexplained. In many couples the cause of their RSA is never found, partly because there may be different causes for each miscarriage. Chromosomal anomalies are known to be the single most common cause of spontaneous abortions. Around 50% of spontaneously expelled abortuses have been thought to be chromosomally abnormal. The majority (95%) of chromosomal anomalies are numerical. About 60% are trisomies (trisomy 16 being the most common) and 20% are monosomies; while another 15% have ploidy, especially triploidy. In cases of numerical chromosome anomaly in spontaneous abortions, the parental chromosomes are usually normal. However, the percentage of miscarriages in which a chromosome abnormality is detected decreases from 70% to 80% for a first miscarriage to 40–50% after three or more miscarriages. We now know that the vast majority of trisomic conceptuses are maternal in origin, that increased maternal age is associated with nondisjunction, and that the amount and position of recombination on nondisjoined chromosomes is altered [1]. Previous studies of such cases have suggested many risk factors, such as: maternal age, history of prior fetal losses, abortions and previous deliveries, abnormal corpus luteum function, coagulation, hematologic or immunological factors, caffeine, alcohol, tobacco and drug use, uterine anatomic defects, endocrine disorders, deregulation of a component of the immune system [2–4]. All these factors (definite or probable causes of RSA) occur with equal frequency in women with only two pregnancy losses versus those who have had a greater number of losses [5]. Additionally, the risk of a further miscarriage increases sequentially in women who have already had one or two miscarriages [6].

Therefore, the purpose of this study was to evaluate: (a) the association between RSA and the incidence of SA among the

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doi:10.1016/j.ejogrb.2011.12.027

parents' first (I), second (II) and third (III) generation relatives; and (b) whether parental and fetal chromosomal status may predispose to the occurrence of RSA.

2. Materials and methods

2.1. Patients

Five hundred sixty-seven couples, representing the Genetic Counseling Unit, Pediatric Clinic, Clinical Hospital Center Split, Croatia, who suffered one or more (up to six) spontaneous abortions (SA) in the period from 1987 to 2010, were included in this retrospective case-control study. Altogether, the couples suffered from 1174 miscarriages which happened prior to the 16th week of gestation. The couples were classified as having unexplained etiology of spontaneous abortion after the exclusion of all known SA causes. The control group consisted of 65 couples who were matched by ethnic origin, with neither miscarriages nor complicated pregnancies in their medical history, and with healthy and chromosomally normal offspring. All couples were of European Caucasian origin.

2.2. Data

A pedigree analysis was done for each couple. The family reproductive history data for the first, second and third generation relatives was collected from their hospital medical charts. Clinical data, such as karyotyping (the G-banding technique), from both partners' peripheral blood and aborted material, was collected from each mother's medical chart that was completed at the Genetic Counseling Outpatients Unit and Cytogenetic Laboratory.

The study was approved by the Ethics Committee of the Clinical Hospital Split. Informed consent was obtained from each couple.

2.3. Statistical analysis

Statistical analysis was done using STATISTICA for Windows version 8.0. The age data are shown as medians and interquartile ranges (IQR). The difference between the groups was tested using the Kruskal–Wallis test and the Bonferroni test. p values less than 0.05 were considered statistically significant. All applied tests were two-tailed.

3. Results

In the period between 1987 and 2010, 567 couples who suffered at least one miscarriage prior to the 16th week of pregnancy attended the Genetic Counseling Unit, Pediatric Clinic, Clinical Hospital Center Split, Croatia. The total number of unsuccessful pregnancies (UP) and spontaneous abortions (SA) among the 567 couples was 1174 (Table 1).

Table 1
Number of SA per couple.

Number of SA per couple	Number of couples	Number of SA
1	102 (18%)	102 (8.7%)
2	355 (62.6%)	710 (60.5%)
3	81 (14.3%)	243 (20.7%)
4	27 (4.7%)	108 (9.2%)
5	1 (0.2%)	5 (0.4%)
6	1 (0.2%)	6 (0.5%)
Total	567 (100%)	1174 (100%)

The median age of the females and males who suffered from 1, 2, 3 or more spontaneous abortions was not significantly different from the age of the control group (Table 2). Age did not influence the life-time prevalence of abortions except among females (Kruskal–Wallis, $p = 0.0183$, Bonferroni test, $p < 0.05$) and males (Kruskal–Wallis, $p = 0.0018$, Bonferroni test, $p < 0.05$) who experienced 3 or more abortions. However, the difference is negligible from a practical point of view because the observed difference reflects the power of the study rather than the real difference between the groups. The largest number of SA occurred between 8 and 10 weeks of pregnancy (data not shown).

Tables 3 and 4 and Fig. 1, show the pedigree data of the couples investigated in this study, regarding reproductive history among their relatives of I (sister, brother), II (mother, father, uncle, aunt) and III (grandmother, grandfather, grandparents' sisters and brothers) family generations. It is worth mentioning that a majority of their relatives, regardless of the family generations, suffered spontaneous abortions. In the general population, the risk of spontaneous abortion is 12–15% [7]. Among the women, 85 (17.3%) had normal reproductive pedigree data, while for 75 (out of 567) women data were not available. For 407 (82.7%) women there was information about spontaneous abortions, sterility, stillbirth, sudden infant death syndrome and mental retardation and Down syndrome among their relatives in the first, second and third generations. Their pedigree data indicated that, in total, 195 relatives (48%) of generations I, II and III experienced spontaneous abortions. The number of SA among the women's I, II and III generation relatives occurred two to three times more often than in the general population (55.5, 47.6 and 32.6%, $p < 0.05$).

Among the men there were 95 (19.4%) with normal family reproductive history, while for 78 (out of 567) men data were not available. For 394 (80.6%) men there was information about spontaneous abortions, sterility, stillbirth, sudden infant death syndrome and mental retardation and Down syndrome among their first, second and third generation relatives. Their pedigree data indicated that, in total, 166 relatives (42%) of generations I, II, and III experienced spontaneous abortions. Similar to the women's relatives, the number of SA among the men's I, II and III generation relatives occurred two to three times more often than in the general population (45.8, 44.1 and 15.1%, respectively, $p < 0.05$).

Table 2
The median age of females and males who suffered from 1, 2, 3 and more spontaneous abortions.

Gender	Number of spontaneous abortions			
	0 (controls)	1	2	3 and more
Females[a]	$N = 65$	$N = 94$	$N = 331$	$N = 121$[†]
Median (IQR)	31 (25–35)	29 (25–32)	29 (19–48)	31 (27–36)
Males[b]	$N = 63$	$N = 93$	$N = 324$	$N = 116$[††]
Median (IQR)	33 (30–38)	31 (22–53)	32 (29–36)	34 (31–37)

N, number of persons; IQR, interquartile range.
[a] For 21 women the age-data were not available.
[b] For 34 men the age-data were not available.
[†] Kruskal–Wallis, $p = 0.0183$, Bonferroni test versus 1 and 2, $p < 0.05$.
[††] Kruskal–Wallis, $p = 0.0018$, Bonferroni test versus 1 and 2, $p < 0.05$.