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REVIEW

The effect of coagulation factors polymorphisms on abortion

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OBJECTIVE: Recent studies showed coagulation factors play important role in controlling pregnancy duration in addition to controlling homeostasis. Recent studies showed several polymorphisms of coagulation factors genes increase the clot formation and lead to abortion. In this study, we evaluated the polymorphisms of coagulation factors and their effects on the development of the fetus.
MATERIAL and METHODS: Relevant literature was identified by a PubMed search (1988-2017) of English language papers using the terms Abortion, pregnancy woman, coagulation factor and polymorphism.
RESULT: Several polymorphisms of coagulation factors disturb the exchange of food and other materials between the fetus and the mother, and impairs the formation of the placenta during embryonic stages.
DISCUSSION: Evaluation of functional polymorphisms in coagulation factors gene during fetal development can be used as a prognostic factor in the prevention of the abortion.

Keywords polymorphism, thrombosis, abortion, prognosis

Introduction

Miscarriage is the termination of the pregnancy before the 20th week of the pregnancy and it is the most common event in the first and the second trimester of the pregnancy. The women who experience the Miscarriage more than two times recurrently and before the 20th week are supposed to be Recurrent Pregnancy Loss (RPL) (Chodirker and Dawson, 2011; Wolski et al., 2017). According to American society for reproductive medicine (ASRM) recurrent abortion definition is losing pregnancy two or more times and emphasized to consider the reasons of the abortion in these cases and recommended the scrutiny of the reasons after three times abortion (Tulandi and Al-Fozan, 2011; Egerup et al., 2016). Recurrent abortion divided to two types of primary and secondary abortion, in the primary abortion several consecutive abortions occur so that no live birth occurs but in secondary abortion consecutive abortions occur after a successful pregnancy (Tulandi and Al-Fozan, 2011; Medicine, 2013). In recurrent abortion as a multifactorial disease, multiple factors from several categories can be involved in abortion. Approximately 50% of recurrent abortions occur as a result of anatomical, immunological, genetic, endocrine, thrombophilic and environmental factors however 50% of RPL have no specific etiologic agent and their reasons are uncertain (Wang et al., 2017). Polymorphism might be responsible for several immune diseases relate to platelet count such as Immune thrombocytopenic purpura (ITP) (Rezaeeyan et al., 2017), Genetic complications especially thrombophilic factors, can be considered as one of the reasons of RPL. Hence up to 50% of the RPL cases occur with an undetermined cause associated with thrombophilic disorders so the analysis of genes polymorphisms which are effective in thrombophilia should be studied in several aspects (Franssen et al., 2005; Avila-Vergara et al., 2018). The processes of clot formation in pregnant women increases in compared to pre-pregnancy duration (Antza et al., 2017). However several polymorphisms of coagulation and fibrinolysis genes can lead to functional impairment of their protein and leads to clot formation or bleeding (Pereza et al., 2017). Additionally the most important relationship between mother and fetus is placenta. Several polymorphisms of coagulation factors disrupt the formation of the placenta. As a result, the fetus

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is not able to receive the food and other materials which lead to abortion (Coolman et al., 2006). Women with thrombotic event rise higher risk of pregnancy complications in compare with normal cases and treatment with aspirin and low molecular weight heparin (LMWH) which is associated with improved outcomes for women with previous miscarriage or early delivery as a result of placental dysfunction (Mowla et al.,). In these women, disorders can increase the incidence of venous or arterial thrombosis. The association of these changes with abortion is based on hypothetical and proven changes on the growth and development of the placenta. Abnormal vessels and inappropriate thrombus in the placenta describe the association of this thrombophilic condition with abortion although it might be acquired thrombophilic conditions but most often occurs as a result of hereditary condition (Middeldorp, 2007). Several polymorphisms of coagulation factors such as Factor V leiden, prothrombin, and antithrombin III, as well as deficiency of the function of proteins c and s, can lead to RPL (Aarabi et al., 2011). Homeostasis disorders can be inherited or acquired. The reason of hereditary homeostasis disorders is a mutation in anticoagulant genes such as antithrombin III, S and C proteins, or mutation in coagulation factors genes such as prothrombin (Pickering et al., 2001; Abbate et al., 2002). In addition to genetic problems mentioned above mutations of other genes, such as the plasminogen activator inhibitor-1 (PAI-1), FXIII, and angiotancine converting enzyme (ACE), have been considered recently (Aarabi et al., 2011). It seems that mutations in these genes can cause spontaneous abortion through affecting thrombophilic pathway (Glueck et al., 2004; Kotze et al., 2005). Genetic studies on spontaneous abortions have reported the association between gene mutations including mitotic arrest deficient 2 (Mad2), Methylene tetrahydrofolate reductase (MTHFR) and budding uninhibited by benzimidazoles (Bub1) with the spontaneous abortions (Shi et al., 2010; Kim et al., 2011). The aim of this review is to review the relevant studies to find polymorphisms affecting the abortion in order to obtain sufficient information for nursing and midwifery counseling so diagnosis of these polymorphisms is a useful step in decreasing spontaneous abortions associated with several polymorphisms (Table 1).

Factor V leiden

In G1691A point mutation in the Factor V Leiden gene the arginine amino acid replace with glutamine in the 506 position. The mutation in Factor V leiden gene is a single nucleotide polymorphism (SNP) located at exon 10 and eliminates a fracture site in the coagulation factor V, and ultimately, by affecting the function of the thrombinase complex develops the resistance of Factor V leidento the activated protein C (APC) (Castoldi et al., 2000). This mutation causes the overproduction of thrombin and resulting in increased fibrin production and blood coagulation in which case the blood coagulation respectively in the veins and this process leads to the occurrence of Deep Vein Thrombosis (DVT) and pulmonary embolism (PE) (MacCallum et al., 2014). In pregnant women, the occurrence of DVT can lead to abortion (Simcox et al., 2015). Although it has been determined that women who are carrying mutation in Factor V Leiden (G1691A) the titer of the autoantibody anti-phospholipid increase in their serum so the incidence of thrombosis and implantation of the uterus increase in the fetus (Mtiraoui et al., 2004). Factor V Leiden plays a role in implantation of the uterus in the fetus, a mutation in it leads to abortion so the in vitro fertilization (IVF) fails in patients with G1691A mutation as a result of lack of exposure of the fetus in the womb (Qublan et al., 2006). Therefore, increasing in the titer of autoantibody anti-phospholipid in women can be associated with an increased risk of abortion and poor prognosis. A study on patients carrying G20210A mutation in the prothrombin factor gene investigated they were twice as likely to develop the risk of spontaneous abortion in compare with the control group (Karatas et al., 2014) .Also, women with G20210A heterozygote develop the risk of abortion before 13 weeks (Karatas et al., 2014). In other hand G1691A mutation in Factor V Leiden and G20210A mutation in prothrombin increase the risk of abortion in the first trimester of the pregnancy (López-Jiménez et al., 2016). Gluc et al. reported that patients with the history of spontaneous abortions have higher frequency of Leiden's allele and it was approximately 11.1% in compare to control group. Factor V leiden polymorphism increases the risk of abortion three

Table 1 summary of coagulation factor polymorphism in abortion

Gene	Polymorphism	Mechanism	Prognosis	Ref.
Thrombin (factor II)	20210 G > A 20209C-T	Lead to increase level of thrombin	Unfavorable	Prat et al., 2014; Djurovic et al., 2017
TAFI	TAFI 1040C/T	Prevent of fibrinolysis	Unfavorable	Masini et al., 2009; ElDanasori et al., 2017
	+ 505G/G	Prevent of fibrinolysis	Unfavorable	
	+ 505A/A	Reduce level of TAFI	Favorable	
VII	Arg353Gln −122T > C	Lead to reduce level and activity of VII factor	Favorable	Barlik et al., 2016
ANXA5	−302T > G	Increases of coagulation generation	Unfavorable	Hayashi et al., 2013
TFPI	T-287C	Downregulates coagulation by inhibiting tissue factor-factor VIIa complex	Favorable	Guerra-Shinohara et al., 2012
a-fibrinogen	Thr312Ala	By hemorrhage, placental abruption, and thrombosis	Unfavorable	Kamimoto et al., 2017

times in compare to the normal population (Glueck et al., 2004). Several SNPs of Factor V leiden such as A4070G, Arg306Gly and Arg306Thr are involved in the RPL.

If Factor V leidenpolymorphisms are accompanied by other polymorphisms of other coagulation factors, the risk of developing RPL will increase. Therefore, Factor V leidencan be one of the main causes of abortion due to fibrinolysis and congestion disorders.

MTHFR

The health of the fetus directly associates with the maternal blood circulation. Any factor that disrupts the maternal blood circulation is harmful to the fetus (James, 2009).The formation of thrombosis in the venous of the placenta can disturb exchange of the nutrition between the mother and the fetus and eventually lead to abortion (Kupferminc, 2003). SNP in genes that encodes regulator enzymes of important metabolic pathways such as MTHFR are considered to be a considerable reason of the thrombophilia (Barlik et al., 2009). The MTHFR enzyme plays a central role in the metabolism of folate, methionine and homocysteinePlasma homocysteine is a toxic amino acid. Increasing homocysteine due to its negative pathological effects on vascular endothelium and the activity of coagulation factors such as VIII and V can lead to increased thrombin levels, platelet aggregation and finally leads to venous thrombosis (Barlik et al., 2009). The catalytic enzyme encoding gene MTHFR has 11 exons and is located at the end of the short arm of chromosome 1 (Van der Put et al., 1997).The two polymorphisms A1298C and C677T of this gene clearly alter the MTHFR enzyme activity. The result of a point mutation in nucleotide 677 in exon No. 4 of the MTHFR gene is the conversion of cytosine to thymine, which results in the replacement of valine instead of alanin in amino acid 222 in the sequence of the MTHFR enzyme. This point mutation forms an unstable and heat-sensitive MTHFR enzyme with low activity (Bailey and Gregory, 1999). However, it has been shown that homozygote form of the point mutation in nucleotide 677 has a higher homocysteine and folate level in the plasma in compare with heterozygote form (Elkin and Higham, 2000). The conversion of adenine to cytosine in nucleotide 1298 in exon 7 in the gene (MTHFR A1298C) also leads to the replacement of alanine instead of glutamine in amino acid number 429 of the protein sequence of the MTHFR enzyme (Al-Azzawie and Sabri, 2014). Study have shown that there is no significant relationship between A1298C polymorphism and abortion rates However, the coincidence of heterozygote A1298C form with heterozygote C667T form, will increase the abortion rate and the plasma level of the homocysteine (D'Elia et al., 2014).

Thus, C667T polymorphism disrupts the development of the fetus due to decreased folate levels during the pregnancy.

PAI-1

PAI-1 is a glycoprotein that plays an essential role in preventing fibrinolysis reactions. The important step in the process of dissolving the clot is converting plasminogen into plasmin and is regulated by Tissue Plasminogen Activator (t-PA) and Urokinase-type Plasminogen Activator (U-tPA) (Rijken and Lijnen, 2009; Cardenas et al., 2014). PAI-1 is the fastest t-PA inhibitor and regulates the amount of clot formation in the coagulation system. Plasma and placenta level of the PAI-1 inhibitory is higher in the women with pre-eclampsia history in compare with healthy and fertile women, also the increase of the plasma level of the PAI-1 decrease the activity of the fibrinolysis (Kuhli et al., 2005). Studies have shown that the activation of plasminogen in early stages of the pregnancy cause the decidua to decompose in order to carry out the trophoblast invasion process (Coolman et al., 2006). Trophoblast invasion is an important step in establishing the maternal-fetal association through angiogenesis (Lyall et al., 2001; Coolman et al., 2006). The PAI-1 gene is made up of 9 exons and is located on chromosome 7 at position q21.3-q22. The common polymorphism in the promoter region of the PAI-1 gene is clearly associated with its level change (Luo et al., 2014). This polymorphism is a change in the sequence of five sequential guanosine in the area of 675 bp prior to the transcription site and decreases it to 4 guanosine, leading to an increase in PAI-1 production in response to various stimuli. PAI-1 is a physiologic inhibitor for activating plasmin in the blood and mutation in the promoter of the PAI-1 gene is a considerable factor in thrombophilia (Vora et al., 2009). Naturally PAI-1 gene expression is performed by the 5G/5G allele (Festa et al.,2003). Polymorphism due to the addition or removal of guanosine 4G/5G in place 675- in the promotor region plays an essential role in regulating the expression of the PAI-1 gene. 4G/5G polymorphism in the promoter of the PAI-1 gene is one of the major factors in developing thrombophilia among the women with recurrent abortions history (Vora et al.,2009). The 4G allele homozygosity in the PAI-1 gene in the promotor region is associated with increased transcription of the gene and leads to increased gene expression. The high amount of PAI-1 produced by 4G allele can increase clot production and consequently impair the fibrinolysis and coagulation system, and ultimately cause repeated thrombosis and placenta premature aging (Festa et al., 2003).

Therefore mutation in PAI-1 can leads to abortion as a result of abnormal fibrinolysis mechanism.

ACE

ACE regulates clot formation by converting Angiotensin1 to 2. In fact, the synthesis of endothelial PAI- 1 is controlled by Angiotensin 2 (Buchholz et al., 2003). An increase in the production of angiotensin 2 is associated with an increase in

blood vessel contractions and, consequently, an increase in blood pressure (Chen et al., 2012). Insertion/Deletion (I/D) in the ACE gene cause a change in ACE activity level. The results of the studies showed that the D/D genotypes derived from I/D polymorphism in compared to the D/D and I/D genotypes increase circulated ACE. Studies showed that this polymorphism is associated with abortion (Badenhop et al., 1995). In a meta-analysis study, 11 eligible studies including a total of 1275 patients and 2049 controls were analyzed through a predominant genetic model. The results showed that ACE I/D polymorphism was significantly associated with recurrent abortion and that women with D/D, I/D genotype is at 29% higher risk of abortion in compare with the women with I/I genotype (Su et al., 2013).

Several polymorphism of the ACE gene cause impaired blood pressure and ultimately leads to abortion.

Factor XIII

One of the important factors in the coagulation system is factor XIII (Fibrin Concentrate Factor). Factor XIII is a transglutaminase that plays a pivotal role in the coagulation process (Aleman, et al., 2014). After Factor XIII activation, XIII activates the catalysis of covalent bands between gamma-glutamyl and delta-lysine in fibrin monomers; also it plays a role in connecting to proteins such as α-antiplasmin, collagen and fibronectin. All of these effects increase the resistance of fibrin to parsimination by plasmin and cause the fibrin network to be converted to a blood clot (Walton et al., 2015; Anokhin et al., 2017). The change of guanine to thymine in nucleotide 103; in the exon 2 of the subunit A gene of factor XIII converts valine to leucine and ultimately forms the fibrinolysis resistant clotting network (Vívenes-de Lugo et al., 2008). Due to the role of this factor in the coagulation pathway and the effect of the clot on abortion, this factor is expected to be related to RPL and this fact has been proven in several studies (Pickering et al., 2001; Mtiraoui et al., 2005). On the other hand, it has been shown that G103T polymorphism in XIII has no effect on the plasma concentration of the XIII, but leads to a change in its activity so that factor XIII is not able to integrate the clots made up of fibrins (Jeddi-Tehrani et al., 2010). FXIII is a tetramer composed of two subunits A (FXIII-A) and two sub-units B (FXIII-B) in the blood circulation. FXIII deficiency can be caused by mutations in both genes of subunits A and B. Hereditary FXIII deficiency is usually occur due to a mutation in the FXIII-A gene. This subunit is synthesized in monocytes and megakaryocytes, while FXIII-B is synthesized in liver cells (Muszbek and Katona, 2016). Also, the FXIII-A subunit plays a role in the formation of a cytotrophoblastic shell (which is a layer at the external surface of the placenta and plays a role in the relationship between the mother and the embryo through placenta) (Dorgalaleh and Rashidpanah, 2016). Meanwhile, Val34leu polymorphism in exon 2 of subunit A may also have anti-fibrinolysis effects in fibrin binding sites (Kohler, 2001). Patients with severe FXIII deficiency are at high potential of bleeding due to having less than 1% of plasma FXIII levels. Clinical manifestations of these diseases include delayed wound healing, RPL, soft or subcutaneous hemorrhage, and Intracranial Hemorrhage (ICH) (Naderi et al., 2013). Recurrent abortion is one of the potential symptoms of FXIII deficiency (Dorgalaleh and Rashidpanah, 2016).

So several polymorphisms of XIII factor can leads to clot insolubility and increase the risk of abortion.

Glutathione *S*-transferases

Glutathione S-transferases (GSTs) are a family of enzymes involved in detoxification of a wide range of chemicals. One of the topics of the human Glutathione S-transferase Mu 1 gene (GSTM1) is a broad-based deletion polymorphism in this gene that generates a GSTM1 * 0 or Null allele, so that the GSTM1 allele is inactive (Ford et al., 2000; Tusskorn et al., 2018). Considering the important role of antioxidants in preserving the health of the fetus and the natural pregnancy, as well as the role of oxidative stress in abortion, many studies have been done in this regard. These studies have shown that GSTM1 has an antioxidant role and the poly Morphic elimination of the GSTM1 gene stops the enzyme production so that the antioxidant activity will stop, which, as stated, is a risk factor in spontaneous abortion (Garlantézec et al., 2012). Sata et al. study Showed there is a significant relationship between abortion and homozygote null genotype. Meanwhile, the results of the research showed that GSTM1 homozygote null genotype was higher in women with recurrent abortion in compare with the women with one or two abortions (Sata et al., 2003).However other studies have been shown that Null individuals, in terms of GSTM1, increase the transcriptional expression of the p450-encoding gene (one of the factors involved in detoxification in the body) while individuals with at least one of the GSTM1 alleles have lower serum levels of p450 (Karimlo et al., 2015).

Therefore, the evaluation of GSTM1 activity can be used to evaluate the likelihood of abortion in environments where women are more exposed to oxidizing agents and environmental toxins.

Discussion

Abortion is one of the most common problems that has recently been increased due to several coagulation factors polymorphisms (BEN‐AMI et al., 2012). Coagulation factors play role in a blood flow regulation and prevent the clots formation in blood vessels (Matsumoto et al., 2013). Also, most of these factors lead to the formation of blood-related connection of fetus-maternal. The incidence of

polymorphism in these factors not only prevents the production of blood vessels in the placenta, but also leads to thrombosis in the veins and the appearance of clots and coagulation in the blood vessels (Coolman et al., 2006). Additionally several polymorphisms in coagulation factors can reduce the serum folate which is one of the essential vitamins for the fetus development. However, several coagulation factors polymorphisms may interfere with fibrinolysis and enhance coagulation formation (Nowak et al., 2017). On the other hand, the polymorphism in several genes such as factor V Leiden, disrupts the formation of the fetus due to the IVF technique (Qublan et al., 2006). Generally it can be concluded that identification and evaluation of coagulation factors polymorphisms can have a prognostic value for the monitoring the pregnant women during the first two months of pregnancy.

Future perspective

Considering that coagulation factors and other factors which are involved in homeostasis play several roles in placenta formation during the pregnancy, evaluation of these polymorphisms can be used as a diagnostic biomarker in the identifying high risk pregnancies.

Authors' contributions

H.R. conceived the manuscript and revised it; N.F., Z.D., N.M. and M.Z. wrote the manuscript.

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Conflict of interest

Authors declare that they have no conflict of interest.

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