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Infertility and Inherited Thrombophilia

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1. Introduction

Infertility is a condition that affects between one-fifth and one-sixth of couples of reproductive age. It is defined as a reduction in or a lack of ability to reproduce and its cause may lie either in the male or female partner (Stedman, 2006). According to the American Society for Reproductive Medicine, infertility should be considered when pregnancy fails to occur after one year of regular sexual activity without the use of any contraceptive method.

In view of its high incidence, infertility currently constitutes a significant health issue. The social structure prevalent today in which women are conditioned to consider motherhood at a later age results in an increase in the number of couples seeking medical assistance to fulfill their dream of having children (Neuspiller, 2003). Nevertheless, the forms of treatment available today within the realm of assisted reproduction result in a pregnancy rate of approximately 40%, an unsatisfactory percentage, since it means that the majority of couples are still denied the opportunity to conceive (Qublan, 2006; Vaquero et al., 2006). In 30% of the couples currently undergoing treatment for infertility, the factors preventing them from becoming pregnant have yet to be identified (Grandone, 2005).

The majority of the studies conducted to evaluate failure to conceive in assisted reproduction have focused on the problems that occur following laboratory fertilization, i.e. implantation of the embryo in the woman's uterus (Vaquero et al., 2006). Various studies have concentrated on improving factors associated with the embryo, such as the quality and quantity of embryos, and on female factors. Some that need to be taken into consideration include improving endometrial receptivity and identifying intervening factors associated with immunological response and the genetic characteristics of the woman, including her potential for coagulation during pregnancy and implantation of the embryo (Glueck, 2000).

Because of the success rate of 34%, the assisted reproduction clinics try to improve the pregnancy rate by transferring more than one embryo. This procedure has as a consequence, another problem of great significance and social impact, which is the multiple pregnancy (Haggarty, 2006).

Recently, a hypothesis has been raised that the same factors associated with the occurrence of recurrent pregnancy loss may also affect the early phase of the embryo implantation process (Vaquero et al., 2006). The possible causes for a failure in embryo implantation have been widely investigated; however, there is no consensus in the literature on this subject.

The qualities of the embryo and endometrial receptivity are believed to represent significant factors in the failure of in vitro fertilization (IVF) (Simur et al, 2009). The hematological changes that lead to hypercoagulability, with a consequent increase in the occurrence of thrombosis, have been cited as factors that hamper the process of embryo implantation (Grandone, 2001; Sarto, 2001; Vaquero et al., 2006). Hence, thrombophilia should be considered an adverse factor in cases of embryo implantation failure.

Thrombophilia may be congenital or acquired and is related to changes in hemostatic mechanisms, characterized by an increased tendency for the blood to clot and a consequent risk of thromboembolism (Machac at el., 2006). Congenital factors suspected of being responsible for this propensity for thrombosis are: protein C deficiency, protein S deficiency, antithrombin III deficiency, the presence of factor V Leiden, a mutation in the 20210^{A} allele of the prothrombin gene and a mutation in the methylenetetrahydrofolate reductase (MTHFR) enzyme gene (D'Amico, 2006).

The hereditary causes of thrombophilia have been investigated since 1956, when Jordan and Nandorff introduced the term thrombophilia. In 1965, it had been identified the antithrombin deficiency as a cause of genetic thrombophilia.These studies have become wider in 80 years, when the deficiencies of proteins C and S were described and, later, in 1994, description of factor V Leiden. (Reitsma, 2007). About 40% of thrombosis cases with arterial or venous occlusion are hereditary. Venous thromboembolism often occurs as a result of mixed factors. In general, thrombophilia should be considered a multifactorial disorder and not as an expression of a single genetic abnormality (Buchholz, 2003).

The relationship between thrombophilic factors and infertility should be taken into consideration because of the possibility of alterations in hemostasis of a thrombophilic nature at the implantation site. This vascular change affects trophoblast invasion and placental vasculature, hampering implantation of the embryo (Sarto, 2001).

We performed a review of the pertinent literature to evaluate whether any relationship exists between thrombophilia and the presence of infertility.

A literature review was performed for the 1996-2010 period using the Medline and Lilacs databases on the following websites: www.bireme.br and www.pubmed.com. The key words used to search for relevant papers were: thrombophilia, infertility, blood coagulation, embryo implantation failure and hyperstimulation syndrome.

2. Thrombophilia and infertility

Compared to fertile women, a finding of a higher incidence of thrombophilia in women submitted to repeat cycles of in vitro fertilization (IVF) and implantation failure has become increasingly common. Azem et al. conducted a case-control study including 45 women with implantation failure, 44 fertile women and 15 infertile women who had, however, become pregnant at their first IVF attempt. The women evaluated were submitted to tests to investigate the following thrombophilic factors: prothrombin gene mutation, MTHFR gene mutation, the presence of factor V Leiden, and antithrombin, protein C and protein S deficiency. A high frequency of thrombophilia was found in the subgroup of women with implantation failure (17.8%) compared to the group of fertile women and the group of women who became pregnant at the first IVF attempt (a frequency of 8.9% in both groups). This fact reinforces the association of this pathology with vascular impairment and a consequent difficulty in embryo implantation (Azem, 2004).

Grandone et al. also reported similar results in a case-control study involving a smaller sample of women (18 women with implantation failure and 216 fertile controls) (Grandone, 2001). The results of the two abovementioned studies, although indicative of a possible association between thrombophilia and failed implantation, do not positively confirm this association.

On the other hand, Martinelli et al. conducted a case-control study with the largest sample size evaluated up to the present time and found no evidence of a higher frequency of thrombophilia in infertile women. A total of 234 infertile women were compared with 234 fertile women. The women with implantation failure were not, however, evaluated as a separate group. Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody), factor V Leiden mutation, prothrombin mutation and MTHFR mutation were evaluated. No evidence was found of any association between the thrombophilic factors and infertility (Martinelli, 2003).

Vaquero et al. evaluated 59 women with implantation failure and 20 fertile women in a case-control study and failed to find a higher occurrence of congenital thrombophilia in the infertile population. Nevertheless, a higher rate of acquired thrombophilia and thyroid antibodies was found in the infertile population (Vaquero et al., 2006).

In a prospective study conducted by Bellver et al., 119 women were evaluated. Thirty-two Caucasian women included in the control group were egg donors with no endocrine or autoimmune disorders, with normal karyotype and no history of obstetric pathology. A second group consisted of 31 women with infertility of no apparent cause, while a third group was composed of 26 women with implantation failure and a fourth group consisted of 30 women who had a history of recurrent pregnancy loss. The group of women with implantation failure and the recurrent pregnancy loss group had been diagnosed as normal prior to implantation. The following factors were investigated in these four groups: protein C, protein S, antithrombin III, lupus anticoagulant, activated protein C resistance, IgG and IgM anticardiolipin antibodies, homocysteine, factor V Leiden, prothrombin mutation, MTHFR mutation, thyroid-stimulating hormone (TSH), free thyroxine, antithyroid peroxidase antibody and antithyroglobulin antibody. In the group of women with implantation failure, a higher prevalence was found of activated protein C resistance and lupus anticoagulant, as well as the presence of more than one thrombophilic factor. Thyroid autoimmunity was more common in the group of women with implantation failure and in the group with infertility of no apparent cause (Bellver et al., 2008). The authors suggest an association between thrombophilia and implantation failure, but do not recommend screening for all infertile women. Moreover, they raise the hypothesis of an association between thyroid autoimmunity and infertility of no apparent cause and embryo implantation failure (Bellver et al., 2008).

In 2009, a Turkish group published the findings of a study in which the relationship between thrombophilia and implantation failure was evaluated. This was a case-control study comparing a group of 51 women with implantation failure and a group of 50 fertile women. Three hereditary thrombophilic factors were evaluated: the presence of factor V Leiden, MTHFR mutation and prothrombin mutation. No statistically significant difference was found in the frequency of thrombophilic factors between the groups evaluated. Nevertheless, a finding of at least one thrombophilic factor (62.7%) was more common in the group of women with implantation failure compared to the control group (53.9%). Although this difference was not statistically significant, the authors suggest that the difference may become significant if the sample population were larger (Simur et al., 2009).

In 2010, Casadei et al. published a case-control study that included a total of 300 women, 100 with infertility of no apparent cause and 200 fertile women. The following hereditary factors were investigated: factor V Leiden (G1691A), prothrombin gene mutation (G20210A) and MTHFR enzyme mutation (C677T). This study found no difference in the frequencies of thrombophilic factors between the two populations evaluated (Casadei, 2010).
Also in 2010, Sharif et al. conducted a prospective cohort study and analyzed 273 cases of implantation failure (two or more transfer of good quality embryos without the occurrence of pregnancy). In this group, serial ultrasound examinations, hysteroscopy and research of hereditary and acquired thrombophilias were performed. One hundred and twelve patients had abnormal tests and 84 out of these women had tested positive for thrombophilia (63 hereditary thrombophilia and 21 acquired thrombophilias). This study confirms the importance of microthrombosis deployment in the implantation site as a factor that prevents the trophoblastic invasion and subsequent embryo implantation (Sharif, 2010).
A study was recently published on the prevalence of thrombophilia in a fertile and infertile female population in Brazil. This study found a high frequency of thrombophilia among infertile women. Although this was a prevalence study, i.e. no comparison was made between the two groups, thrombophilia was more common in the group of infertile women. Women with implantation failure were not evaluated as a separate group (Soligo, 2007).
The association between thrombophilia and infertility remains controversial; however, studies have tended to associate this coagulation disorder with implantation failure. In 2008, Qublan conducted a case-control study to evaluate the use of low-molecular-weight heparin for the treatment of embryo implantation failure in view of the association between thrombophilia and implantation failure. Although the exact mechanism behind implantation failure and infertility remains to be fully clarified, this study suggests that maternal blood vascularization with adequate syncytiotrophoblast invasion may be affected by microthrombosis at the implantation site. Furthermore, thrombophilia may also affect the various trophoblast functions including invasion, differentiation, proliferation and hormone function with consequent implantation failure (Qublan, 2008).
The table below shows a summary of the results of the studies evaluated:

Author/ year	Fertile women (n)	Infertile women (n)	Implantation failure (n)
Grandone, 2001	**(-) 216**		**(+) 18**
Martinelli, 2003	**(-) 234**	**(-) 234**	
Azem, 2004	**(-) 44**	**(-) 15**	**(+) 45**
Vaquero et al., 2006	**(-) 20**		**(+) 59**
Bellver, 2008	**(-) 32**	**(-) 31**	**(+) 26**
Simur, 2009	**(-) 50**		**(+) 51**
Casadei, 2010	**(-) 200**	**(-) 100**	

Legend:(+) A higher frequency of thrombophilia was found.
(-) A higher frequency of thrombophilia was not found.

Table 1. Thrombophilia in Fertile and Infertile Women

Combining the published data in the afore mentioned studies, there was no increased risk of thrombophilia between the groups of fertile women, infertile and implantation failure. The studies did not show statistical difference between the groups studied and highlight the limit of the sample for statistical evidence in cases of thrombophilia. There is also evidence that the normal MTHFR genotype is related to the ability to produce good quality embryos. This is a result of a prospective study to evaluate vitamin B12, folate and MTHFR gene mutation and their influence on the success of IVF programs (Haggarty, 2006).

The ovarian hyperstimulation syndrome (OHS) is a complication of ovulation induction in assisted reproduction treatment. It is estimated that 0.5% of women undergoing ovulation induction have OHS (Saul, 2009). This iatrogenic condition is characterized by an extensive clinical and laboratory manifestation, including an increase of ovarian volume, fluid into the extravascular space, intravascular volume depletion, rapid weight gain, hemoconcentration, leukocytosis, oliguria and electrolyte disturbance (Rongolino, 2003). It may also occur ovarian torsion, ascites, hydrothorax, liver dysfunction, thromboembolism, and renal failure. Despite technological advances there is still no effective strategy to eliminate this complication in cases of medical treatment of assisted reproduction. It is estimated, at present, different strategies of ovarian stimulation protocols for patients considered at risk. These patients considered at risk include young women suffering from polycystic ovaries, with or without hormonal abnormalities associated with the sonographic findings, previous history of high ovarian response to hormonal induction (Engmanan, 2008)

The exact origin of OHSS is unknown, but is related to arteriolar vasodilation and increased capillary permeability triggered by vasoactive substances. Factors belonging to the renin-angiotensin system, including cytokines, interleukins (IL-8 and IL-9), tumor necrosis factor-α, endothelin 1, vascular endothelial growth factor (VEGF) leading to increased vascular permeability. Currently, it is believed that increased platelet activation is related with the elevation of VEGF (Varnagy, 2008). Because the presence of hypercoagulable changes observed in the OHS has attracted the interest of evaluating a possible association of thrombophilic factors to the occurrence of OHSS (Dulitzky, 2002).

In 2002, Dulitzky et al. performed a prospective study to evaluate the presence of thrombophilic factors in women hospitalized due to severe OHS. It was conducted a case-control study, where twenty women hospitalized due to OHS were selected and forty-one women who underwent ovulation induction and did not develop OHS. The following thrombophilic factors were evaluated: antithrombin, protein C, protein S, antiphospholipid antibodies, mutation of Factor V and MTHFR gene mutation. Among the women studied, 85% of the women with OHS and 26.8% of non-OHS women had one or more associated thrombophilic factor. This study demonstrates the positive association between thrombophilia and OHS, as well as suggests a screening for thrombophilia in patients at risk for OHS (Dulitzky, 2002). However, Machaca et al., despite a higher prevalence of FVL mutation in the infertile population, did not find a higher incidence of OHSS in this group of women (Machac et al., 2006).

Fabregues et al, in 2004, conducted a case-control study to assess the frequency of thrombophilic factors in women with OHS and to assess the cost benefit of performing a screening for Factor V Leiden and prothrombin mutation in women who were undergoing IVF treatment. They studied three groups of women. In the first group twenty women with OHS were included. In group 2, with forty women, were included women undergoing IVF, but who did not develop OHS. In group 3, one hundred healthy women were included. All

women were investigated for the following thrombophilic factors: Factor V Leiden, prothrombin gene mutation, antithrombin, protein C and S, lupus anticoagulant and anticardiolipin antibody. In this study, was not evidenced a higher frequency of thrombophilic factors in women with OHS, even were no differences between groups of fertile and infertile women. (Fabregues et al., 2004).

However, as the thrombophylic factors are of rare occurrence, the evaluation of such a small sample of patients, as in the above studies, may not be sufficient to establish the association between the proposed data.

3. Conclusion

Thrombophilia is rare, hence difficult to evaluate in the population. Consequently, to establish a precise correlation between this event and infertility, a study with a very large sample size would have to be conducted, rendering such an endeavor costly and difficult.

The studies available in the literature were conducted in small samples, a fact that may compromise the validity of the results obtained.

This literature review and the consequent analysis of the above mentioned studies tend to suggest that thrombophilia is indeed more common in infertile women, particularly in the subgroup with embryo implantation failure. Nevertheless, data in the literature up to the present moment remain controversial.

The importance of angiogenesis in embryo implantation must be taken into consideration, since thrombophilia may lead to the occurrence of microthrombosis at the implantation site. Therefore, screening for thrombophilia in infertile women, particularly in those with implantation failure, is pertinent.

Infertile women, who have tested positive for thrombophilia and who achieve their objective of becoming pregnant, merit particular attention during prenatal care. Obstetric care must be rigorous, since thrombophilia is known to be associated with an increased risk of complications during pregnancy such as preeclampsia, intrauterine growth restriction, placental abruption, premature delivery, recurrent pregnancy loss and chronic fetal distress in addition to ischemic events during pregnancy (Kuperfenic, 2000; Brenner, 2003; Couto, 2005; Ren, 2006).

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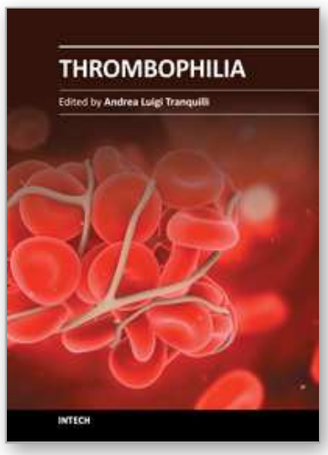

Thrombophilia

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Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologysts became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

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