



Factors associated with spontaneous abortion: a systematic review


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Abstract

Objectives: to compile studies produced regarding genetic and non-genetic risks factors associated with occurrence of spontaneous abortion.

Methods: it talks about a systematic review article, with studies between January of 2008 to November of 2018 according to SciELO, PubMed, Lilacs and BVS.

Results: in total, 567 articles were found. After applying the defined eligibility criteria, 44 articles made part of the review, being the majority published on Asia between 2008 and 2011, and 10 articles published on Brazil. Not genetic causes like sociodemographic factors and healthy state were among the most associated conditions of spontaneous abortion. Asiatic continent had predominance about the correlation of spontaneous abortion with factors related to life style like obesity, smoking and labor activities, on the other hand, in the Americas, causes related to sociodemographics factors like low pay and low studies are highlighted.

Conclusions: the risk factors change about the occurrence region, being important to make local studies capable of subsidize the implantation of public politics and to reduce abortions.

Key words *Spontaneous abortion, Risk factors, Reproduction, Systematic review*



Introduction

Spontaneous abortion is the most common gestational adversity and is often of unknown etiology. In most patients, it has a multifactorial cause, which difficult its investigation.¹⁻³ This problem is defined as the involuntary termination of pregnancy, up to 20-22 gestational weeks.⁴ Its recurrent form is characterized by the loss of three or more pregnancies, consecutively.²

Of all diagnosed pregnancies, 15 to 20% end in spontaneous abortion, most within the first 13 weeks of pregnancy.^{4,5} Among the consequences, the emotional and psychological damage to the couples involved stands out, with the risk of death of the pregnant woman as a result of complications, in addition to high costs to the public funds, constituting an important public health problem.⁶

Spontaneous abortion has a multifactorial origin, of genetic and non-genetic causes, which can be interconnected. Among the genetic factors, chromosomal abnormalities and polymorphisms stand out; as non-genetic causes, the presence of infectious agents, socioeconomic, environmental, occupational causes, life history and endocrine and thrombophilic disorders stand out.^{5,7} It is estimated that 25% of spontaneous abortions would be preventable if the risk factors could be mitigated. However, about 50% of abortion cases have unknown causes.^{5,8}

Given the above and the great variety of studies that addressed possible causes and risk factors about spontaneous abortion and, taking into account the variations related to the population and region studied, this study aimed to review the scientific knowledge produced in the last 10 years on the theme.

There are a large number of publications related to risk factors associated with spontaneous abortion. However, due to differences in lifestyle, behavior and environmental circumstances, it is difficult to extrapolate the causes to all women in the world. It was possible to verify that there is a great commitment from the scientific community to investigate the various risk factors involved with this gestational adversity. However, it is necessary to carry out a survey of possible causes in a regionalized manner, so that public policies for investigation and treatment/mitigation of the main risk factors, appropriated to their populations, are implemented in order to contribute to the reduction of spontaneous abortion rates.

Methods

This systematic review was conducted in accordance with the PRISMA recommendation (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Eligibility criteria

a) Types of studies: Articles that involved investigations of factors associated with spontaneous abortion, from January 2008 to November 2018, published in English, Portuguese and Spanish. Original clinical and experimental articles, series and case reports were included; review articles, research with IVF (*in vitro* fertilization) were excluded. The unavailability of the full articles in free version was considered a loss for this review.

b) Types of participants: Patients who presented isolated or recurrent spontaneous abortion. Voluntary abortion studies that included isolated data on spontaneous abortion were included.

c) Types of intervention: The articles that comprise this review deal with the investigation of genetic and non-genetic factors associated with spontaneous abortion at any gestational age, with early or late diagnosis. However, given the nature of the event, there was follow-up (cohort, case-control) without intervention.

d) Types of results: Identification of risk factors that contributed to spontaneous abortion.

Information sources

The search for articles was carried out between October and December 2018, in the databases Scientific Electronic Library Online (SciELO), United States National Library of Medicine (PubMed), *Literatura da América Latina e do Caribe em Ciências da Saúde* (Lilacs – Latin American and Caribbean Literature on Health Sciences) and *Biblioteca Virtual de Saúde* (BVS – Virtual Health Library).

The search strategy used for all databases using uniterms was: “spontaneous abortion” or “miscarriage”. It was also searched for these terms in Portuguese, as “aborto” (abortion) or “aborto espontâneo” (spontaneous abortion), or “aborto espontâneo” and “fatores de risco” (risk factors).

The selection of articles was carried out independently by two authors (Oliveira MTS and Oliveira CNT). Then, the duplication of articles in the databases and reading of the abstracts was performed, excluding those that did not address risk factors for spontaneous abortion. Finally, it was established the reading of the full articles, including only those that

addressed risk factors associated with the development of spontaneous abortion. Doubts were solved by the consensus of the authors.

After reading the articles already mentioned, data from each study included in this review were extracted, using a standardized form available in supplementary material.

Information was extracted from each study on: (1) characteristics of the studies (year of publication, language, geographic location and methodology used); (2) study objectives (genetic and non-genetic risk factors).

Two reviewers worked independently and deter-

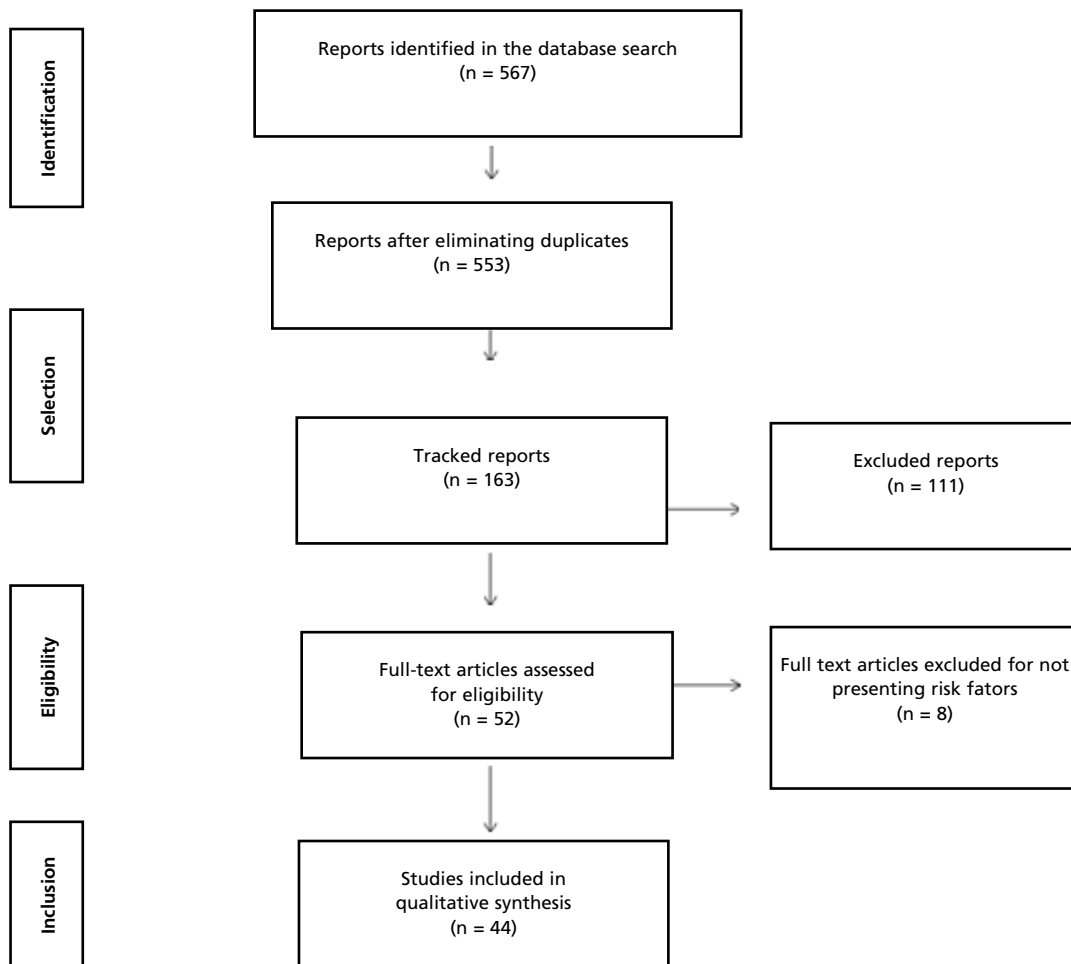
mined the main risks of bias in the studies evaluated, verifying that the selection, survival and Berkson bias were the main ones for case-control studies. For cross-sectional studies, there was a greater risk for instrument, interviewer, detection and memory bias. For cohort studies, there was a greater risk for bias in follow-up and memory loss.

Results

After applying the keywords, 567 articles were found, distributed as follows: 82 in SciELO, 370 in PubMed, 13 in Lilacs, and 102 in the VHL. Articles

Figure 1

Study selection flowchart, Adapted from PRISMA.



present in more than one database were identified and using previously established eligibility criteria, at the end, 44 articles were selected and analyzed for the present review. Figure 1 shows the selection and distribution of articles, according to the databases searched, from the first search to application of all selection criteria.

Most articles were published between 2008 and 2011 (38.6% / n = 17). The remaining, between 2012 to 2015 (34.1% / n = 15) and 2016 to 2018 (27.3% / n = 12). The predominant language of publications was English (75.0% / n = 33), followed by Portuguese (18.2% / n = 8) and Spanish (6.8% / n = 3).

Regarding the distribution of articles in geographical location, South America (31.8% / n=14) and Asia (34.1% / n = 16) were the continents with the highest production on the topic. In Brazil, 22.7% (n = 10) studies dealing with the topic were written.

With regard to the methodologies used in the studies, most of the articles used the case-control strategy (54.5% / n = 24), and with regard to the data source, most were carried out through the collection and analysis of biological material (31.8% / n = 14). The biological samples consisted mostly of peripheral blood, placental tissue and vaginal discharge (Table 1).

On the main objective, 25 articles (56.8%) dealt with non-genetic risk factors and 19 (43.2%) on genetic risk factors. Among the non-genetic causes, the following stand out: sociodemographic factors involving maternal age > 35 years; less education, characterized by women who had up to 8 years of study; multiparity; early menarche; lower family income; and health status (hypertension, heart disease, overweight and obesity) (38.6% / n = 17). In addition, there were infectious factors, which include infection by cytomegalovirus, rubella, toxoplasmosis, bacterial vaginosis (11.3% / n = 5), environmental contaminants (2.3% / n = 1) and hormonal changes, including progesterone, hyperinsulinemia and hyperandrogenesis (4.6% / n = 2). Genetic causes included: gene polymorphisms and, HLA-A * 31, HLA-A * 24, HLA-B * 35, -1154G>, vascular endothelial growth factors (VEGF, SFT-1), cytokines (IL-18, IL-1 β , IL-10), genotypes (MTHFR, Tim 3), chromosomal changes, congenital heart diseases and receptors for vitamin D (VDR). The main characteristics of the articles studied are shown in Table 2.

Table 1

Methodological characteristics of the studies.

	N	%
Study design		
Case-control	24	54.5
Transversal	11	25.0
Cohort (prospective/retrospective)	08	18.2
Descriptive	01	2.3
Data source		
Biological source	14	31.8
Interview/questionnaire and biological sample	11	25.0
Questionnaire/interview	08	18.2
Data base	04	9.1
Medical records	03	6.8
Others	03	6.8
Descriptive	01	2.3
Project type		
Unicentric	37	84.1
Multicentric	07	15.9

Table 2

Characterization of the articles selected for review.

Author / Year	Study design	Factors associated with spontaneous abortion
Baba <i>et al.</i> ^{23/} 2011	Case-control study	Smoking, Work activity and history of spontaneous abortion..
Zhang <i>et al.</i> ^{9/} 2010	Case-control study	History of family abortion, passive smoking, BMI over 24.
Zhou <i>et al.</i> ^{5/} 2016	Cohort study	History of abortion in the mother, age> 35 years, obesity, overweight, underweight, hypertension, irregular menstruation, leukorrhea, IgG for cytomegalovirus.
Madar <i>et al.</i> ^{17/} 2013	Case-control study	High profile of pro-inflammatory cytokines and reduction of alpha-1-antitrypsin.
Silva <i>et al.</i> ^{41/} 2015	Case-control study	The HLA-A * 34 allele is a risk factor for abortion and the HLA-A * 24, HLA-B * 35 alleles are associated with protection against abortion.
Alijotas-Reig <i>et al.</i> ^{18/} 2010	Case-control study	Presence of anti-β-glycoprotein-I antibody.
Al-Khateeb <i>et al.</i> ^{16/} 2011	Case-control study	BMI, menarche and IL-18 reduction
Miskovic <i>et al.</i> ^{15/} 2011	Case-control study	History of family abortion and between 1 st , 2 nd and 3 rd degree relatives
Xu <i>et al.</i> ^{1/} 2014	Case-control study	History of miscarriage, sleeping late and night work
Hure <i>et al.</i> ^{25/} 2012	Prospectivecohort study	Smoking, infertility problems, level of education and physical activity
Ostojic´ <i>et al.</i> ^{44/} 2008	Case-control study	Polymorphism of IGF-2 in female partners
Whitcomb <i>et al.</i> ^{13/} 2008	Case-control study	High maternal age and high levels of thrombopoietin
Parveen <i>et al.</i> ^{37/} 2013	Case-control study	Reductions of some IL-10 haplotypes
Vidyadhari <i>et al.</i> ^{40/} 2015	Case-control study	IL-10 polymorphism
Rodriguez-Guillen <i>et al.</i> ^{28/} 2010	Case-control study	Maternal paid employment and paternal smoking and polymorphism of the MTHFR genotypes.
Rah <i>et al.</i> ^{43/} 2012	Case-control study	KDR-604T / C polymorphism
Lee <i>et al.</i> ^{42/} 2010	Case-control study	Polymorphism of -1154G>
Correia <i>et al.</i> ^{14/} 2018	Cross-sectional study series	Studied for less than eight years, knowledge of the morning-after pill and not having children

continue

Table 2

Characterization of the articles selected for review.

Author / Year	Study design	Factors associated with spontaneous abortion
Mora-Alferez <i>et al.</i> ^{4/} 2016	Descriptivecross-sectional study	Chromosomal alteration, aneuploidies with a predominance of trisomies and increased maternal age
Barbaresco <i>et al.</i> ^{33/} 2014	Cross-sectional study	Positive serology for a cytomegalovirus, rubella and toxoplasmosis
Guimarães <i>et al.</i> ^{26/} 2011	Cross-sectional study	Higher occurrence in contaminated areas, but without significant association
Cecatti <i>et al.</i> ^{12/} 2010	Cross-sectional study	High maternal age, more than 1 child born alive, not from the South, less education and having a stable partner.
Garcia <i>et al.</i> ^{29/} 2009	Case-control study.	Progesterone reduction and low levels of Progestogen
Noguez <i>et al.</i> ^{19/} 2008	Cross-sectional study	Menarche age 11 and 13, presence of three or more children
Morales-Machin <i>et al.</i> ^{3/} 2009	Case-control study.	Polymorphism has not been demonstrated C677T from MTHFR
Li <i>et al.</i> ^{38/} 2017	Case-control study.	Elevation of vitamin D in deciduous
Kiss <i>et al.</i> ^{2/} 2009	Cross-sectional study	Chromosomal abnormalities
Rolnik <i>et al.</i> ^{45/} 2010	Descriptive study	Cytogenetic changes and trisomy of chromosome 16
Pang <i>et al.</i> ^{8/} 2013	Case-control study.	Elevation of VEGF and sFlt-1 in chorionic villus
Zhuang <i>et al.</i> ^{39/} 2018	Case-control study.	Tim-3 elevation
Zhao <i>et al.</i> ^{27/} 2017	Case-control study.	Gestational age, passive smoking, exposure to heavy metals
Matin <i>et al.</i> ^{34/} 2017	Cross-sectional study	Contamination by <i>T. gondii</i>
Rashid <i>et al.</i> ^{11/} 2017	Prospective cohort study	Parity, early pregnancy BMI, gestational age, fetal growth restriction and socioeconomic status
Ruiz-Delgado <i>et al.</i> ^{46/} 2017	Prospective cohort study	Sticky platelet syndrome
Koerten <i>et al.</i> ^{48/} 2016	Cross-sectional study	Heart problems
Bhandari <i>et al.</i> ^{21/} 2015	Retrospectivecohort study	Obesity

continue

Table 2

concluded

Characterization of the articles selected for review..

Author / Year	Study design	Factors associated with spontaneous abortion
Kazerooni <i>et al.</i> ^{47/} 2012	Case-control study	Hyperinsulinemia, hyperandrogenemia, hypofibrinolysis and hyperhomocysteinemia, activated protein C mutations and Leiden factor V
Borsari <i>et al.</i> ^{20/} 2013	Prospective and case-control study	Less education, lower family income and more frequent negative feelings in the suspicion and confirmation of pregnancy.
O'Dwyer <i>et al.</i> ^{22/} 2012	Prospective observational cohort study	Obese primiparous
McElroy <i>et al.</i> ^{24/} 2012	Prospective study	Maternal smoking and rural residence
Rodríguez-Guillén <i>et al.</i> ^{28/} 2010	Case-control study	MTHFR polymorphisms
Seo <i>et al.</i> ^{30/} 2017	Cross-sectional study	Presence of <i>L. amnionii</i> , <i>A. vaginae</i> , <i>S. sanguinegens</i>
Reid <i>et al.</i> ^{32/} 2017	Cohort study	Presence of infection by <i>Clamidia trachomatis</i>
Mengistie <i>et al.</i> ^{31/} 2014	Cross-sectional study	Presence of bacterialvaginosis

Discussion

When analyzing the 44 studies included in this review, it was observed that most of the articles were aimed at identifying factors related to idiopathic or recurrent spontaneous abortion. There are several inherited causes of spontaneous abortion, which include structural and numerical chromosomal abnormalities, mutations and genetic polymorphisms. However, several researchers in the world have also started to investigate non-genetic factors.⁹ In this review, it was found that publications in the last 10 years addressed genetic and non-genetic factors in an equivalent way (43.2% and 56.8%, respectively). However, some articles that addressed genetic characteristics also addressed non-genetic factors associated with spontaneous abortion, highlighting the need to investigate what other causes could play an important role in this obstetric complication.

Regarding the methodology used in the studies, most of them used case-control, which is effective to investigate causality or risk factors. It is important to note that most studies presented well-established criteria in the control group, in which women could not have a history of spontaneous abortion and have at least one child born alive and, in the case group, they should have a history of more than one abortion. It was also possible to verify that the works always presented comparison of results in relation to other studies. However, some emphasized that risk factors should not be extrapolated to other countries or nationalities due to differences in lifestyle and environmental circumstances.¹ This review brings approaches in different countries on the main continents of the world regarding genetic and non-genetic causes.

Among the main factors associated with spontaneous abortion of non-genetic causes, it is noteworthy that, in Asia, there was a predominance of factors related to lifestyle such as obesity, smoking and work activities; in the Americas, the causes related to sociodemographic factors such as low income and low education are highlighted.

Regarding non-genetic risk factors for spontaneous abortion, the following stood out in this survey: sociodemographic factors (maternal age, age at menarche, education and income), health status (BMI, obesity), lifestyle (smoking), gestational history (previous abortion, family abortion), excessive work activity, infectious factors (contamination by cytomegalovirus, rubella, toxoplasma and bacterial vaginosis) and hormonal factors (alteration of progesterone, hyperinsulinemia and hyperandrogenesis).

High maternal age, above 35 years, was considered a risk factor for spontaneous abortion and fetal malformations due to the senility of the eggs cells that are more subject to chromosomal changes, in case of fertilization.¹⁰ A 5-year increase in maternal age increases the risk of miscarriage 1.5 times.^{5,11,12,13} However, some studies have noticed a contrary association.^{1,14-18} One explanation for this divergence lies in the fact that the studies that associated the maternal age above 35 years of age with abortion were performed in developed countries, where women are likely to become pregnant at an older age; and studies that address maternal age below 35 as a risk factor have been carried out in developing countries, where women become pregnant earlier, increasing the likelihood of miscarriage. Early menarche was another important factor associated with spontaneous abortion, as it accelerates puberty and the occurrence of pregnancy at younger ages, when the woman's body is not yet fully mature.^{14,19}

In this review, less education (women who had up to 8 years of study) was an important risk factor for the occurrence of spontaneous abortion. Misinformation leads to a delay in prenatal care, which hinders the identification of gestational changes early, making it difficult to carry out preventive and therapeutic actions in time to prevent abortion.^{12,14} It is noteworthy that these studies were carried out in Brazil. Due to its continental dimension, these data may vary in relation to the regional context, and the lower access to health information and services is also related to the low income of women.^{11,20,21}

Regarding the risk factors for spontaneous abortion related to health status, there is an increase in body weight, characterized by overweight and obesity. This association can be explained by the various endocrine and metabolic changes, such as altered secretion and ineffective action of insulin, leptin, resistin, ghrelin, in addition to changes in the metabolism of steroids that can lead to spontaneous abortion.^{5,9,11,16,21,22} In contrast, this association has not been found in other studies,^{9,18,20} which noticed increased fertility in obese women. However, the chance of miscarriage in these women was also greater than in eutrophic women. This finding demonstrates that metabolic disorders caused by obesity can alter the woman's body and affect fetal development, leading to an abortion.

Among the risk factors associated with lifestyle, maternal smoking provides an additive effect in the development of spontaneous abortion, due to calcification and placental insufficiency with fetal hypoxia

due to deprivation of blood flow. In addition, it also triggers placenta praevia, premature placental displacement and, also, crosses the transplacental barrier, causing problems to the fetus as restriction of fetal growth.²³⁻²⁶ As in other cases, this relationship has not been identified in other studies.^{9,16,18} Spontaneous abortion was also associated with passive smoking in Japanese young women,^{9,23,27} with an increase of 11.5% in women aged 20 to 29 and 5.8% in women aged 30 to 39, constituting an emerging public health problem in Japan for women of reproductive age.

The previous history of spontaneous abortion is also reported as an important risk factor. This association indicates that the etiology of spontaneous abortion may be genetic, being one of the explanations for recurrent spontaneous abortion.^{1,5,9,15,18,23}

Maternal working hours, characterized by night work and long hours, were also found to be a risk factor for miscarriage in Japanese,²³ Chinese¹ and Mexican women.²⁸ Work stress in women who have full-time work is associated to menstrual disorders, thereby interfering with reproductive health, which may increase the risk of spontaneous abortion.²³

The reduction of progesterone in women has also been shown to be associated with the threat of abortion or actual abortion, being an important hormone in the formation of the corpus luteum at the beginning of pregnancy, which can trigger bleeding and abortion.²⁹

Regarding infectious factors, an association was found between spontaneous abortion and the vaginal microbiota, with the presence of microorganisms that cause bacterial vaginosis, but further studies are needed to verify this relationship.^{30,31} A study carried out in England investigated the prevalence of *Chlamydia* in pregnant women, but no association with spontaneous abortion was observed.³² A positive relationship was also identified between *Toxoplasma gondii* and spontaneous abortion.^{33,34} These studies also demonstrate that the seropositivity of an infectious agent that causes toxoplasmosis, rubella and cytomegalovirus, can cause spontaneous abortion. The performance of laboratory tests, which demonstrate previous infection with cytomegalovirus before pregnancy, was also associated with an increased risk for spontaneous abortion.⁵

In Brazil, the Ministry of Health (MS) recommends the gynecological exam with specular examination and collection for cytopathological examination right at the first prenatal consultation, and serology for syphilis, HIV, IgG and IgM toxoplasmosis, Hepatitis B, urine and urine culture. The

Brazilian Federation of Gynecology and Obstetrics (FEBRASGO – Portuguese acronym) recommends, in addition to the tests already mentioned, the performance of serologies for Hepatitis C, Rubella and research of *Chlamydia trachomatis*. These findings have an important impact on the outcome of pregnancy, and confirm the need for early diagnosis of pregnancy and tests within the recommended deadlines, so that it can establish treatment in a timely manner and reduce the chances of spontaneous abortion, in addition to incorporating preconception counseling actions and screening of the high-risk population.^{35,36}

In addition to research on microorganisms that may be associated with spontaneous abortion, it is worth noting that some studies have also identified increases in the concentrations of cytokines such as IL-1, IL-18 and IL-10. During the egg cell implantation period, invasion of blastocysts and angiogenesis is necessary. This process is mediated by the early exposure of the pro-inflammatory cytokines of the TH1 profile. However, if this exposure remains for a longer period, it can be severely harmful and cause spontaneous abortion.³⁷ The studies analyzed identified changes in pro-inflammatory cytokines such as IL-1 β , IL-18^{13,16,17,38,39} and IL-10, which can have an anti-inflammatory or pro-inflammatory effect.^{37,40} Another contribution of the immune system in spontaneous abortion is referred to as a response, in which Human Leukocyte Antigens (HLA) stimulate the maternal immune system against the presence of the fetus.⁴¹

Regarding genetic changes, the polymorphisms of the vascular endothelial growth factor - VEGF stand out (this being an important factor in the regulation of fetal and placental angiogenesis),^{8,42} VEGF⁴³ receptor polymorphism and growth factor polymorphism similar to insulin-2 - IGF-2 (main fetal-placental growth factor that stimulates trophoblast invasion and growth).⁴⁴

Chromosomal abnormalities represent one of the main causes of pregnancy loss, requiring a karyotype analysis in couples. These changes were found in 9.3% of the cases with predominance of mosaicism,² 68.8% with predominance of autosomal trisomy,⁴ and 55.4% with predominance of trisomy of chromosome 16.⁴⁵

Venous and cardiovascular disorders can be associated with spontaneous abortion. An association of thrombophilia and spontaneous abortion was observed,^{46,47} which may trigger uterine-placental venous thrombosis, characterizing a possible etiology for spontaneous abortion. A study conducted in three countries (Japan, Hungary and

Germany) showed that women with congenital heart disease are at increased risk of developing miscarriage compared to healthy women.⁴⁸

As can be seen, the etiology of spontaneous abortion is quite heterogeneous and 50% have no identified causes. Among the genetic factors addressed in this review, were associated with spontaneous abortion: cytokine imbalance, allele polymorphisms, vascular endothelial growth factors, genotypes, chromosomal changes, congenital heart disease and vitamin D receptors. And among the non-genetic risk factors, sociodemographic factors such as age, education, endocrine and infectious factors stand out.

Authors' contribution

Oliveira MT and Oliveira CN contributed in a similar way in the research and writing of the manuscript. Marques LM and Souza CL contributed to the methodological design and review of the final version. Oliveira MV contributed in all stages of the manuscript's conception. All authors approved the final version of article.

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