Altered Levels of Fibrinogen in Relation to the Pathophysiology of Recurrent Spontaneous Abortions

Corresponding Author:
Dr. Monika Gandhi,
Assistant Professor, University School of Biotechnology, Guru Gobind Singh Indraprastha University, Sector 16C, Dwarka, 110075 - India

Submitting Author:
Dr. Monika Gandhi,
Assistant Professor, University School of Biotechnology, Guru Gobind Singh Indraprastha University, Sector 16C, Dwarka, 110075 - India

Article ID: WMC001964
Article Type: Review articles
Submitted on: 07-Jun-2011, 09:14:06 AM GMT Published on: 07-Jun-2011, 02:43:44 PM GMT
Article URL: http://www.webmedcentral.com/article_view/1964
Subject Categories: OBSTETRICS AND GYNAECOLOGY
Keywords: Fibrinogen, Haemostasis, Pregnancy, Recurrent Spontaneous Abortion, Therapeutics, Thrombosis
How to cite the article: Singh N, Gandhi M. Altered Levels of Fibrinogen in Relation to the Pathophysiology of Recurrent Spontaneous Abortions. WebmedCentral OBSTETRICS AND GYNAECOLOGY 2011;2(6):WMC001964
Source(s) of Funding:
University School of Biotechnology, Guru Gobind Singh Indraprastha University
Competing Interests:
None
Altered Levels of Fibrinogen in Relation to the Pathophysiology of Recurrent Spontaneous Abortions

Author(s): Singh N, Gandhi M

Abstract

Introduction: Recurrent Spontaneous Abortion (RSA) is one of the most common complications of pregnancy and is a major healthcare concern for the medical fraternity. Women experiencing recurrent pregnancy loss are a heterogenous population, therefore specific markers are necessary to identify those who will respond to various treatments. During normal healthy pregnancy there are substantial changes in the haemostatic system. This results in variations in the plasma levels of many clotting factors in the blood coagulation cascade. Any change in these factors reflects hypercoagulability and therefore, represents an imbalance in the haemostatic system which leads to thrombotic haemostasis defects. In humans, fibrinogen is required to support pregnancies by maintaining haemostatic balance.

Data sources: Some studies have shown that women with thrombophilias have 66-83% recurrence rate of fetal loss in subsequent pregnancies and also that fibrinogen deficiencies result in abortions in the early gestational period.

Objective: However none of the studies have confirmed the role of fibrinogen levels in the context of RSA. Measuring the altered levels of fibrinogen to predict occurrence of RSA, could be a major direction to be followed to gain insight into the thrombogenic potential of this protein.

Results and conclusion: The information about the thrombogenic potential of this protein could inspire new strategies against the thrombotic complications of RSA.

Introduction

Recurrent Spontaneous Abortion (RSA) is one of the most common complications of pregnancy. RSA is defined as 3 or more clinical pregnancies lost before the 20th week of pregnancy or before the fetus attains a weight greater than 500 g in humans (Meka and Reddy 2006). 10-15 % of all pregnancies end up as early spontaneous pregnancy losses. These losses however, are those recognized pregnancies which are confirmed with usually 2 to 3 months of gestation. There is now evidence that the pregnancy loss rate before this period i.e., during the 2 to 3 weeks following conception, may be as high as 50% (Jalan, URL). At the same time, the risk of miscarriage increases proportionately to the number of previous miscarriages experienced. Unfortunately, a definite cause has been difficult to determine. Over the years, miscarriages have been observed as a somewhat “normal” finding. Often it has been thought to be “nature’s way” of ending a pregnancy which was doomed to fail in any regard. However, there has developed a somewhat more aggressive approach over the last 5 to 10 years towards evaluation and management of women with spontaneous abortion. It is now well recognized that a definition of recurrent pregnancy loss includes three or more consecutive spontaneous miscarriages and that this warrants a full evaluation (Paul et al. 2008). Furthermore, it is becoming more and more recognized that there appears to be an association between infertility and spontaneous abortion (Ching et al. 1995). The etiology of the RSA is often unclear and may be multifactorial. In some cases of the recurrent fetal loss, genetic or chromosomal abnormalities, anatomic abnormalities, endocrine or hormonal problems, and coagulation defects could be the possible reason (Paul et al. 2008). However, the majority of cases of recurrent pregnancy loss are unexplained or associated with a non-conclusive diagnostic result. Although immunological and environmental factors have been speculated to be involved in the loss, still no confirmatory evidences are available for these speculations.

The Coagulation Process

Haemostatic system

The process by which the body prevents blood loss is referred to as coagulation. Coagulation involves the formation of a blood clot (thrombus) that prevents further blood loss from damaged tissues, blood vessels or organs. This is a complicated process with a cellular system comprising of cells called platelets that circulate in the blood and serve to form a platelet
plug over damaged vessels (Fig-1) and a second system based upon the actions of multiple proteins (called clotting factors) that act in concert to produce a fibrin clot (MacFarlane. 1964). These two systems work in concert to form a clot; disorders in either system can yield disorders that cause either too much or too little clotting.

Platelets serve three primary functions: 1- sticking to the injured blood vessel (called platelet adherence), 2- attaching to other platelets to enlarge the forming plug (called platelet aggregation), and 3- providing support (molecules on the surface of platelets are required for many of the reactions) for the processes of the coagulation cascade.

When a break in a blood vessel occurs, substances are exposed that normally are not in direct contact with the blood flow. These substances (primarily collagen and von Willebrand factor) allow the platelets to adhere to the broken surface. Once a platelet adheres to the surface, it releases chemicals that attract additional platelets to the damaged area, referred to as platelet aggregation. These two processes are the first responses to stop bleeding. The protein based system (the coagulation cascade) serves to stabilize the clot that has formed and further seal up the wound (Furie and Furie. 2005).

The goal of the coagulation cascade is to form fibrin, which will form a mesh within the platelet aggregate to stabilize the clot. All of the factors have an inactive and an active form. Once activated, the factor will serve to activate the next factor in the sequence until fibrin is formed.

The coagulation cascade takes place at the site of a break in a blood vessel that has the platelet aggregate. Tissue factor and factor Vlla (the ‘a’ denotes the active form of the factor) activate factor X, forming factor Xa. Factor Xa is then able to activate prothrombin (also referred to as factor II) to form thrombin (factor IIa). Thrombin converts fibrinogen to fibrin (factors I and Ia respectively). Fibrin forms a mesh that, in concert with the platelets, plugs the break in the vessel wall. The fibrin mesh is further stabilized by factor XIII, which sews up the clot (much like forming an intricate network of cross-stitched strands of fibrin) (Fig-2) (Bereczky et al. 2003).

Role in immune system

The coagulation system overlaps with the immune system. Some products of the coagulation can contribute to the innate immune system by their ability to increase vascular permeability. They can also act as chemotactic agents for phagocytic cells. In addition, some of the products of the coagulation system are directly anti-microbial. For example, beta-lysine, a protein produced by platelets during coagulation (Tew et al. 1974), can cause lysis of many Gram-positive bacteria by acting as a cationic detergent (Donaldson and Tew. 1977). Many acute-phase proteins of inflammation are involved in the coagulation system. In addition, pathogenic bacteria may secrete agents that alter the coagulation system, e.g., coagulase and streptokinase (Bergmann and Hammerschmidt. 2007).

Significance of haemostatic System in Pregnancy

Normal pregnancy is often referred to as a hypercoagulable state (Stirling et al. 1984; Bonnar et al. 1987), which is associated with many changes in the haemostatic system. These changes are considered to be in preparation for the maintenance of the placental functions which occurs during pregnancy. Such changes protect women from the haemostatic challenges during delivery and prevent excessive bleeding (Prisco et al. 2005). However it is also considered to be a risk factor for venous thrombosis.

The incidence of venous thromboembolism is 6-fold higher during pregnancy than in the general female population of the child bearing age (Holmes and Wallace. 2005). The haemostatic system plays an important role in the success of pregnancy and in the process of implantation, and placentation. Implantation of the fertilized egg into the uterine decidua establishes a contact between the fetus, the placenta and the maternal circulation. This contact between placenta and maternal circulation is crucial for the success of pregnancy. Pro-thrombotic changes and thrombosis may interfere with these processes leading to miscarriage (Kupfermine et al. 2003). This may explain many cases of previously unexplained recurrent miscarriage. Pregnancy changes the plasma levels of many clotting factors (Brenner. 2004) (Table 1). The increase in these factors reflects hypercoagulability and therefore, represents an imbalance in the haemostatic system. This phenomenon protects the woman from haemorrhage during pregnancy and in puerperium. In several studies it has been proposed that this imbalance may act as a useful tool in different pathological situations to predict and monitor the severity of a hypercoagulable state that could lead to thrombosis associated with the abnormal development of the fetus, pregnancy losses, and obstetric complications (Iwaki et al. 2002).

The thrombotic defects result in the thrombosis of the early placental vessels, which lead to imbalance in the haemostasis system. These thrombotic defects have been associated with recurrent fetal loss occurring in the first trimester (Kupermine et al. 2003). Thus, thrombophilia is identified as the principal cause of RSA (Bick. 2000). It is now widely accepted that recurrent miscarriage is a heterogeneous condition,
with several etiological factors such as prothrombolic states, structural uterine anomalies, chromosomal anomalies, and endocrinological defects. The causes for thrombophilia associated with RSA include lupus anti-coagulants, antcardiolipin antibodies (Bick and Baker. 1994), factor XII deficiency, fibrinogen deficiency, dysfibrinogenemias associated with thrombosis, protein C deficiency, antithrombin deficiency and fibrinolytic defects (plasminogen deficiency, tissue plasminogen activator deficiency, and elevated plasminogen activator inhibitor type 1) (Gris et al. 1993; Patrassi et al. 1993) (Table 2).

Fibrinogen Protein
Fibrinogen is a 340-Kd soluble glycoprotein. The plasma content of fibrinogen is synthesized in the liver (Iwaki et al. 2002). It is a symmetrical heterodimeric protein consisting of 3 pairs of polypeptides ([(Aα][Bβ][γ ]j2. The 6 chains are covalently linked near their N-terminals through disulfide bonds. The A and B portions of the Aα and Bβ chains comprise of the fibrinopeptides, A and B respectively. The fibrinopeptide regions of fibrinogen contain several glutamate and aspartate residues imparting a high negative charge to this region and aid in the solubility of fibrinogen in plasma. Active thrombin is a serine protease that hydrolyses fibrinogen at four arg-gly (R-G) bonds between the fibrinopeptide and the a and b portions of the protein (Hayes. 2002).

The primary physiological role of fibrinogen is in haemostasis. In the final step of the coagulation cascade, fibrinogen is converted to fibrin, with the formation of a fibrin clot. The first step in this conversion is the thrombin mediated cleavage of fibrinopeptides A and B from the fibrinogen α and β chains; the residual molecule is referred to as fibrin monomer (Blomback et al. 1978). A loose fibrin clot develops, as fibrin monomers spontaneously polymerize (Herman and McDonagh. 1982). The formation of a firm insoluble fibrin gel depends on cross-linking of the polymer by the transglutaminase activity of factor XIIIa. The fibrin clot has an essential role in limiting bleeding at sites of blood vessel injury; it also provides the structure for assembly and activation of the fibrinolytic proteins (Minno et al. 2004). Fibrinogen also plays important roles in other pathophysiological processes, apart from clot formation in the haemostatic process.

These processes are infection (McRitchie et al. 1991), wound healing (Kuijper et al. 1997; Martin. 1997) and clot retraction (Gartner and Ogilvie. 1988).

Pathophysiology
By various studies, it has been proposed that increased levels of fibrinogen can contribute to thrombophilia, whereas decreased levels of fibrinogen are associated with an increased risk of bleeding. Increased fibrinogen levels are postulated to enhance thrombus formation by altering the kinetics of the coagulation cascade, thereby resulting in increased fibrin formation, augmenting platelet interaction by increased binding to the glycoprotein IIb/IIIa receptor, and increasing plasma viscosity (Chandler. 2002). Congenital abnormalities of fibrinogen are divided into 2 types: type I, or quantitative abnormalities (afibrinogenemia and hypofibrinogenemia), and type II or qualitative abnormalities (dysfibrinogenemia and hypodysfibrinogenemia) (Evron et al. 1985; Asselta et al. 2006). Afibrinogenemia and hypofibrinogenemia result from mutations that affect plasma fibrinogen concentration and are frequently associated with a bleeding diathesis. Dysfibrinogenemia is marked by functional abnormalities of fibrinogen that may result in either bleeding or thrombosis (Hayes. 2002).

Clinical conditions
Fibrinogen levels can be measured in venous blood. Normal levels are about 2-4 g/L, depending on the method which is used. Typically fibrinogen is measured in citrated plasma samples in the laboratory; however the analysis of whole blood samples by use of thrombelastometry (platelet function is inhibited with cytochalasin D) is also possible (Lang et al. 2009). The normal range for fibrinogen is quite varied. Levels can also fluctuate in an individual in response to events like blood transfusions and systemic injuries, which can make it challenging to obtain a baseline (Bremme and Ostlund. 1992). Increased levels of fibrinogen also have a strong and consistent association with an increased risk of atherosclerotic vascular disease (Chandler. 2002). Hyperfibrinogenemia (higher levels) has been consistently associated with cardiovascular risk factors, such as smoking and diabetes mellitus (>3.43g/L) (Stec et al. 2000). It can also be elevated in any form of inflammation, as it is an acute phase protein; for example, it is especially apparent in human gingival tissue during the initial phase of periodontal disease (Page and Schroeder. 1976). In such conditions, fibrinogen protein can act as a potential marker for arterial thrombosis and an underlying inflammatory process. Low levels of fibrinogen most commonly result from acquired conditions, such as decreased synthesis in the liver and increased consumption in disseminated intravascular coagulation, which indicates a systemic activation of the clotting system, with consumption of clotting factors faster than synthesis. In afibrinogenemia, there is a complete absence of fibrinogen. The fibrinogen level is
Discussion

It has been estimated that 12-15% of clinically recognized pregnancies and as many as 17-22% of all pregnancies result in spontaneous abortions (Gracia et al. 2005). The diagnosis of spontaneous abortion is mainly focussed on some diagnostic strategies such as ultrasonography, intravenous immunoglobulin (IVIG) (Coulam et al. 1995; Coulam et al. 1996; Clark et al. 2001), allogeneic leukocyte, thrombocyte immunotherapies and serum human chorionic gonadotrophin (hCG) levels (Gracia et al. 2005). From the above reports, the role of fibrinogen levels in the RSA has been established apart from the other anatomical and immunological factors. Thus fibrinogen protein can help in devising an optimal diagnostic strategy to evaluate patients with RSA and normalize this phenomenon by supplementation of fibrinogen to elevate its levels in the RSA pregnant females. This may strengthen the predictive value of this protein and may help in defining new therapeutic interventions. Such diagnosis would not only have successful implications for immediate management of pregnancy, but also for management of future pregnancies. Further clinical investigations are necessary to verify whether recurrent miscarriage and bleeding complications arising due to thrombosis are associated with altered levels of the immunological or functional fibrinogen

References


Illustrations

Illustration 1

Table 1- Coagulation system changes in normal pregnancy

<table>
<thead>
<tr>
<th>Coagulation factor/protein</th>
<th>Alteration in the levels of expression during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor XIII</td>
<td>Increases in early pregnancy, returns to non-pregnancy values by third trimester</td>
</tr>
<tr>
<td>Factors XII, X, IX, VIII, VII, Vc</td>
<td>Increases throughout pregnancy</td>
</tr>
<tr>
<td>Factor V</td>
<td>Increases in early pregnancy, followed by a decrease and stabilization</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Decreases throughout pregnancy</td>
</tr>
<tr>
<td>vWF, fibrinogen</td>
<td>Increase throughout pregnancy</td>
</tr>
<tr>
<td>Factor II (prothrombin)</td>
<td>Increase in early pregnancy, returns to non-pregnant values by third trimester/no change</td>
</tr>
<tr>
<td>Soluble TF</td>
<td>No change</td>
</tr>
<tr>
<td>Monocyte TF</td>
<td>Decreases throughout pregnancy, returns to non-pregnant values by 3 days post-partum</td>
</tr>
<tr>
<td>Protein C</td>
<td>Decreases during pregnancy</td>
</tr>
<tr>
<td>Protein S</td>
<td>Increases throughout pregnancy</td>
</tr>
</tbody>
</table>
Illustration 2

Table 2: Changes in various factors in thrombophilia associated with Recurrent Spontaneous Abortions

<table>
<thead>
<tr>
<th>Factors</th>
<th>System change in thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant</td>
<td>Presence detected</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>Presence detected</td>
</tr>
<tr>
<td>Factor XII</td>
<td>Decreases</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Decreases</td>
</tr>
<tr>
<td>Protein C</td>
<td>Decreases</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>Decreases</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor type I</td>
<td>Increases</td>
</tr>
</tbody>
</table>
Illustration 3

Table 3- Clinical conditions associated with the alterations in the expression of fibrinogen

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Afibrinogenemia</th>
<th>Hypofibrinogenemia</th>
<th>Dysfibrinogenemia</th>
<th>Hyperfibrinogenemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Absence of fibrinogen</td>
<td>Lower than normal level</td>
<td>Improper functioning</td>
<td>Higher than normal level</td>
</tr>
<tr>
<td><strong>Fibrinogen levels</strong></td>
<td>&lt;0.2 g/l of plasma</td>
<td>Between 0.2 g/l and 0.8 g/l of plasma</td>
<td>Between 2 g/l and 4 g/l of plasma</td>
<td>&gt;4 g/l of plasma</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>-umbilical cord bleeding -cutaneous mucous bleeding -gastrointestinal hemorrhage -intra-cranial bleeding -articular bleeding</td>
<td>-umbilical cord bleeding -cutaneous mucous bleeding -gastrointestinal hemorrhage -intra-cranial bleeding (infrequent) -articular bleeding -excessive bleeding following trauma or surgery.</td>
<td>-No symptoms -Thrombosis -Hemorrhage</td>
<td>-acute ischemic stroke -arterial thrombosis -inflammation</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Fibrinogen</td>
<td>Fibrinogen or anticoagulant</td>
<td>Anti-inflammatory agent</td>
<td>Anti-inflammatory agent</td>
</tr>
</tbody>
</table>
Illustration 4

Fig-1: Coagulation cascade
Illustration 5

Fig-2: Formation of the platelet plug
Illustration 6

Fig-3: Fibrinogen and its significance in pregnancy

Fig 3
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.