Anticoagulant Therapy in Pregnant Patients with Metabolic Syndrome: A Review

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Abstract: Pregnancy is a specific state of heightened coagulability related to the increase in procoagulant agents and to the reduced fibrinolysis. Pregnancy is associated with a 4-fold increased risk of developing venous thromboembolism (VTE) and this risk still increases to 14-fold during puerperium. A correlation between the metabolic syndrome and development of cardiovascular events and cerebrovascular incidents has been described. Such a relationship is referred to a hypercoagulable state due to increased serum levels of the plasminogen activator inhibitor-1 (PAI-1), fibrinogen, factor (F) VII and VIII, von Willebrand factor and from endothelial activation, caused by increased circulating adhesion molecules. As to the risk of VTE, the probability for its association with cardiovascular incidents is increased by common underlying mechanisms such as the activation of platelets and the blood coagulation. A correlation between idiopathic VTE and the metabolic syndrome has been reported. The anticoagulant therapy may be recommended during the pregnancy for the treatment or the prophylaxis of VTE and, in women with artificial heart valves, for the prevention of the valve thrombosis and systemic embolisation. There are also specific conditions during pregnancy which benefit from anticoagulant use, such as recurrent fetal loss, thrombophilia and assisted reproductive technology. There are no published specific data about using of anticoagulant agents in pregnant patients with the metabolic syndrome except for a few articles addressing reproductive problems. The mechanisms of anticoagulant action were studied with the focus on heparinoids, because of their safety not only for the patient but also for the fetus. The new oral anticoagulants were also shortly described although they have been contraindicated during the pregnancy.

Keywords: Aspirin, fondaparinux, heparin, low molecular weight heparin, metabolic syndrome, pregnancy, warfarin.

INTRODUCTION

Metabolic Syndrome

In 1998 the WHO introduced the term “Metabolic Syndrome” formerly known as insulin resistance syndrome, to characterize the combination of diseases and of risk factors accompanying the type 2 diabetes mellitus, mainly the obesity, hypertension and dyslipidemia. In non-diabetic patients with metabolic syndrome abnormal insulin sensitivity was required [1]. Two of the most popular definitions of the metabolic syndrome are the WHO definition with the minor revision in 1999 [2] between the preliminary report and the final statement and the clinical definition of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III [3] which seems to be more useable for epidemiological studies. In NCEP ATP III definition the most important criteria for the metabolic syndrome are included. The key features of the hyperglycemia/insulin resistance, visceral obesity, atherogenic dyslipidemia and hypertension are incorporated. According to the this definition, the metabolic syndrome is identified if three or more of the following five criteria are presented: the waist circumference is over 40 inches (men) or 35 inches (women), blood pressure is over 130/85 mmHg, fasting triglyceride (TG) level is over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level is less than 40 mg/dl in men or 50 mg/dl in women and fasting blood sugar is over 100 mg/dl [3]. Common definitions of the metabolic syndrome are not useful during the pregnancy. The physiological changes that occur during the uncomplicated pregnancy contains a few elements of the metabolic syndrome: a comparative degree of insulin resistance, heightened adiposity, hyperlipidemia and an up-regulation of the inflammatory cascade [4]. The physiological pregnancy has been deliberated to be as a transitional incursion into the metabolic syndrome and it has been suggested that pregnancy may be a good stress test for carbohydrate, lipid and vascular physiology of an individual woman. The identification of the metabolic syndrome during the pregnancy could help to identify a subpopulation of women who not only may progress a pregnancy-related complication but potentially, have a higher risk for either metabolic or cardiovascular health problems in life postpartum as well.

Physiological Changes in Coagulation During the Pregnancy

Pregnancy is a specific state of heightened coagulability related to the increase in procoagulant agents and to the re-
duced fibrinolysis. It may prevents excessive bleeding, but the possibility for maternal vascular complications, especially for venous thrombosis, is considerably increased during the pregnancy. Pregnancy is associated with 4-fold increase in the risk of the venous thromboembolism (VTE) and this risk increases to 14-fold during the puerperium. The relative risk of thromboembolic complications during pregnancy is 1/1000-2000 deliveries [5]. The caesarean section alone has approximately 5 times higher risk of the vascular thromboembolism in comparison to the vaginal delivery [5]. This risk further increases if an underlying thrombophilia is present. The pulmonary embolism is still a main cause of maternal mortality in the Western world. Pregnancy is a state of the increased coagulability and a period of the high risk for thrombotic complications due to the increased serum levels of procoagulants, such as the factors II, VII, VIII, X, XII, and fibrinogen. The blood levels of the factor VIII (FVIII), the von Willebrand factor (vWF), the ristocetin cofactor (RCoA) and the factors X (FX) and XII (FXII) increase during the pregnancy. The higher level of fibrinogen is also observed during the pregnancy with the levels at term 200% above pre-pregnant levels [5, 6].

Other factors of coagulation are compared with non-pregnant levels or diminish during the pregnancy. During the pregnancy fibrinolysis is reduced due to the decrease in tissue plasminogen activator (t-PA) activity, are at low level until 1 hour postpartum when this activity returns to normal. It is caused by a gradual, threefold, increase in plasminogen activator inhibitor-1 (PAI-1) and the increasing levels of the plasminogen activator inhibitor-2 (PAI-2). It has been described that the placenta produces PAI-1 and is the primary source of PAI-2. PAI-2 levels in the time of delivery are 25 times higher than in normal plasma. After delivery, t-PA concentration rapidly return to pre-pregnant as PA-1 levels, however, PAI-2 levels remain higher for a few days. The levels of the thrombin-activatable fibrinolysis inhibitor (TAFI), an antifibrinolytic factor which catalyze cleavage the C-terminal lysine in fibrin renders it resistant to be cleave by plasmin, are increased in the third trimester [6].

The levels of the protein S decrease during the pregnancy, and an increased resistance to the activated protein C is observed in the second and third trimesters of pregnancy [5]. The venous stasis are additional predisposing factors to VTE. It is probably caused by the impaired venous outflow from abdomen and lower limb as a result from increase in intra-abdominal pressure. It is well known, that pregnancy increases intra-abdominal pressure. Raised intra-abdominal pressure is the main reason of disturbance in venous outflow, particularly from abdominal and lower limb region [7]. These changes combine to reduce the risk of a severe maternal peripartum haemorrhage but relatively increase the risk of thrombotic complications during the pregnancy. The risk of the pregnancy-related VTE is elevated 4-16 fold in heterozygous carriers of factor V Leiden, elevated 15 fold in the prothrombin mutation, and women with antiphospholipid antibodies have 5% incidence of VTE [6].

Approximately 85% of the deep vein thrombosis (DVT) of the lower extremity occur on the left side during pregnancy. This is attributed to the more tortuous course of the venous drainage of the left leg through the pelvis and to the compression of the left common iliac vein by the overlying right iliac artery.

**Risk of VTE in Metabolic Syndrome**

The metabolic syndrome is a cluster of traditional risk factors for atherosclerosis. These include the abdominal obesity, impaired fasting glucose plasma levels (IFG), arterial hypertension and dyslipidemia; high triglycerides and low HDL-cholesterol [8]. The metabolic syndrome may play an important role in the pathogenesis of an unsuccessful pregnancy, because it is associated with higher proinflammatory and prothrombotic markers. It was suggested that in case of the metabolic syndrome the administration of low molecular weight heparin (LMWH) and/or aspirin from the time of conception has a favourable effect. A correlation between the metabolic syndrome and development of cardiovascular events and cerebrovascular incidents has been documented [9]. Such a relationship is referred to a hypercoagulable state due to increased serum levels of the plasminogen activator inhibitor-1 (PAI-1), fibrinogen, factor (F) VII and VIII, von Willebrand factor and from endothelial activation, caused by increased circulating adhesion molecules i.e. Inter-Cellular Adhesion Molecule 1 (ICAM 1) and Vascular Cell Adhesion Molecule 1 (VCAM 1) [10]. As to the risk of the VTE, the possibility for its association with cardiovascular incidents is increased by common underlying mechanisms such as platelets activation and of blood coagulation. A correlation between the idiopathic VTE and the metabolic syndrome has been reported [11]. These authors have also described those patients with otherwise unexplained DVT have a significantly higher predominance of the metabolic syndrome than control group without thromboembolic complications [11].

Patients with metabolic syndrome are at a high risk of developing thromboembolic disorders during the pregnancy because apart from normal changing observing during the pregnancy these patients very often have abnormal body mass index (BMI) as well [12].

The obesity may increase the risk of many health problems. The maternal obesity and the primary insulin resistance are significant short- and long-term risk factors for both the mother and the fetus. Pregnancy is a metabolic stress test for those obstetric disorders, which are predictive of the metabolic syndrome in the later life, e.g. the gestational diabetes mellitus (GDM) and preeclampsia for obese women with the subclinical decreased insulin sensitivity. In recent years the obesity has emerged as an independent and important risk factor for VTE [13]. It was described an association between the obesity and thrombosis, comprising an increased expression of the prothrombotic factors the plasminogen activator inhibitor-1 and tissue factor (TF) and an increased platelet activation. Although TF has been clearly linked to a procoagulant state in the obesity, emerging genetic and pharmacologic evidence indicate that TF signaling via G protein-coupled protease-activated receptors (PAR2, PAR1) additionally drives multiple aspects of the metabolic syndrome. The TF-initiated coagulation leading to the thrombin-PAR1 signaling also contributes to diet-induced hepatic steatosis and to inflammation in certain models [14]. It has been described a correlation between the obesity and the increased coagulability and it could be seen in the increased thrombin
production. Plasma PAI-1 levels are increased in patients with insulin resistance and obesity with consequent inhibition of fibrinolysis [11]. The effects of the elevated PAI-1 may also be intensified by the elevated homocysteine eventually leading to thrombosis [11]. In addition, the elevation of the oxidative stress has been correlated with the adipose tissue in the models of obesity [13]. The oxidative stress can activate the platelets, cause endothelial damage and shedding of activated platelet and endothelial cell derived microparticles, which in turn are thrombogenic. In obese individuals, reduced fibrinolytic activity has been described [14] and probably this is the essential mechanism predisposing to both venous and arterial thrombosis.

Inflammation has been suggested to involve in obesity development but is not well explained the precise role of thrombosis per se in obesity [15]. The triggered inflammation may explain the mechanisms in pathogenesis of obesity with pathological manifestations including the diabetes and developing of cardiovascular events, e.g., the atherosclerosis and hypertension. The heparin has a variety of anti-inflammatory potentials. A heparin-bonded circuit prevents the increases in the levels of IL-6 and IL-8 while heparin bolus diminish neutrophil activation without changing platelet aggregation [16].

In summary the metabolic syndrome could play a role in the pathogenesis of idiopathic VTE and may act as the link between VTE and atherosclerosis.

Anticoagulant Therapy

An appropriate knowledge of the use of anticoagulants in pregnancy, especially when metabolic syndrome is observed, is substantial for the prevention and effective treatment of VTE. The studies show not just the acute vascular events that are important in etiology of DVT since it can be also correlated with a significant risk of the recurrent venous thrombosis and deep venous insufficiency (DVI), and PTE carries a risk of the subsequent pulmonary hypertension [17]. The risk of the DVI is essential: 80% of women with VTE will have post-thrombotic syndrome and over 60% will have objectively proved DVI following a treated DVT [14] in less than five years in almost all cases. When the VTE is diagnosed during the pregnancy it could be the first manifestation of an inherited or acquired thrombophilia. Both types of thrombophilia are associated not only with the venous thrombosis, but may increase risks of such pregnancy outcomes as miscarriage, pre-eclampsia and intrauterine growth restriction (IUGR) [18]. Anticoagulant therapy in such situations could be useful and appropriate.

This type of therapy may be indicated during pregnancy for the treatment or for the prophylaxis of the venous thromboembolism and, in women with artificial heart valves, for the prevention of the valve thrombosis and systemic embolisation. Sometimes, anticoagulants are also indicated in pregnant women with a valvular or congenital heart disease. Anticoagulant therapy is indicated for the prevention of pregnancy-related complications in women with the antithrombin deficiency or with the antiphospholipid antibody syndrome (APLAs) and other thrombophilias who have had prior VTE [17, 18].

There are also specific terms related to pregnancy which benefit from anticoagulant use, such as recurrent fetal loss in the setting of thrombophilia [18].

There are no published data specific to using of anticoagulant agents in pregnant patients with metabolic syndrome.

ANTICOAGULANTS

Anticoagulants Currently in Use Comprise

- Heparinoids: unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) (enoxaparin, Lovenox, Clexane; dalteparin, Fragmin; tinzaparin, Innohep; nadroparinum, Fraxiparine) and fondaparinux, Ariixtra.
- Vitamin K antagonists (VKA): warfarin (Coumadin), phenindione (Dindevan) and acenocoumarol (Sintrom).
- Antiplatelet agents (acidum acetylsalicylicum, Aspirin).
- New oral agents.

HEPARIN

Heparin was discovered more than ninety years ago, when it was was isolated from the canine liver, and in smaller amounts from the canine spleen and pancreas [19]. In 1973, the mechanism of action of heparin was explain by the demonstration that it enhances the ability of the plasma protein antithrombin to produce complexes with thrombin, factor Xa, and factor IXa about 1000-fold, and inhibiting their pro-coagulating activity [20]. Administration of heparin has been the milestone of therapy and prophylaxis of thrombosis for many years. Heparin is commonly administered by intravenous route. Intramuscular injections of heparin are unusual because of the possibility for forming hematomas. Heparin is consisted of disaccharide repeating units composing of 1→4 linked residues of uronic acid and D-glucosamine. The dominant sugars occurring in heparin are (a) α-liduronic acid 2-sulfate, (b) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (c) β-D-glucuronic acid, (d) 2-acetamido-2-deoxy-α-D-glucose, and (e) α-L-iduronic acid. These sugars are occurred in decreasing proportions, typically in the succeeding order i.e. (b)≥(a)> (d)>(c)>(e). The mayor repeating unit is the trisulfated disaccharide 2-O-sulfo-α-L-iduronic acid 1′4 linked to 6-O-sulfo-N-sulfo-α-D-glucosamine ("4]IdoA2S (1′4)GlcNS6S[1") [21].

The degree of sulfatation and the length of the polysaccharide chain outlines the features of the molecule; shorter chains are low molecular weight heparins and longer chains are high molecular weight (or unfractionated) heparins [21].

Heparin catalyzes the inactivation of the factor Xa and of the thrombin in a similar degree [22, 23]. Heparin exerts catalysis of the factor Xa through enhanced activation of antithrombin by a distinct pentasaccharide sequence presented on the heparin molecules. The binding of the pentasaccharide induces a conformational change in the reactive center loop of antithrombin that stimulates its interaction with the active site of the factor Xa [23]. To stimulate the rate of thrombin inactivation by antithrombin, heparin must bind antithrombin and thrombin as well, and bridging the inhibitor and the enzyme together. The interaction of heparin
with antithrombin is mediated by a unique pentasaccharide sequence found on one-third of the chains of heparin and about one-quarter of this contains anticoagulant action [24]. This pentasaccharide sequence is randomly deployed among the heparin chains. The remainder of the chains that lack this pentasaccharide sequence have the little or no anticoagulant activity [25]. The interaction of heparin with thrombin is not related to the pentasaccharide sequence and needs a penta-saccharide-containing chain of sufficient length to concomitantly bind to antithrombin and thrombin as well [25]. Heparin connects to plasma proteins, platelets, and endothelial cells, endowing it with unforeseeable pharmacokinetic and pharmacodynamic properties. Achieving a therapeutic drug level is rather complicated with UFH because of factors which could change absorption, clearance, and the quantity of unbound UFH accessible in the plasma. It has been noted that these binding sites are saturated, the remaining unbound UFH may produce its anticoagulant effect [22]. Unfractionated heparin can connect also to some proteins, which are acute-phase reactants. These proteins are increased in patients who have infectious diseases or who are stressed [22] thus further contributing to the unpredictable side effects of UFH. The rapid and unforeseeable clearance of the UFH increases the difficulty of achieving a therapeutic concentration [26].

The clearance of heparin is a biphasic process consisted of rapid saturable and slower first-order mechanisms. The first phase is influenced by heparin’s non-specific binding via uptake by endothelial cells and macrophages, as well as heparin-binding proteins. Once these binding sites are saturated, the slower non-saturable clearance phase for the most part reflects the renal clearance. Heparin that binds to macrophages is internalized and depolymerized. The small part of heparin then again re-enter the circulation and are eliminated by the kidneys [22].

It has been described that heparin has a relatively fast clearance, from half an hour to 2.5 hours, depending on the dose, which allows for relatively easy and frequent adjustments of therapeutic level. Heparin therapy can be monitored with the activated partial thromboplastin time (aPTT) or anti–factor Xa level. The APTT ratio (APTR) provides a measure of anticoagulant effect of UFH; the usual target ratio is between two and three times higher than a normal APTT. Dosing of UFH requires a bolus dose for initiation of an UFH infusion, followed by a continuous infusion. APTR monitoring allows subsequent adjustment of dosage. The dosage of UFH for administration by SC injection is fixed [27].

Anywise using of heparin is an effective, relatively safe and inexpensive method in the prophylaxis and treatment of VTE there are a few restrictions. Heparin must be given parenterally. Because levels of heparin-binding proteins in plasma vary between the patients, the anticoagulant response is unpredictable. Heparin has low bioavailability at low doses. During a long term of heparin administration the development of heparin-induced thrombocytopenia and osteoporosis can be observed [28].

LOW MOLECULAR WEIGHT HEPARIN (LMWH)

Over the past few decades, low molecular weight heparin (LMWH) preparations, which are manufactured from standard heparin by controlled enzymatic or chemical depolymerization, is seeing a rise in popularity. LMWH preparations are now the heparin of choice in anticoagulant therapy during pregnancy because of a less often observed side effects than UFH, good safety record for mother and fetus and easy once daily dosing for prophylaxis. Chemically, LMWH are smaller fragments of the UFH produced by a kind of hydrolytic depolymerization reactions. A lot of the pharmacokinetic and pharmacodynamic disadvantages associated with UFH are displaced in LMWH because of their smaller size. Low molecular weight heparins with an average molecular weight of 4000-6500, and a mean chain length of 15 saccharides are obtained from UFH [22].

Only 15 to 25 percent of the chains of LMWH have the unique pentasaccharide sequence that is needful for binding to antithrombin, even less than in the unfractionated heparin. Heparin exert catalysis of the factor Xa through enhanced activation of antithrombin by a distinct pentasaccharide sequence presented on the heparin molecules that results in a conformational change. Unlike to thrombin inactivation, heparin must bind antithrombin and thrombin as well, and creating a ternary complex [29]. This complex can be made only by heparin chains comprising the pentasaccharide at least 18 saccharide units, corresponding to a molecular weight of 5400 Da or higher, which is the case for most of the chains of UFH but fewer than half of those of LMWH [30, 31]. The first generation LMWH comprise 25–50% of fragments with 18 or more saccharides whereas the second generation or ultra-LMWH comprise a much greater percentage of short chains (molecular weight < 3000 D). The newer LMWH have also a high percentage of chains containing the high affinity specific pentasaccharide [32].

It has been described that LMWH has greater inhibitor activity against factor Xa than thrombin [22, 23, 33]. This is known as the anti-factor Xa to anti-factor IIa (thrombin) ratio. While heparin has a ratio of 1 to 1, LMWH has a ratio of 2 or 3 to 1 and it depends on the type of LMWH [22, 33].

After administration of LMWH the anticoagulant response is more foreseeable than that of UFH. This difference reflects the predisposition of longer heparin chains to bind to plasma proteins, the concentrations of which can be different between the patients [34]. A part of these heparin-binding proteins are proteins in acute phase and concentration of some of these proteins increase in patients with VTE, whereas some are proteins such as platelet factor 4 (PF4) or high molecular weight multimers of von Willebrand factor, which comes from activated platelets or endothelial cells. Low molecular weight heparins are more selective inhibitors of factors IXa and Xa than UFH [23].

The UFH and LMWH can release the tissue factor pathway inhibitor (TFPI) from endothelial cells [35]. This reaction appears to be correlated with the heparin chain length and the degree of sulfation. The highest sulfation is observed in UFH. As the chain length is shorter, the release of TFPI decreases [36, 37]. Over-expression of tissue factor, in connection with its procoagulant effect, is also known to being associated with the pathophysiology of sepsis, acute lung injury, disseminated intravascular coagulation, angiogenesis and cancer [38, 39, 40]. It is suggested that the long half-life of TFPI can be the reason of the prolonged protection from
thrombosis due to heparins action. The less possible mechanism is related to alone activation of anti-factor Xa and anti-factor IIa, which have a relatively short plasma half-life [39].

Due to the relatively slight impact of LMWH on thrombin, the influence on the partial thromboplastin time (PTT) is non-essential [22]. Therefore, monitoring of the PTT is not informative. If necessary, efficacy of treatment with LMWH can be checked by monitoring of anti-Xa activity [23]. With this test, therapeutic heparin levels range from 0.3 to 0.7 U/mL. But, anti-Xa values can vary because of using the type of assay. So, the standardization of the anti-Xa activity measuring is necessary [23].

There are a few LMWH which are widely used. The most popular are enoxaparin and dalteparin. LMWH are produced from UFH by varied chemical reactions. Enoxaparin is produced by benzylolation of UFH followed by alkaline depolymerization. Dalteparin is formed by nitrous acid depolymerization of UFH [41]. This two types of LMWH have a bit different pharmacokinetic, pharmacodynamic, and anticoagulant profiles. They have also a slightly various chemical structures and molecular weights [37, 41].

Protamine sulfate is a 5-kDa cationic polypeptide derived from salmon sperm that can reverses the anticoagulant activity of UFH. This highly cationic protein binds heparin with high affinity and the resultant protamine-heparin complex is rapidly cleared by the reticuloendothelial system [33]. It has been described that the binding of heparin to protamine sulfate is chain-length-dependent. Animal studies have shown that although protamine completely reverses the thrombin-inhibitory activity of LMWH, which is effected by the longer chains but it can only in 60% neutralize their anti-factor Xa (FXa) activities [22, 33]. So, the clinical efficacy of protamine for reversing LMWH-induced anticoagulation remains unclear [22].

The FDA and Aventis have released a warning about the use of LMWH in pregnant women with artificial heart valves [22]. It was based on publications with randomized trial and comparison the enoxaparin to warfarin in pregnant patients with artificial heart valves. But Montalescot et al., described that LMWH is safe and effective as anticoagulant when given for an average of 14.1 days to 102 nonpregnant women with artificial heart valves [42]. Clearly more data from specific clinical studies is required to determine risk factors for the use of available LMWH preparations in pregnant and non-pregnant patients with artificial heart valves.

**HEPARIN IN RECURRENT PREGNANCY LOSS (RPL), THROMBOPHILIA AND ASSISTED REPRODUCTIVE TECHNOLOGY (ART)**

Pregnancy is a hypercoagulable state. It was suggested that some cases of RPL and other pregnancy complications which can be observed in a second or third trimester of pregnancy are caused by inadequate haemostatic response during pregnancy leading to the placental thrombosis and infarction [43]. Because of the abnormal placental perfusion due to thrombosis, placental infarctions and maternal complications can be observed [44]. The risk factor for thrombosis is hyperhomocysteinemia (HHcy). It has been described as a possible cause of recurrent abortions or placental abruption [44].

The association between insulin resistance and HHcy was presented [45], with frequency of the latter being increasingly a common observation among women with polycystic ovary syndrome (PCOS) [46]. It has been published papers which suggested a correlation between obesity and miscarriage, while obesity appears to be closely associated with PCOS [47]. PCOS involves a few factors which can lead, individually or in combination, to thrombosis and eventually lead to RPL [47].

Maternal hypercoagulability related to the presence of acquired or hereditary thrombophilia, has been connected to a numerous pregnancy complications such as recurrent early pregnancy loss, late miscarriage, pre-eclampsia, IUGR, placental abruption and intrauterine death [48]. Recently, the use of heparin in different forms has become very useful in assisted reproductive technology [48].

There are numerous publications describing the use of heparin as the treatment to prevent pregnancy complications in thrombophilia [49, 50]. A correlation between the fetal loss and the recurrent miscarriage with some acquired and inherited thrombophilias has been described [50]. Nowadays, the antiphospholipid syndrome (APS) is recognized as the most significant cause of recurrent pregnancy loss and growth restriction [49]. It has been noted that recurrent miscarriages in APS, and probably in connection with other thrombophilic changes, have been caused by thrombosis of the uteroplacental and fetoplacental vasculature and placental infarction [49]. Even though the thrombosis is very common in the decidua and placentas of patients with APS, it has not been proven that pregnancy loss is associated with APS [51]. The treatment with anticoagulant medications, is widely accepted as beneficial for both mother and the fetus in pregnant patients with APS [49-51]. It is suggested that causes of unexplained RPL and APS- associated RPL are comparable [50]. It has been described the presence of inflammation, thrombosis and infarction in the placenta and decidua of women with RPL. [52]. Because of this findings anticoagulant therapy, the most often in the form of LMWH, has been introduced as a treatment option during pregnancy including unexplained RPL [52]. The therapy with LMWH is probably useful in preventing RPL, but the optimal time for introducing the treatment is not confirm. Based on the hypothesis that the principle therapeutic effect of LMWH is the inhibition of thrombosis, some authors have advocated the treatment in the first trimester when the platelets become thrombophilic. The other researchers has been suggested that the main role of LMWH is improving implantation. Thus, beginning of therapy in RPL since the time of ovulation or even earlier has been recommended [53].

Qublan et al. described that heparin modulates the adhesion, apoptosis and cell-cell interaction in the time of the implantation. Heparin also induces in vitro trophoblast invasiveness via matrix metalloproteinases (MMP) [54]. Heparin has been also administered in in vitro fertilization protocols in women with thrombophilia and was correlated with improved pregnancy outcome in this group of patients [54]. It was reported that in patients with thrombophilia and with the recurrent in vitro fertilization-embryo transfer (IVF-ET) failure, administration of heparin improves the implantation and pregnancy rates compared with the placebo group when be-
gan from the time of embryo transfer [54]. In recent in vitro studies has been described that varied heparin preparations may produce similar effects on endometrial stromal cells by modulating their decidualisation [55]. It is not improved if systemically administered heparin may have direct contact with the blastocyst or increase its effects only on the decidual side of the embryo – maternal interphase.

The influence of heparin on pro-inflammatory cytokines including the leukemia inhibitory factor and granulocyte macrophage colony stimulating factor (GMCSF), both of which modulates first trimester extravillous trophoblast adhesion and invasiveness is well known [53].

Treatment with LMWH has become an accepted type of treatment during pregnancy because of its presumed anti-thrombotic mechanism of action and no requirement for the strict monitoring of coagulation parameters [56]. There are four main possibilities explaining the positive effect of heparin in decreasing RPL. Heparin may modulate cell-mediated or humoral immune response to preserve the production or change the mechanisms of action of antiphospholipid antibodies (aPL). Heparin may also have an antithrombotic effect regardless of aPL that overrides the action of antiphospholipid antibody. Heparin could also block the activity of aPL directly or indirectly and may simplify the elimination of antiphospholipid antibodies [55-57].

It was reported that heparin acts as an anti-inflammatory agent [56]. Salmon et al. has described in animal models that heparin disaccharides decrease tumor necrosis factor α (TNFα) production by macrophages, and reduce the immune-mediated inflammation [57]. Using mouse models of APS heparin has been found to inhibit activation of complement on the trophoblast [57]. The activation of complement has also been found in thrombophilia [53]. Apart from complement pathway, recent study implicates that heparin can bind Toll-like receptors and block dendritic cell activation [58]. The anti-apoptotic action of heparin involve inhibition of first trimester villous trophoblast apoptosis by stimulating the epidermal growth factor receptor survival pathway, and by blocking a PL-mediated trophoblast cell death [59, 60]. It is suggested that heparin inhibits villous trophoblast apoptosis in response to pro-inflammatory cytokines in a dose-dependent relationship [59]. Heparin can inhibit the depletion activity of trophoblast by impact on MMP, and by inhibiting tissue inhibitor of metalloproteinase (TIMP) [61].

Because of lower binding activity to plasma proteins, it is suggested that LMWH have a more predictable anticoagulant effect [56]. It was described that in patients with aPL and the RPL syndrome estimated a live-birth rate of 75% when UFH in combination with aspirin was administered [56, 62, 63]. Some studies suggest that a similar live-birth rate could be obtained with LMWH preparations [64].

It is suggested that heparin may inhibit binding of antiphospholipid antibodies by binds to and interferes with β2glycoprotein (GPI) [65]. Di Simone et al. have described that β2 GPI binds to heparin, which in turn might interfere with the aPL binding [66] and so it is probable that the positive effects of the administration of heparin in APS pregnancies may be caused by it preventing the interaction between these antibodies and β2 GPI. When very high doses of heparin were administered, a direct interaction of heparin with the antiphospholipid IgG binding to primary trophoblast cells has been demonstrated [51, 66].

It has been published that enoxaparin also probably have an inhibitory role in acute inflammation by blocking monocyte adhesion to the vascular endothelial cells, likely through inhibiting the expression of adhesion molecules on endothelial cells [67].

It is believed that heparin could facilitate embryonic implantation. Some authors have suggested that heparin could cause a significant increase in in vitro trophoblast invasiveness and differentiation [66]. In vitro studies demonstrated that LMWH restored placental invasiveness and differentiation in trophoblasts incubated with aPL in a dose-dependent manner [66]. The interferon gamma (IFN-γ), one of the cytokines expressed by decidual natural killers (NK) cells, has been shown to influence the endometrial vascular remodeling as well as the decidual differentiation [68]. The IFN-γ might also be involved in the pathophysiology of implantation failure and early miscarriage [69-71]. It was published that heparin inhibits the binding of the IFN-γ to human endometrial stromal cells (ESC) in the presence of a broad range of IFN-γ concentrations [72]. Hatakeyama et al. have found that heparin can increase the cellular motility in the first trimester extravillous trophoblast cells [72]. Other studies suggest that heparin may be directly connected with the adhesion of the blastocyst to the endometrial epithelium and the subsequent invasion [73]. Heparin can have a similar activity indirectly via heparan sulfate proteoglycans or heparin-binding epidermal growth factor (EGF) [73]. Heparin may inhibit the apoptosis of cytrophoblast and extravillous trophoblast cells [71]. It has been described that heparin can accelerate differentiation of extravillous trophoblasts into multinuclear trophoblast giant cells and can induce syncytial differentiation of cytrophoblasts in in vitro models when IgG from patients with APS were given [66].

It was previously reported that complement activation is a possible mechanism of antiphospholipid antibody-induced RPL in a animal model, in which pregnant mice received human IgG containing antiphospholipid antibodies or monoclonal antiphospholipid antibodies [52]. So, it is possible that the blocking of the complement activation by heparin could prevent antiphospholipid antibody-induced pregnancy loss [74].

**COMPLICATIONS OF HEPARIN AND LMWH ADMINISTRATION**

Serious complications can be associated with unfractionated heparin and LMWH therapy. Bleeding is a potential side effect of heparin administration [75]. Although the dose of unfractionated heparin and the intensity of its anticoagulative action contribute to the bleeding risk, other patient related factors are also important, for example antiplatelet therapy, serious diseases and recent surgery [75]. It was published that in patient treated due to acute VTE using UFH, the risk of serious bleeding was less than 3% [76]. In retrospective analysis of 19 trials, administration of LMWH was correlated with a significantly reduced frequency of serious hemorrhage compared with UFH (1.2% vs 2.0%, odds ratio = 0.57; 95% confidence interval [CI], 0.39-0.83) [77]. When
major bleeding may be observed in a patient on heparin (UFH and LMWH), during the whole pregnancy and most common in postpartum hemorrhage the anticoagulant activity can be reversed by the administration of protamine sulfate. For UFH, 1 mg of protamine reverses the effect of 100 units of heparin [75].

The heparin-induced thrombocytopenia (HIT) is an immune-mediated form of thrombocytopenia observed in 1–5% of patients exposed to heparinoids [78]. The HIT develops when antibodies of the IgG, or less commonly of the IgM or IgA classes react against complexes of heparin and PF4 and bind to platelet membrane receptors [78]. This binding leads to platelet activation with the release of procoagulant factors, the activation of other cells, and the resulting hyper coagulable state [78]. Thrombocytopenia has been described in this setting as a decrease in the platelet count to below the normal range even a 50% decrease in the platelet count from the pretreatment value [78]. The HIT begins 5 to 15 days after the starting of the therapy with UFH but sometimes, it could be observed within several hours [79]. If left untreated, up to 50% of patients with HIT can develop arterial or venous thrombosis, including deep vein thrombosis (DVT), stroke, arterial occlusion leading to limb loss, and pulmonary embolism [79]. The HIT is observed less often when LMWH is used compared to LMWHs than with UFH, 0.6% versus 3.5%, respectively [80]. It has been noted that the reduced binding between LMWH and platelets may account for the lower frequency of HIT [79]. However, in patients with HIT after UFH administration, the replacement of UFH with LMWH is not recommended, because the antibody which can induced HIT has an almost 100% cross-reactivity with LMWH [78]. The incidence of HIT during pregnancy is lower than in the nonpregnant population, especially when LMWH is used at either prophylactic or therapeutic doses [81].

Osteoporosis may be induced by heparin administration [82]. The correlation between the dose and the duration of administration and osteoporosis has been found, but the pathophysiological mechanisms are poorly understood [82]. Individual predisposition also may contribute to the progression of this prevalent and serious disease [82]. The risk of osteoporosis is very important in the obstetrics where pregnant patients may be exposed to heparin for longer periods than in other clinical situations [83]. Heparin-induced osteoporosis causes a vertebral fracture in 2-3% of patients and the significant reduction in bone density in about 30% of patients receiving long-term UFH [83]. The administration of LMWH causes less osteoporosis and HIT than the administration of UFH [80]. Subclinical osteoporosis, as measured by bone mineral density [80] has been observed in up to one third long-term UFH treated patients [83].

The limited data are available regarding the risk of LMWH-associated osteoporosis. In a study of 80 patients being treated with UFH or LMWH, the frequency of osteoporosis was smaller in the LMWH group than in the UFH group (2.6% versus 17.6%, respectively) [82]. In the study, published in 2008, prophylactic use of LMWH in pregnant patients and the risk of decrease in bone mineral density was analyzed. The risk was not significantly higher in this group. It is not explain whether higher doses might be a risk factor for osteoporosis [84].

Unfractionated heparin and LMWHs are not excreted into breast milk and can be safely used in women who are breastfeeding [82]. Molecules of UFH cross the placenta only minimally if at all, and LMWH does not cross the placenta. So, heparins do not induce fetal bleeding or teratogenicity, although bleeding at the utero-placental junction and fetal loss are possible.

**ORAL HEPARIN**

There is still an unmet medical need to produce a safe and effective oral anticoagulant for patients to use on a long-term basis. The goal of this new formulation is to attain the highly effective clot-prevention ability of parenteral heparin with an easily administered oral form of the drug. Because of this need to produce an oral form of heparin researchers use a new oral drug delivery technology that enables absorption of the molecules in the gastrointestinal tract [85]. LMWH have a more useful molecules for intestinal absorption in comparison with UFH when formulated with an absorption enhancer [85]. Oral heparin preparations can be used as an alternative to both “classic” heparin as well as other oral anticoagulants such as warfarin. The main disadvantage of heparin therapy is the parenteral route of administration. It is thought that the oral route is the most convenient and acceptable for patients. The few types of oral heparin are described, e.g. enteric coating materials, intrapulmonary aerosol of sodium heparin [85]. Because of the relatively large size and the negative charge of the heparin molecule oral absorption of UFH administration is very poor [86] and inadequate to provide optimal therapeutic response. The major barriers hindering the oral delivery for heparin comprise enzymatic degradation caused by a heparinase which is presented in the liver, the intestinal microflora including Bacteroides spp., the reduced chemical stability at the acidic pH of the stomach and a reduced absorption across the mucosal barrier in the gastrointestinal tract [86-89].

Due to the polarity of molecule the availability to the systemic circulation is limited as well [89]. It is thought due to problems as mentioned above the clinical usefulness of oral administration of heparin is limited [90].

The common strategies of improving on the therapeutic efficacy of heparin following the oral delivery are based on the following mechanisms [91]:

1. Enhancement of the cell-membrane permeabilization using bile salts and derivatives and polycationic lipophilic-core dendrons; partial dendrimers
2. Tight-junction changes with the potential use of absorption enhancers
3. Enhancement of the drug lipophilicity
4. Protection from the acidic pH of the stomach

The ion-pairing approach for increasing oral bioavailability of a polar molecule has several advantages [91]. Polycationic, lipophilic-core dendrons filled with LMWH have also been produced and trials were conducted for their effectiveness as the enhancer of intestinal mucosal penetration [91]. It has been proposed that polyanionic LMWH composing ion-
pair complex with polycationic dendrons may have improved diffusion through the mucosa of the gastro-intestinal tract [92].

The carrier molecules, which are consisted of small organic compounds (200–400 Da), interact with the drug molecules to form a weak, non-covalent association and the drug remaining chemically unchanged. One of the carriers is the sodium N[10-(2-hydroxybenzoyl) amino] decanoate (SNAD). Combining UFH with the other carrier molecule, sodium N-(2-hydroxybenzoylamino) caprylate, or SNAC form a non-covalent interaction that allows the passage of this complex through the mucosa of the gastrointestinal tract and into the bloodstream [92]. The heparin plasma concentrations achieved with the oral heparin-SNAC (aPTT, anti-factor Xa assay) reached the therapeutic range in human studies, and were found to be effective in decreasing the incidence of DVT in experimental rats and apparently was effective in prophylaxis of thrombosis. These results were very similar to those where the heparin was subcutaneously injected [93, 94].

In the initial clinical studies the objectives of the oral heparin-SNAC preparation were to demonstrate; a) the safety and tolerability of unformulated solutions of heparin/SNAC combination, b) that heparin without SNAC administered orally is not absorbed, c) that SNAC by itself has no effects on coagulation, and d) to establish the minimal dose of oral heparin required for a pharmacological effect when combined with maximal safe dose of SNAC [95].

It was described that oral heparin-SNAC decreased the incidence of proximal venous thrombosis in patients who have had hip replacement surgery in a dose-dependent manner in comparison to a standard LMWH administered parenterally [95]. Baughman et al. (1998) reported an anticoagulant activity of the oral heparin in humans when it was co-administered with an absorption enhancer SNAC [93]. Heparin, given orally binding with the SNAC, induces significant increasing in 4 indexes of anticoagulant effect in healthy human volunteers.

With each oral dose of heparin, a significant and prolonged increases in aPTT, anti-factors IIa and Xa, and tissue factor pathway inhibitor (TFPI) levels were observed between 0 and 3 hours after the administration [95].

A new and completely others types of enhancers are thiolated polymers or so-called thiomers [96]. In opposite to low molecular weight enhancers, they are not absorbed from the mucosal tissue because of large size of molecule. Thiomers are mucoadhesive polymers containing thiol groups, which are responsible for strongly improved mucoadhesive and permeation enhancing properties [96].

It has been described that thiomers reduce oxidized glutathione to GSH and following thiol group of these polymers is oxidized to disulphide bonds, which provide enhancement of its mucoadhesive force [97]. The addition of reduced glutathione (GSH) being very poorly absorbed from the gastrointestinal tract (GIT) cause a increasing uptake of LMWH from the GIT in rats [90, 96].

The other possible penetration enhancers are fatty acids and their salts. They change the phase transition temperature of the lipid correlated with the mucosal membrane and thus enhance its permeability by increasing the fluidity of the intercellular lipid bilayers [97].

Chitosan is a non-toxic, mucoadhesive, biocompatible polymer that has found a number of applications as a absorption enhancer. The use of chitosan derivatives or thiolated polymers alone or with glutathione, EDTA, and thiolated polycarbophil, demonstrated a powerful ability to increase the absorption heparin administered orally [98].

The efforts of using as a enhancers the polymeric drug delivery systems which include hydrogels, nanoparticles, as well as lipid-based drug delivery systems, eg, microemulsions, liposomes, and solid lipid nanoparticles, has been described [99, 100]. They seem to improve the transfer of the drug through the mucosa and protect against the enzymatic degradation [97].

In a recent study a drug delivery system consisted of thiolated polycarbophil and glutathione compared with unchanged polycarbophil, improved the permeation and bioavailability of LMWH after oral administration [98-100]. It has been described that when the delivery system contains 3 kDa LMWH, a relative bioavailability of 19.1% was reached compared to hydroxyethylcellulose (HEC) as control enhancer (8.1% bioavailability). In case of 6 kDa LMWH, the relative bioavailability of 10.7% was noted, which was significantly lower than 3 kDa LMWH. This data confirmed the usefulness of this systems in oral administration of LMWH [100].

UFH and LMWH have been used for many years. Although after their administration serious side effects could be observed, such as bleeding, heparin-induced thrombocytopenia, and osteoporosis the heparins are well acknow-
edged, managed and it is unlikely that new side effects will be discovered with further use of these drugs.

An oral form of heparin could be a better option for the patients. However, no oral form of heparin has reached the market to date.

**FONDAPARINUX**

Pentasaccharides are new synthetic antithrombotic medications that accelerate the interaction between the factor Xa and antithrombin by inducing a conformational activation of antithrombin [101]. In contrast to UFH and LMWH, pentasaccharides do not influence on the interaction between antithrombin and thrombin and thus selectively inhibit the factor Xa activity [25].

Fondaparinux sodium is the first in a new class of selective, indirect factor Xa inhibitors. Fondaparinux is a synthetic analogue of the pentasaccharide sequence found in UFH and LMWH and is produced by total chemical synthesis. The structure of fondaparinux was changed to increase its relatedness to AT [101]. Fondaparinux has a molecular weight of 1,728Da. The anti-factor Xa activity of fondaparinux is higher than that of LMWH (about 700 U/mg and 100 U/mg, respectively). Fondaparinux has a longer half-life after injection than LMWHs (17 h and 4 h, respectively) [102]. It was described that fondaparinux has no direct effect on thrombin activity but may change thrombin generation by inactivation of factor Xa in a linear and dose-dependent fash-
ion that plateaus at nearly equimolar fondaparinux and ATIII concentrations [102]. It has been also revealed that fondaparinux may inhibit clot-bound factor Xa, but not factor Xa within the prothrombinase complex [103]. When released from ATIII, fondaparinux can influence on its action again [104]. Fondaparinux has a favorable pharmacokinetic profile after parenteral administration including rapid and complete absorption (maximal concentration by approximately 2 hours). Due to this profile and because of predictable dose response it can be given in fixed doses without blood coagulation parameters monitoring [104, 105].

Fondaparinux is not metabolized in liver and is almost completely excreted by the kidneys as the unchanged compound. Fondaparinux does not cross the placenta in vitro [105]. Because fondaparinux is a totally synthetic molecule it eliminates the risk of pathogen contamination associated with animal-sourced agents in comparison both to UFH which is extracted from animal tissues and to LMWHs which is derived from heparin. There is no specific antidote for fondaparinux when serious bleeding is observed, whereas protamine sulfate can neutralize UFH completely and LMWHs partially [105]. Fondaparinux does not affect platelet function [103] and can inhibit thrombin generation in the presence of platelets.

As a heparin analog, fondaparinux have been accepted for the use as a prophylactic and therapeutic agent in VTE, i.e. deep vein thrombosis-DVT and pulmonary embolism-PE and for the treatment of acute coronary syndromes [105]. There are no published specific data about using of anticoagulant agents in pregnant patients with metabolic syndrome. A few studies about using of fondaparinux in obese patient have been published [106].

Due to its high bioavailability, predictable dose response and a distribution volume limited to blood volume, fondaparinux is supposed to have good tolerability in obese patient [106]. In all clinical trials of fondaparinux obese patients were not excluded [107, 108]. Several VTE prevention trials specifically pay the attention to the ratio of obese patients, for example 53% of the patients with BMI above 30 kg/m2 in PENTAMAKS trial [107] and 25% in PENTHIFRA trial [108] but no dose modifications were made. Eikelboom et al. [109] used the data from all prophylaxis trials (n = 13085) to assess risk factors for serious bleeding and mortality. The obesity was not connected with the serious bleeding or mortality.

In has been found in ex vivo model, that fondaparinux does not cross the placenta [110]. Small placental transfer may be demonstrated using chromogenic assay of anti-factor Xa activity (anti-Xa) and of activated-partial thromboplastin time (aPTT) in umbilical blood from pregnant patients treated with fondaparinux 2.5 mg daily [110]. But the concentration of fondaparinux was very low and no side effects were noted. It has been described in a number of studies successful prophylactic administration of fondaparinux in pregnant patients [110-112]. There were no difference in pregnancy success rates, miscarriage, gestational age at the time of delivery and fetal weight. No serious complications have been noted. In recent published article Knol et al. reports on 12 pregnancies with administration of fondaparinux 2.5 mg due to VTE. The pregnancy success rate was 100%. It has not been observed thromboembolic complications, no congenital abnormalities, no bleeding complications in the newborn and no excess of bleeding in the mothers [111]. This results clearly indicating high level of safety of this efficacious synthetic heparin analog.

Stopping of administration of fondaparinux is recommend 24 hours before labour or when the first contractions of the uterus are observed [111]. In post-delivery period, application is possible after 6 hours or after 12 hours after removal of a catheter, when epidural anesthesia was applied [111].

Fondaparinux seems to be safe and effective in patients with thrombophilia. It has not been observed repeated thrombembolic complications and only in one patient the small bleeding was occurred during the administration of fondaparinux [112]. It was published a few case reports about the successful treatment with fondaparinux of patients with APS and of patients with antithrombin deficiency [74, 111, 113]. But recent animal studies revealed that fondaparinux does not prevent the antiphospholipid antibody-induced miscarriage, in spite of achieving anticoagulation serum concentration compared to heparin. These findings suggest that administration of anticoagulants may not be sufficient to prevent miscarriages in patients with APS [74]. It has been described that fondaparinux does not bind to PF4 and does not exhibits inhibitory effect on platelet aggregation, clinical HIT and its related complications are very rare [114, 115].

The frequency of HIT antibody formation with fondaparinux is comparable to that with LMWH. It suggests that antibody formation alone is not sufficient to induce thrombocytopenia [115]. It is thought that the heparin chain must be of appropriate length to cluster PF4 particles together for the antibody binding [114, 115]. A possible disadvantage of fondaparinux is in its reduced ability to catalyze the inhibition of factor Xa by antithrombin when compared to heparin [114]. Even though the rate of factor Xa inhibition by antithrombin is increased about 100-fold after fondaparinux administration, heparin produces a 1000-fold increase in this rate [116]. This one order of magnitude difference reflects the capability of longer heparin chains to bridge antithrombin to factor Xa. The capability for such bridging has been ignored in studies performed in plasma systems because the heparin-binding site on factor Xa is only available in the presence of calcium and factor Xa tests are typically performed in citrated plasma [116].

**VITAMIN K ANTAGONISTS - WARFARIN**

Vitamin K antagonists (VKAs) or the coumarins belong to the group of most frequently used drugs worldwide. There are no published specific data about using of anticoagulant agents in pregnant patients with metabolic syndrome.

Warfarin is the most common VKA in clinical use. It was originally introduced as a pesticide against rats and mice. It is the most widely used oral anticoagulant due to its onset and times of action are predictable and because following oral administration it has a 100% bioavailability. The VKAs exhibit their anticoagulant effect by inhibition of vitamin K epoxide reductase, and in this manner activating hepatic pro-
duction of partially carboxylated and decarboxylated proteins with decreased procoagulant activity [117].

It has been described, that vitamin K is a cofactor for the post translational carboxylation of glutamate residues to gamma-carboxyglutamates on the N-terminal regions of vitamin K-dependent proteins [118]. The VKAs are synthetic vitamin K analogues which change vitamin K metabolism, activating of the vitamin K-dependent formation of biologically active forms of clotting factors II, VII, IX and X.

These coagulation factors require gamma-carboxylation for their biological activity [118]. It is believed that oral anticoagulants also can inhibit the synthesis of the vitamin K-dependent anticoagulant proteins C and S and therefore possess the potential to change a procoagulant effect. When the calcium ions are presented, carboxylation activate a conformational modification in coagulation proteins and these changes promote binding to cofactors on phospholipid surfaces. It is known that VKAs also interfere with the carboxylation of Gla proteins synthesizing in bone [119]. Therefore, it may cause fetal bone abnormalities when VKAs are administered during pregnancy [120, 121]. It is unclear how they might affect children.

Warfarin is a natural product and chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and exist in a racemic mixture of the R- and S-enantiomeric forms. S-warfarin is 3-5 times more forceful an inhibitor of the vitamin K epoxide reductase complex, the goal of action, than R-warfarin [120]. Warfarin has high bioavailability, is quickly absorbed from the gastrointestinal tract, and achieves maximal blood level in healthy volunteers in 90 min after oral administration. Racemic warfarin has a half-life of 36 to 42 h [122] (R-warfarin, 45 h; S-warfarin, 29 h respectively); and is mainly bound to albumin, and accumulates in the liver, where the two enantiomers are metabolized in the different pathways [122]. The S enantiomer of warfarin is metabolized mainly by the CYP2C9 hepatic microsomal system of the cytochrome P450 [123]. Some genetic polymorphisms in this enzyme is observed and it is correlated with lower dose requirements and higher risk of serious bleeding complication in comparison with the wild-type enzyme CYP2C9 [124, 125]. It has been noted, that the less forceful R enantiomer is metabolized mainly by two cytochrome enzymes, 1A2 and 3A4 [123].

A full anticoagulant effect of warfarin typically requires 72 hours after oral administration of the first loading dose. Therefore, an overlap period of 4-5 days of heparin treatment is generally required.

Factor VII has the shortest half-life (a few hours) whereas factors II, VII, IX and X have half-lives of 8 to 72 hours [123] that is why warfarin takes several days to have full anticoagulant effect. Warfarin demonstrates a high degree of binding to plasma proteins. Spontaneous haemostatic recovery from warfarin may take 72 hours or more. The use of vitamin K antagonists is limited because of the specific therapeutic index and an unforeseeable dose-response relationship, and depends on these agents frequent bleeding complications or insufficient anticoagulation can be observed. The clearance of warfarin and the response to this drug can be changed by genetic differences in metabolic enzymes, interactions between drugs, diet, and comorbid diseases. The response to warfarin depends on the pharmacokinetic and pharmacodynamic factors as well, which change the hemostatic response to dose for administered drug [126, 127]. For example, cholestyramine which could be used in cholestasis of pregnancy may reduce the anticoagulant effect of warfarin, because of changing of its absorption profile. It has been observed that the response to warfarin is heightened by the second- and third-generation cephalosporins, which inhibit the conversion of vitamin K [128, 129] and by thyroidine, which can intensify the metabolism of coagulation factors [130]. Hepatic dysfunction potentiates the reaction to warfarin via narrow-minded synthesis of coagulation factors. Other drugs could potentiate the anticoagulant effect by inhibiting warfarin clearance via stereoselective or nonselective pathways. The types of interactions may change oxidative metabolism of either the S- or R-isomer of warfarin [127].

Warfarin requires laboratory monitoring which is based on the prothrombin time (PT) and it is the most common laboratory test which is applied to monitor oral anticoagulant therapy. The PT is changed because of the reduction of 3 of the 4 vitamin K-dependent procoagulant clotting factors (II, VII, IX and X) that are decreased by warfarin proportionally to their respective half-lives [131]. Variability in reagents used to determine PT has led to international standardization of the assay, now known as the international normalized ratio (INR), a PT-based measure of the anticoagulant effect [131].

It has been described that administration of warfarin be avoided in the first trimester of pregnancy because it is correlated with a characteristic combination of fetal malformations called warfarin embryopathy [132]. Coumarin embryopathy includes midface hypoplasia, scoliosis, short proximal limbs, short phalanges and stippled chondral calcification. It may be observed after exposure to coumarin between 6 and 9 weeks of gestation, occurs in around 5% of the fetuses exposed to coumarin at this stage in pregnancy. It has been noted that the risk of the warfarin embryopathy can be dose-dependent to increase with doses greater than 5mg/day [132]. Because warfarin anticoagulates the fetus, its use in pregnant patients is also associated with fetal bleeding complications and may cause the central nervous system abnormalities, higher rates of intrauterine fetal death and pregnancy loss [133]. The true incidence of warfarin embryopathy is unclear [133]. It is believed that exposure to warfarin in second and third trimester of pregnancy is not correlated with warfarin embryopathy.

It was published several reports about serious maternal complications (increased maternal haemorrhagic and thromboembolic risks) [134, 135] in patients with prosthetic heart valves. This lead to recommendations that warfarin be used instead of heparin in pregnant patients with mechanical heart valves. Therefore, an overlap period of 4-5 days of heparin treatment is generally required.

Although heparin failure in such patients could be caused by inappropriate dosing, it also is possible that heparin is no so effective anti thrombotic agent as warfarin [134, 135]. Compared to heparin oral anticoagulants, better stabilise the anticoagulation effect and thereby reduce the risk of serious bleeding and thromboembolic events. It has been reached a consensus for their use during the second and most of the
third trimester but not during the peripartum period [135]. Heparin may increase the frequency of thromboembolic incidents [135, 136], especially during the critical period of changing from heparin to oral anticoagulant [135, 136]. Recognition of this dangerous therapeutic switch prompted some authors to suggest the exclusive use of oral anticoagulants within the first trimester of pregnancy [137] when the required dose of warfarin is low. Generally speaking, low doses of warfarin may be adequate when the target INR is between 2 and 3, as in patients with the third generation aortic valves who are in the sinus rhythm [136, 137]. After implantation of mitral valves in patients with atrial fibrillation or sinus rhythm require an INR between 3 and 4.5 [136, 137]. In these patients, the required anticoagulant dose is typically higher. Due to the high dose of warfarin the risk of embroyopathy is increased and in this group the use of heparin for the end of the first trimester is recommended. It is thought that warfarin should be replaced by intravenous or subcutaneous heparin at the 37th week of gestation [136, 137].

Recently, it has been noted that prenatal exposure to coumarins is correlated with a higher risk of minor neurological dysfunction or a low intelligence quotient in school age children [133]. The use of VKAs is also correlated with a higher risk of maternal and neonatal hemorrhagic complications. It was described that the Vitamin K dependant coagulation factors levels are low in the fetal liver. Drugs such as aspirin [138], nonsteroidal antiinflammatory drugs [139] and high doses of penicillins [140, 141] increase the risk of warfarin-associated bleeding due to platelet function. Low doses of aspirin, 75-100 mg/day which could be used during pregnancy were correlated with higher risk of minor bleeding when warfarin in low and moderate doses was administered concomitantly (target INR 2.5) [138].

Although coumarins cross the placenta but they are not secreted in breast milk in clinically significant concentrations and there are no contraindications to use these agents during the lactation period [142].

It was described in warfarinised patients that when INR levels are above the therapeutic range it correlates well with bleeding [132]. Strict anticoagulant control will therefore help to prevent such complications. Therapeutic control of anticoagulation with warfarin is more complicated during pregnancy because of physiological changes in the haemostatic system and the expanding plasma volume. Regular monitoring of the INR is therefore advisable during pregnancy [132].

Skin necrosis, non-haemorrhagic complication of therapy with VKAs is observed not so frequently [132]. It is caused by thrombosis of venules and capillaries in sub-cutaneous fat tissue and it may be related to depletion of the internal anticoagulants protein C and S after the beginning of therapy because of a transient heightened coagulability [132]. Protein C deficiency is a major risk factor of serious complications in warfarinised patients. In this group of patients, who may be prophylactically treated by VKAs in the postnatal period, it is advised to avoid high loading doses of warfarin and to ensure appropriate overlap with heparin for at least 4-5 days until the INR is in sufficient therapeutic range [132]. The disorder is more often observed in patients with unrecognized protein C or S deficiency [132]. Starting a therapy with low doses of vitamin-K antagonists and simultaneous administration of heparin, particularly if protein C or S deficiency is known or suspected may prevent a withdrawal of this complication [132].

Vitamin K antagonists may cause a variety of health problems in pregnancy and therefore heparin is usually the anticoagulant of choice in the antenatal period [134]. However, warfarin may be introduced safely in the puerperium and is generally a more convenient method of anticoagulation therapy. In the postnatal period in patients who suffer DVT or pulmonary embolism warfarin and heparin may be administered simultaneously as in non obstetric practice, and continuing heparin until the INR is in the therapeutic range A minimum overlap period of heparin administration of 4 days is advised.

ACETYL SALICIC ACID - ASPIRIN

Aspirin has been known as an analgesic, antiinflammatory and antipyretic drug. In last decades, administration for vascular and antiplatelet effects have been added. As the latter is a forceful platelet aggregator and vasoconstrictor, the effect of aspirin is anti thrombotic. Administration of low-dose aspirin inhibits thromboxane production more than prostacyclin production. Thus, it is thought that aspirin may prevent vasoconstriction and pathologic blood coagulation in the placenta [143]. Aspirin is the most popular and the most widely used antiplatelet drug.

Aspirin inhibits arachidonic acid metabolism by inactivating the cyclooxygenase (COX) enzyme system. The precise mechanisms of action of aspirin is related to inhibition the cyclooxygenase (COX) activity of prostaglandin H-synthase-1 and prostaglandin H-synthase-2 (also referred to as COX-1 and COX-2, respectively) [144]. COX isozymes catalyze the first reaction in prostanoid biosynthesis, the conversion of arachidonic acid to prostaglandin H₂ (PGH₂). PGH₂ is the direct precursor of TXA₂ and PGI₂ [144]. Aspirin acts by irreversibly acetyling a serine residue at position 530 (Ser 530) located 70 amino acids from the C terminus of the enzyme. After acetylation the irreversible COX inhibition is observed. Due to these reactions a new enzyme must be formed before more prostanoids are synthesized. When the purified enzyme is acetylated, only the COX, not the hydroperoxidase, activity is inhibited [143].

Aspirin in low doses, 75-100 mg/day almost completely inhibits cyclooxygenase in both platelets and arterial walls. It has been observed that inhibition of COX-2-dependent pathophysiology processes (eg, hyperalgesia, inflammation) requires higher doses of aspirin administered at a much shorter dosing interval. It is caused by rapid resynthesis the enzyme by nucleated cells. Due to this reaction 10- to 100-fold higher daily doses of aspirin are required in antinflammatory administration of the drug compare to antiplatelet administration. The plasma concentration of aspirin decreases fast with a half-life of 15 to 20 min [144]. In spite of the rapid clearance of aspirin from the circulation, the platelet-inhibitory effects last the life of platelets because aspirin irreversibly inactivates platelet COX-1 [143]. Aspirin can inhibits thromboxane production in newly created platelets as well as in circulating platelets because of its megakaryocyte COX-1 acetylation [143].
After a prolonged treatment with aspirin, the recovery of thromboxane production and thromboxane-dependent platelet aggregation is quicker than what would be anticipated based on the rate of platelet turnover. It can be caused by the nonlinear correlation between inhibition of platelet COX-1 activity and TXA2 biosynthesis. The potential role of the small quantity of thromboxane produced by nonaspirinated platelets to sustain thromboxane-dependent platelet aggregation is also emphasized [143]. Aspirin suppresses the blood concentration of inflammatory markers, C Reactive Protein (CRP), TNF-alpha, IL-6 and TXB2 and the platelet aggregation mediator TXA2 in patients with metabolic syndrome [145].

It was reported recently that aspirin’s traditional mechanism of action does not explain the mechanism of anti-inflammatory activity of this drug [143, 146]. A leukocyte-targeting mechanism was discovered, which involves aspirin-triggered lipoxins (ATL) biosynthesis from arachidonic acid via acetylated COX-2. This new mode of action of aspirin during cell-cell communication between cells bearing COX-2 enzyme such as vascular endothelial cells or epithelial cells, and leukocytes is called transcellular biosynthesis [130]. Aspirin acetylates COX-2 and re-directs the catalytic activity of COX-2, to forming another intermediate, 15(R)-hydroxyeicosatetraenoic acid [147]. ATL also induces nitric oxide synthesis [148]. ATL cause the resolution, the final stage of inflammation response and is an angiogenic and immune modulator, which shows promise in the possible treatment of preeclampsia [147]. It was published that the generation of reactive oxygen species in endothelial cells is blocked by ATL [149]. ATL is a strong anti-inflammatory factor, inhibiting cell chemotaxis of polymorphonuclear neutrophil cells, leukocyte-endothelial interaction [150], nuclear factor kappa B activation [151], and tumor necrosis factor-alpha (TNF-α) secretion in activated T cells [152].

A number of reports address the efficacy of aspirin for disorders of pregnancy [153] which was shown to be effective in reported studies and meta-analyses [154]. It is thought that aspirin administration is not to be able to completely prevent but only cause a reduction of frequency and intensity of pregnancy complications, such as preeclampsia, intrauterine growth restriction, placental abruption, and intrauterine or neonatal death [155]. In systematic review of 59 clinical trials involving a total of 37,560 patient investigating anti-platelet therapy for prevention of PE it was reveal that low-dose aspirin therapy reduces the risk of preeclampsia by approximately 17% [144, 156]. There is evidence indicating that the complication-reducing effect is restricted only to high-risk patients (e.g. with severe preeclampsia or IUGR in the previous pregnancies) [157]. In low-risk patients, aspirin was not effective in decreasing the risk. Robege et al. have described that this effect for aspirin is higher if administered in high-risk patients before 16 weeks of pregnancy compared to administration after this week [157]. The women with high risk of preeclampsia are identified by different methods and it could be a reason why in several studies only moderate effect of aspirin or even no effect at all was found [158]. It was reported that the use of biophysical and sonographic methods can be more effective in identifying patients at high risk of pregnancy complications [159]. It was also described that UFH and LMWH alone or together with aspirin may have beneficial effects in high-risk pregnancies to prevent PE and IUGR [160].

It has been published in several studies that aspirin can be used in treatment pregnant patients with recurrent pregnancy loss (RPL) associated with antiphospholipid syndrome (APS), an acquired or hereditary thrombophilia, and other autoimmune conditions [62]. In women with RPL associated with antiphospholipid syndrome (APS), treatment with aspirin and heparin has been proposed to improve the pregnancy outcome, but not in all reported randomized trials [62, 64, 161]. It has been discussed why anticoagulant therapy in women with unexplained RPL may improve the pregnancy outcomes. It is suggested that in some patients thrombotic damage and increased generation of thrombin may not be recognized by routine laboratory testing [162, 163].

It was published that in women with history of RPL the shift in the thromboxane A2: prostaglandin I2 ratio is changed and it can lead to vasoconstriction and platelet aggregation in the trophoblast and can cause thrombosis and placental necrosis. It is very often observed in the placentas of women with recurrent pregnancy loss [164]. It has been thought that use of a combination of heparin and aspirin in women with APS has been established as a gold standard treatment [51]. In RPL it is important to separate the first trimester embryonal loss from the stillbirth after placental formation because their respective etiologies are different. Low dose aspirin significantly improves the live birth rate amongst patients with a previous late pregnancy loss [64]. Low-dose aspirin therapy may be effective in preventing some cases of RPL with undiagnosed etiology. Although there have been a few reports of adverse side-effects of aspirin, such as increasing congenital anomalies and hemorrhage [165, 166] this needs to balanced against the clear benefits in some patients with a history of pregnancy loss.

Although most data suggests that aspirin is a safe and effective drug during pregnancy, there have been a few reports of important complications. In animal model, aspirin may increase the risk of congenital abnormalities, but human observations are conflicting. It has been described specific types of malformations after aspirin administration, such as congenital heart defects, neural tube defects, cleft palate, gastrochisis, central nervous system and pyloric stenosis, but no higher risk was found in a large cohort study [165, 166]. In meta-analysis of twenty-two studies Kozer et al. have found that the risk of congenital abnormalities in newborns of women who were exposed to aspirin was not significantly higher than that in control group. However, a significantly higher risk of gastrochisis (odds ratio, 2.37; 95% CI, 1.44-3.88) was found [167]. The side effects of aspirin in the mother have often been discussed and osteoporosis, pancytopenia and prolonged labor, suggested but remain controversial [165].

In all cases the risk of the possible benefits and disadvantages of aspirin administration should be analyzed individually.

Patients with metabolic syndrome have a high risk of cardiovascular incidents. Clinical trials researching the role of aspirin in primary prophylaxis have led to an adjustment in the recommendation for aspirin in metabolic syndrome patients at intermediate risk of a cardiovascular incidents.
Platelet hyper-reactivity/activation plays a central role in the acceleration of the course of atherosclerosis [168]. It is thought that it is the result of the interaction between the features clustering in obesity and MS [168]. It was noted that the same pathogenic events can be responsible for the less than expected response to antiplatelet agents, for example low-dose aspirin [153]. MS is a significant risk factor for drug resistance. Paul et al. (2013) have found significantly enhanced antiplatelet drug resistance in the patients with MS [169]. In another study, 8-45% of the population has been found to be aspirin resistant [170]. However, biochemical in vitro study results may not match with in vivo pharmacokinetics [171]. Various theories have been put forward to explain mechanisms of aspirin resistance like non-thromboxane mediated platelet activation, genetic polymorphism, or hyperlipidemia-induced increased sensitivity to collagen [171]. In these patients, probably higher dose of the drug is needed for therapeutic benefit. Platelets in diabetic patients are activated with increased expression of surface adhesion molecules and receptors, and also with disturbances in calcium homeostasis and prostaglandin pathways [172]. Another potential mechanism may be oxidative stress, which increases isoprostane production from arachidonic acid and thus increases the thromboxane pathway activation [173]. Despite of this problems it is suggested that the use of aspirin may be beneficial in decreasing the risk of cardiovascular incidents in patients with metabolic syndrome [168].

NEW ORAL ANTICOAGULANTS

Idraparinux, idrabiotaparinux, apixaban, otamixaban and edoxaban are novel oral anticoagulants currently in use, and several others are at advanced stages of development. There are currently no safety data for these agents in pregnancy or breastfeeding therefore, current guidelines recommend that all new anticoagulants should be avoided in pregnancy and during breastfeeding [174].

CONCLUSIONS

In summary, the anticoagulant treatment during pregnancy has benefited from recent progress in therapeutic benefits and a better understanding of the possible disadvantages of anticoagulants. There are no published specific data addressing the use of anticoagulant agents in patients with metabolic syndrome except for a few articles discussing reproductive problems.

In a pregnant patient with metabolic syndrome hepatic disorders are the most common drugs in prophylaxis and treatment of VTE and other special clinical situations because of their safety not only for the patient but for the fetus as well. In specific clinical situations coumarin class of drugs, aspirin and fondaparinux could be used as well. There are currently no safety data for using new anticoagulants in pregnancy or in breastfeeding. Currently, all new anticoagulants should be avoided in pregnancy and during breastfeeding.

CONFLICT OF INTEREST

All coauthors declare that they do not have any possible conflict of interest.

STATEMENT OF AUTHORSHIP

All authors have made substantial contributions to the writing and/or review of the manuscript. All authors have approved the final manuscript.

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