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Analysis of anamnestic data from genetic counseling of couples with history of repeated spontaneous abortions from Split Croatia

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Short report

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Abstract

Aim: To show the importance of how important are in the genetic counselling process of spontaneous abortions, including careful and detailed analyses of anamnestic data and drawing a family tree.

Methods: We included 451 couples with normal karyotypes and treated in the Genetic Counseling Unit due to one or more unsuccessful pregnancies from 1985 to 2010.

Results: Second-generation relatives of both partners had two times higher number of SA than the general population. Almost one third of participans (men and women) were historically exposed to some harmful agent. The "motherhood age effect" is not present, male partners in the group with 3 spontaneous abortions (SA) were older. Both men and women had previous urinary and/or genital infections more often than in the general population. There was no significant correlation between occupation and SA and the frequency of urogenital infections with the type of occupation. Women were affected by computer work or exposure to food and chemicals, while men mostly by heat and cold exposure. Harmful habits predominant in women was smoking and alcohol by men.

Conclusion: The research showed how much important information could be obtained for further investigation of the causes of a complex multifactorial process such as recurrent spontaneous abortions.

Keywords: anamnestic data, spontaneous abortions (SA), pregnancy loss (RPL), genetic counseling

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1. Introduction

Genetic counseling is a process during which patients and their relatives find out about the risks of inheritance or hereditary illness in I, II and III generation (Čulić V. 2007, Čulić V. 2010). The causes of SA can be genetic, infectious, anatomical, endocrine, immune and idiopathic etiologies. Most commonly definition of SA is unexpected loss of pregnancies before 20th week of gestation or those in which weight is less than 500 grams (Kavalier F. 2008, Husar D. and Đelmiš J. 2008). Most pregnancies are lost during the preimplantation period and at the early stage of implantation (50-60%). The loss of preclinical implantable pregnancies of about 19% and clinical pregnancies of about 12% (Kavalier F. 2008). Chromosome aberrations and viral infections, especially those occurring directly or during an early pregnancy period, are the first of many possible causes of abortion. Exceptional working conditions (exposure to radiation, harmful chemicals) and unhealthy living habits (alcohol and coffee consumption, smoking, etc.) are also possible contributors to a prematurely interrupted pregnancy, along with the above mentioned causes. The role of the couples previous illnesses, occupations, mutagenic environmental factors (smoking, alcohol, drugs, radiation, chemicals, etc.), diseases in the broader and narrower family are changes that could lead to recurring pregnancy loss.

2. Material and methods

Retrospective analysis of the data of couples who came to genetic counseling at UHC Split in the period from 1985 till 2010. During the interviews with 451 couples from the Genetic Counseling Unit (GCU) we collected data: the place of residence, age, possible existence of the condition before and during the first weeks of unsuccessful pregnancy, previous pregnancies, spontaneous abortion, deaths, occupation, possible exposure to unusual pollutants at work or harmful living habits (alcohol, tobacco, drugs...) hereditary diseases in the wider family and blood relatives. A family pedigree tree was then created.

All data was statistically processed and we secured consent of all participans to use their answers. The basic data refer to:1) reproductive family history - abortion, morbidity, sterility (yes, no); 2) presence of other risk factors (age, partner disease before and during the first weeks of unsuccessful pregnancy, disease in the wider family); 3) harmful habits in men and women; 4) employment; 5) place of residence.

Data analysis was carried out with GraphPad Prism versions 5 and KyPlot version 4. Statistical data processing for comparison of nominal and ordinal data was $\chi 2$ test, with Yates correction. P values equal to or less than 0.05 considered statistically significant. For the statistical analysis of the data obtained, SPSS for Windows (version 17.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excell (version 11. Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis. Unable to implement exact algorithms, the Monte Carlo method for estimating the exact P value was used, with the precision set at 99.9%. The research also used Fisher's exact test.

3. Results

From 1985 till 2010 we included 451 couples with SA, but not the couples with only one SA, deceased children, parents of chromosomaly ill children and sterile couples. The total number of miscarriages recorded in 451 couples was 1043: 343 had 2 SA (total number of abortions 686); 3 abortions 80 (240 abortions); 4 abortions 25 (100 SA); 5 and 6 SA 3 (17 SA). The age distribution among women showed:1.from 28 to 32 years; 148 women (32.82%); 2. 23 to 27 31 women; (29.05%) 47 women. The age distribution of males was:1. 33 to 37 years 150 (33.26%), 2. 28 to 32 140 (31.04%), 3. 18 to 22 years. Comparison of males and females age distribution showed statistically significant difference, since women are significantly more frequent than men in younger age groups. The largest number of SA occurred in the period up to 16 weeks of gestation, 839 (80.44%), and within this group the largest number of SA, 417 (39.98%) in the period between 8 and 10 weeks, while the lowest number of SA between 20 and 22 weeks of gestation. For 123 SA (11.79%) no time data was recorded. There was no statistically significant difference between the age of participans in relation to the number of SA. By comparing the age of men there was a statistically significant difference, since the age of males in couples with 2 SA was from 28 to 32 years, and couples with 3 SA the age of males were in the range of 33 to 37 years.

Data of previous diseases in each individual of a couple, his or her family history, occupations, harmful habits and exposure to pollutants was collected. Among 451 women 90 or 19.95% had no history data available, 102 or 22.62% were healthy and 259 or 57.43% reported data on the existence of various diagnosis in their personal history. Among 451 men 133 or 29.50% had no history of previous illnesses, 142 or 31.49% were healthy and 176 (39.01%) had various diseases in their own history. Some of these women and men had more than one disease. The higher incidence of previous women's diseases was statistically significant compared to males.

The diseases wer grouped among both participants as follows: 1. Infections and anomalies of the urinary and sexual tract. 2. Infections of the respiratory system. 3. Endocrinopathies and autoimmune diseases. 4. SA in a previous marriage or a sterile or infertile marriage. 5. Anemia. 6. Diseases of other organ systems. The highest incidence of occurrence in both women and men had infections and abnormalities of the urogenital system (57.92% and 39.77%, but significantly more frequent in women.

When this group of infections and anomalies of the urogenital system were separated, 104 women

(69.33%) and 46 (65.71%) men had urogenital surgery.

Males and females did not differ significantly in the family history data. The changes were divided into two large groups: changes in reproductive family history and data on other diseases of organ systems. Within reproductive history data were obtained information about: SA, family sterility, stillbirths, infant death syndrome, intellectual disability, Down syndrome, other malformational syndromes and anomalies. Changes have been followed through three generations of relatives, both for women and men. Within the group of diseases of other organ systems data was collected on cardiovascular diseases, malignancies, endocrinopathies and autoimmune diseases. In both groups most participans reported more than one disease among their relatives.

Interviewing 451 women and drawing family trees: for 74 or 16.41% we did not record information, uncompleted in 57 or 12.64%; while 320 or 70.95% participans had data on changes in family history. The family history of men in 104 or 23.06% produced no data, 71 or 15.74% was uncompleted, 276 or 61.20% had data on changes in family history.

Particularly relevant in reproductive history was the occurrence of SA among partners through the I, II and III generation. This data was compared with the incidence of SA in the general population (12-15%). In 38 or 50.67% participans, SA occurred in the 1st generation. Most participans had SA 106 or 46.50% in the second generation, while the least had SA in the III generation, 12 or 30.00%.

The average incidence among participans across all three generations was 42.39%. In the first generation 48.20% (27) SA was observed, 83 (41.29%) in the second generation, and 6 (27.28%) in the III generation. The average incidence of male participans across all three generations was 38.92%. There was no statistically significant difference between males and females SA in different generations, but in both was significantly higher than among the general population.

In the female group 329 (72.94%) reported data on the type of work, while 122 (27.06%) data were not recorded. In the group of male participans 314 (69.62%) reported data on the type of work, while 137 (30.38%) data were not recorded. In the dominant occupation of women 67 or 14,86% and 46 or 10,20% by men were technical and construction activities 84 or 18.63% and hospitality activities 29 or 6.43%.

Within the occupational category, the question is raised whether there is a statistically significant correlation between the type of occupation and number of SA, and the type of occupation and frequency of urogenital infections.

However, neither the women nor the men had a statistically significant difference in the number of SA, depending on the type of occupation (Monte Carlo method) among men nd women. Tables 1 and 2 show the distribution of particular occupations and the pollutants at the workplace.

Table 1: Job of women

Occupation	N(%)
Healthcare Professionals	31 (6,87)
Employees in the hospitality industry	32 (7,10)
Merchants	46 (10,20)
Beauty, hairdressers, pedicurists	14 (3,10)
Clerks	67 (14,86)
Housewives, students, unemployed	30 (6,65)
Teachers	42 (9,31)
Employees in the ministry of the interior afairs, the army, security institutions	4 (0,87)
Textile workers	25 (5,54)
Technical	38 (8,44)
No data	122 (27,06)
Total	451 (100,00)

Table 2: Job men

Occupation	N(%)
Healthcare Professionals	12 (2,66)
Teachers	3 (0,66)
Clerks	26 (5,76)
Employees in the ministry of the interior afairs, the army, security institutions	22 (4,88)
Sailors and fishermen	19 (4,21)
Workers in technical and construction activities	84 (18,63)
Merchants	19 (4,21)
Employees in the hospitality industry	29 (6,43)
Workers	100 (22,18)
No data	137 (30,38)
Total	451 (100,00)

Table 3: Exposure to pollutants

Pollutants	Women(N)	Men (N)
PC	124	75
Food	60	40
Chemicals	53	50
Radiation	3	12
Infections	24	14
Warmth	11	84
Cold	8	84
Dust	26	55

Table 3 shows the exposure of individual pollutants for both participans. The largest number of participans worked on computers. The next category are cooks, waitresses and hospitality workers who were in contact with food.

A great number of women (hairdressers and beauty salon workers) were exposed at work with various chemicals.

Among men, the order of exposure to individual pollutants was different. Statistically the largest number were exposed to heat and cold, while the lowest number were exposed to radiation. They were most often exposed to heat and cold, then to radiation of computers, food and chemicals.

Responses to harmful habits were obtained from 151 subjects (women), of whom 21.28% had one or more harmful habit and 103 (men) 16.86% also.

There was no significant difference in adverse habits between partners. Among adverse habits statistically the most important was smoking and contact with pets in both partners, whereas alcohol was significantly more frequent in men than in women (Table 4).

Table 4: Rare habits of women and men

Harmful Habit	Women (N)	Men(N)
Smoking	57	55
Alcohol	1	15
Drugs	0	2
Pets	41	42

4. Discussion

The maximum probability of conception is only about 40%, 10-15% of clinically recognised pregnancies end in miscarriage (Kavalier F. 2008, Husar D. and Đelmiš J. 2008). This study spanned a twenty-two-year period of treated couples in the GCU for repeated SA. The risk of SA and late fetal death is greater in couples where a man is aged 35-40 compared to couples where a man is up to 35 years old (Bray I. et al 2006), the risk was greater for couples with a woman older than 35 years and a man older than 40 years with a specific comparison of the occurrence of SA in relation to age, where the incidence of SA 8,9% for women aged 20 to 24 and 74.4% for women older than 45 years (Bray I. et al 2006, Nanassy L. and Carrell D.T. 2008, Barclay L. and Nghiem H.T. 2006, De La Rochebrochard E. and Thonneau P. 2002). The highest incidence of occurrence in both women and men was infections and anomalies of the urogenital system. The most common pregnancy infection is uro-infection, and it can be symptomatic and asymptomatic in 7-10% pregnant women. About 20-30% of children are infected by passing through the delivery channel. Then there are sexually transmitted infections that can be spread both hematological and ascendant such as infections caused by Listeria monocytogenes (10%), streptococci of group B and enterococci. Chlamydia trachomatis and mycoplasma are the most common causes of SA, childhood deaths and various infections and are widespread ascendant (Čulić V. 2004, Čulić V. et al 2009, Nigro G. et al 2011, Morrison R.P. 2003, Pollack J.D. 2001). There is a special relationship between host and parasite in the presence of IFN-γ which contributes to the development of permanent infection with chlamydia. Association between oxidative stress, infections of genital tract and fertility, genital tract infections may provoke increased production of free radicals and generate oxidative stress (Morrison R.P. 2003).

Exposure associated with adverse developmental outcomes includes; air and water pollution, food chemicals, occupational exposure, agricultural chemicals, metals, persistent and volatile organic compounds (Mattison D. 2010, Miskovic S et al 2012, Kolte A.M. et al 2011, Pouta A. et al 2005, McDonald A.D. et al 1989, Gardella J.R. and Hill J.A. 2000).

The special value of this study is the fact that there are data on SA of I, II and III generations of close relatives in the family tree. Rare authors who have made a similar analysis Miskovic et al. which included couples, regardless of the number of SA (Pouta A. et al 2005). Similar conclusions were reached by Kolte et al. that brothers and sisters of subjects who had recurrent SA had a higher risk of SA 25.3% compared to 13.1% in the general population in Denmark (McDonald A.D. et al 1989). Unlike these studies, the results of a major study conducted in Finland have not demonstrated the link between abortion rates between mothers and daughters (Pouta A. et al 2005, McDonald A.D. et al 1989).

Men and women also experienced a variety of occupations. Thus, in men-related research, it was found that the incidence of SA was greater in automobile mechanics, while in the women's group it was found that higher incidence was among nurses and women engaged in food and beverage sales, women in horticultural activities, in the production of metal and electrical parts, making clothing, food and beverage production (Gardella J.R. and Hill J.A. 2000, Koren G. 2003, Lindbohm M.L. et al 2007, Lawson C.C. et al 2012, Morales-Suárez-Varela M. et al 2010, Johnson C.Y. et al 2019, Attarchi M.S. et al 2012, Santiago F. et al 2017, Hu X. et al 2018). The individual pollutant in the workplace in this study is as follows: for women computer work and then the food and chemicals. For men, the order was different: they were most often exposed to heat and cold, then to radiation of computers, food and chemicals. Gardella et al. ponted out radiations, infections, drugs, solvents, heavy metals, hypoxia, hyperthermia and so on were teratogens of their interest, and concluded that radiation, ionizing and nonionizing, favored the onset of abortion, similarly to exposure to atmospheric pressure during air travel. Laboratory testing has shown that ultrasound acts teratogenically in the form of neurological, developmental, hematological, genetic and structural anomalies. Electromagnetic radiation, heat, herbicides, pesticides, organic solvents (xylene, toluene) and heavy metals (mercury, lead) increase the incidence of spontaneous abortions (Gardella J.R. and Hill J.A. 2000, Koren G. 2003).

Studying adverse effects in the work of dentists, dental technicians, nurses, lab staff, women employed in the pharmaceutical industry, the only teratogen that was highlighted as the cause of a large number of SA was ethylene oxide, and in a smaller percentage of mercury amalgams. Cytostatic drugs were associated with the occurrence of congenital malformations, but not SA, while the influence of anesthetic gases, nitrogen oxide, glutaraldehyde and formaldehyde could not be associated with the occurrence of SA (Lindbohm M.L. et al 2007, Lawson C.C. et al 2012, Morales-Suárez-Varela M. et al 2010, Johnson C.Y. et al 2019, Attarchi M.S. et al 2012, Santiago F. et al 2017, Hu X. et al 2018, García-Peñarrubia P. et al 2020, Bretveld R.W. et al 2006, de Almeida Chua L.G. et al 2019, Wennborg H. et al 2005, Bjørklund G. et al 2019).

Numerous studies have been linked with the influence of pesticides and herbicides and the influence of pesticides on estrogen and/or androgen receptors. The influence of pesticides can be seen at a number of levels which eventually leads to menstrual disorders, reduced fertility, spontaneous abortion, premature birth, congenital malformations and a reduction in fertility (de Almeida Chua L.G. et al 2019, Wennborg H. et al 2005, Bjørklund G. et al 2019). The study of DNA methylation and environmental exposure is mostly based on epigenetic regulators in relation to environmental exposure, focused on prenatal, early, and adult

life exposures as aflatoxin B1, air pollution, arsenic, bisphenol A, cadmium, chromium, lead, mercury, polycyclic aromatic hydrocarbons, persistent organic pollutants, tobacco smoke and nutritional factors (Martin E.M. and Fry R.C. 2018).
The responses about harmful habits received from 151 participans, of whom 96 had one or more of these habits were smoking and contact with animals were represented in the greatest number. The relative risk of abortion among smokers is 1.1-1.3 (10-20 cigarettes) (Gaskins A.J. et al 2018, Sundermann A.C. et al 2021, Grosso L.M. and Bracken M.B. 200). Caffeine passes through the placenta and enters amniotic fluid and into the umbilical blood vessels. Concentration in the mother's blood may be a concentration indicator in fetal blood. This equilibrium appears in 7 week gestation since neither the fetus nor the placenta can metabolise the caffeine and the fetus is exposed to prolonged intrauterine influence of caffeine.
The placenta can not metabolise caffeine because it contains only CYP1A1 but not CYP1A2, while fetal enzymes are not sufficiently developed to metabolise caffeine. Caffeine raises the level of catecholamines especially epinephrine in the mother's circulation. Caffeine also raises cAMP by inhibiting phosphodiesterase enzyme activity in those women who took more than 162mg /day of caffeine (Sata F. et al 2005).

5. Conclusion

Couples appeared at GCU most often after two SA (occurred between the 8th and 10th week of pregnancy). The age groups of women were usually 23 to 32 years, and in men 28 to 37 years, "motherhood age effect" is not present. Comparing the age of men with SA of their partners showed a statistically significant difference since the age of males in partners who had experienced 2 SA was 28 to 32 years, and in partners who had experienced 3 SA of males was 33 to 37 years. Relatives in the second generation of participans have twice as many SA as those in the general population, reflecting the inheritence in these families.
Men and women also had frequent infections of the urinary and/or genital system, suggesting that changes due to chronic inflammation are equally important when they are present in both sexes. Within the scope of occupation there was no statistically significant difference in the number of SA or depending on the type of occupation, and in the incidence of urogenital infections in both partners. Women were highest at computer work, then exposure to food and chemicals, while in men dominated exposure to heat and cold, then work on computers, food and chemicals.
Among the worst habits at both partners was smoking and contact with pets, with the presence of alcohol more frequently in men than in women. Before the next pregnancy, the pregnant woman has to leave the working environment that is harmful and remove harmful habits from everyday life.

Conflict of interests

The authors have no conflicts of interest to declare.

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