Fetal and neonatal effects of anticoagulants used in pregnancy: a review

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There are several relative (promising regarding a reduction in placenta-mediated complications such as preeclampsia) and absolute (e.g. a recurrent or recent thromboembolic event, mechanical heart valves) reasons for use of anticoagulant drugs during pregnancy. Warfarin readily crosses the placenta because of its low molecular weight, and is associated with a distinctive embryopathy known as fetal warfarin syndrome when exposure occurs between the sixth and twelfth weeks of gestation. Warfarin embryopathy may be avoided by stopping warfarin and switching to heparin when pregnancy is achieved or as soon as possible after conception.

Heparins, unfractionated heparin and low molecular weight heparin are the preferred agents for anticoagulation in pregnancy because they show no transplacental passage due to their high molecular weights. Both heparins and warfarin are safe for the infant during breastfeeding. Aspirin is prescribed with increasing frequency to reduce the risk of miscarriage and poor pregnancy outcome. Although aspirin crosses the placenta, it is safe in low doses. However, the safety of higher doses of aspirin during the first pregnancy is uncertain.

Key words: anticoagulants, aspirin, fetus, newborn, heparin, warfarin.

Recurrent miscarriage is a major health problem, with 5% of women of reproductive age having two or more miscarriages and approximately 1% having three or more. Most of these pregnancy losses remain unexplained, and there is no effective treatment; many hormonal and immune therapies have been tried, despite a lack of evidence of efficacy. There is a possibility that unexplained recurrent miscarriage may reflect a prothrombotic phenotype, and that miscarriage in affected women may result not only from thrombosis but also from adverse effects of coagulation-cascade activation on the developing trophoblasts. These possible mechanisms suggest the potential for antithrombotic therapy to have benefits beyond its anticoagulant effect in reducing the rate of recurrent miscarriage.[1]

Acquired thrombophilia and heritable thrombophilias, such as factor V Leiden and the prothrombin G20210A mutation, are not yet established as a cause of the placenta-mediated pregnancy complications (pregnancy loss, preeclampsia, small-for-gestational age and placental abruption). A thrombophilia may be only one of many factors that lead to development of these complications. The association between thrombophilia and placenta- mediated pregnancy complications is far from proven. The small step of previously describing an association in case control studies has led a large number of clinicians and opinion leaders to take the large leap of accepting this relationship as being causal and potentially treatable with anticoagulant interventions. Furthermore, while data in women with prior severe preeclampsia, abruption and small-for-gestational age births without thrombophilia suggest some promise for anticoagulant prophylaxis to prevent complications in subsequent pregnancies in these women, in the absence of large well-done and generalizable "no intervention" controlled studies, adopting anticoagulant prophylaxis to prevent these complications is premature. The absence of strong evidence coupled with the

small potential for harm from anticoagulant prophylaxis suggests that these drugs should be considered experimental in thrombophilic and non-thrombophilic women with prior placenta-mediated pregnancy complications.[2]

While treatment with heparin appears promising, with a reduction in placenta-mediated complications (such as preeclampsia, small-for-gestational age, placental abruption) in women without thrombophilia[3], neither prophylactic heparin combined with low-dose aspirin nor aspirin alone improves the rates of live births, as compared with placebo, in women with recurrent pregnancy loss.[4-6] In addition, the number of studies and participants included was small, and to date, important information about serious adverse infant and long-term childhood outcomes is unavailable.[7] Nevertheless, offering these women anticoagulation is relatively common.

There are several absolute indications for anticoagulation treatment during pregnancy. Pregnancy and the postpartum period are especially thrombogenic. Any condition requiring anticoagulation (e.g., a current or recent thromboembolic event or mechanical heart valves) that would normally be treated in non-pregnant patients should generally be treated in pregnant patients as well. In clinical practice, low-molecular-weight heparins (LMWHs) are much easier and more convenient for patients and physicians to use compared with unfractionated heparin (UFH). This is due to their long half-life and few side effects. There is also no need for frequent monitoring of partial thromboplastin time. One exception is thromboprophylaxis for patients with heart valve prostheses. Warfarin is still considered in pregnancy for women with mechanical heart valves because of their high risk of thrombosis even with UFH or LMWH anticoagulation therapy. Several reports, including one from the United States Food and Drug Administration (FDA), recommended not using UHF or LMWH for these patients during pregnancy. Why LMWHs are less effective for patients with this condition is yet to be determined.[8]

The purpose of this article is to review the fetal and neonatal effects of different anticoagulants.

Warfarin

Warfarin is a potent anticoagulant used in the management of a variety of thromboembolic disorders that depresses synthesis of vitamin K-dependent clotting factors. Warfarin readily crosses the placenta because of its low molecular weight, and is associated with a distinctive embryopathy known as "warfarin embryopathy (WE)" or "fetal warfarin syndrome" when exposure occurs between the sixth and twelfth weeks of gestation[9].

The manifestations are varied, ranging from stillbirths and abortions to a variable degree of dysmorphology and malformations involving different organs. Warfarin taken during the critical period of organogenesis (the 4th to 8th week after conception), carries a 15-20% (up to 30%) risk of congenital anomalies. The reported risk of spontaneous abortion and stillbirth is approximately 15-20% (up to 56%)[10-14]. There is a normal outcome in only 60% of at-risk pregnancies[11].

The severity and range of clinical manifestations of WE are variable. The characteristics of WE in the neonate are seen in the skeletal system. Nasal hypoplasia with deep nasal alar grooves and widespread epiphyseal and vertebral stippling (chondrodysplasia punctata) are the most consistent and classical features of WE[15]. X-ray reveals thinned out skull bones and absent nasal bone.

The pathophysiological basis of skeletal anomalies is interference in the process of osteocalcin carboxylation in bone formation, which is a vitamin K-dependent process[15].

Stippling of the epiphyses is a descriptive term used to demonstrate the radiological appearance of multiple calcific foci in abnormal developing bone. The stippling is thought to be due to the interference by warfarin with the formation of vitamin K-dependent protein and matrix G1a protein, present in endochondral pre-ossification. The differential diagnosis in the fetus and neonate includes the heterogeneous Conradi-Hunermann group of genetic conditions and, less frequently, skeletal dysplasia and chromosomal disorders[16].

Cleft lip and/or palate, choanal atresia or stenosis, microphthalmia, optic atrophy, cataract, malformed ears, coarctation of the aorta, situs inversus, bilobed lungs, ventral midline dysplasia, and limb hypoplasia have also been reported after *in utero* warfarin exposure[9,14,15].

Additionally, warfarin is thought to be associated with a 2-4% risk of central nervous system (CNS) abnormalities including hydrocephalus, mental retardation, spasticity, and hypotonia, but less severe warfarin-related CNS abnormalities occur at a higher incidence. These abnormalities can occur with warfarin exposure at any time during pregnancy[16,17].

Consequently, warfarin is rarely prescribed in pregnancy. The exceptional case is the patient at risk of mortality from thrombosis who may not be sufficiently anticoagulated with heparin. Candidates for warfarin in pregnancy include women with mechanical cardiac valves[18].

The optimal anticoagulation strategy remains unsettled. One of the most commonly suggested regimens involves the substitution of heparin for warfarin between six and 12 weeks' gestation[19]. However, substitution should begin at a much earlier gestational age because of the long half-life of warfarin. Following a single dose, the terminal elimination half-life is about one week, with a mean effective half-life of 40 hours[20]. To date, all existing guidelines have ignored this long elimination half-life. A policy of substituting heparin for warfarin starting at six weeks' gestation may be too late to avoid embryopathy[21]. It is safer to switch warfarin to heparin when pregnancy is achieved or as soon as possible after conception. However, since nearly half of the pregnancies are unintended even in developed countries, many women do not realize they are pregnant during the critical period for organogenesis, the fourth to eighth week postconception.

Warfarin should be used after 12 weeks' gestation. Recent data suggest that warfarin exposure even later than the eighth week after the last menstruation seems to be safe[22].

Low-dose warfarin has been advocated but there is evidence that fetal damage is not necessarily dose-dependent[23]. The classical manifestations are related to exposure during the first trimester even in low doses.

Placental transfer of warfarin later in pregnancy can result in fatal bleeding (e.g. intracranial hemorrhage) or stillbirth[10,11,13,24,25]. This is a particular concern at the time of delivery, when the combination of the trauma of delivery and an anticoagulant effect can lead to neonatal bleeding[22]. In most cases, maternal international normalized ratio (INR) is normal. Actually, the anticoagulant effect of warfarin in maternal blood does not correlate with its activity in the fetus. The main reasons for this predisposition are higher unbound warfarin levels in the serum of pregnant women than in nonpregnant subjects, immature drug metabolism in the fetal liver, and normally low fetal hepatic synthesis of vitamin K-dependent coagulation proteins that cannot cross the placenta. Fetal exposure to warfarin is further increased because of the poor development (or absence) of the glucuronide conjugation enzymatic pathway in the fetal liver and subsequently limited renal elimination of warfarin metabolites. By the same mechanism, warfarin also increases the risk of hemorrhagic disease of the newborn[26].

Warfarin should be discontinued after 34-36 weeks of gestation, and cesarean section (C/S) should be considered to avoid birth trauma[27]. Long-term anticoagulation should be restarted 12 hours after C/S and six hours after vaginal birth overlapping with heparin. Heparin could be stopped after INR has reached the therapeutic level with warfarin[27].

Warfarin is minimally secreted into the breast-milk[27], and is therefore considered safe in breastfeeding mothers[28]. The American Academy of Pediatrics Committee on Drugs supports breastfeeding for women who take warfarin[29].

Heparin

Heparins, UFH and LMWH are the preferred agents for anticoagulation in pregnancy. The main advantage of heparins over other anticoagulants is that there is no transplacental passage due to high molecular weights. Therefore, no increase in the incidence of fetal hemorrhage or teratogenicity would be expected, and this has been confirmed in several studies[28,30,31]. Heparins are not secreted in breast-milk and therefore can be safely used by nursing mothers[28].

Although evidence-based findings are not sufficient, heparin is increasingly being used in the prevention of placenta-mediated complications[32]. Ongoing basic and translational investigations concerning the molecular mechanisms of heparin's actions in the setting of placenta-mediated complications have highlighted the many roles of heparin. It

has significant effects on trophoblast cells, in addition to the coagulation system[32-34].

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is expressed in the human placenta during the first trimester, primarily within the villous trophoblasts, but also in extravillous cytotrophoblasts. HB-EGF favors trophoblast differentiation by inducing the invasive phenotype and stimulating cell motility. LMWH is able to increase the expression of HB-EGF, hence favoring the process of placentation[33,34].

A pathological reduction of HB-EGF expression is observed in placentas of patients with the hypertensive syndrome preeclampsia, which is associated with decreased trophoblast invasion and increased levels of trophoblast apoptosis. This finding led us to hypothesize that dysregulation of HB-EGF and the resulting deficiencies in trophoblast function could contribute to preeclampsia, although it remains to be determined when during the course of gestation HB-EGF levels are first reduced in preeclamptic pregnancies. Trophoblast invasion is shallow in preeclampsia possibly due to a lack of HB-EGF-induced cell migration and a rise in apoptosis, exacerbated by reduced cytoprotection. The increased oxidative damage to trophoblast cells and the paucity of HB-EGF in preeclamptic placentas is consistent with the hypothesis that HB-EGF performs an important role as a survival factor throughout gestation. Patients delivering preterm without hypertensive disorder produce placentas with normal levels of HB-EGF. However, there is an intermediate reduction of HB-EGF in extravillous trophoblasts for those women who delivered small-for-gestational-age infants. Intrauterine growth restriction, like preeclampsia, has been linked to aberrant trophoblast invasion and elevated apoptosis, suggesting shared elements in the etiology of both disorders[35].

Since heparan sulphate is an obligate cofactor for HB-EGF, clinical application of heparin during pregnancy could influence the activity of this growth factor. Indeed, UFH inhibits apoptosis induced by diverse signals in first trimester cytotrophoblast cells. It could be speculated that addition of its cofactor activates HB-EGF in trophoblasts to enhance survival. On the other hand, fractionated heparin suppresses the invasive capacity of primary extravillous trophoblasts. This suggests that there could be clinical advantages to using UFH over fractionated heparin[35].

Unfractionated heparin (UFH) has been shown to promote angiogenesis in the context of coronary ischemia and cardiac development, and inhibits vascular smooth muscle cell (SMC) proliferation[36,37]. LMWH appears to retain the SMC inhibitory properties of UFH; however, differential effects on angiogenesis have been described[38].

Heparin increases fibroblast growth factor-2 (FGF-2), a potent angiogenic growth factor, and stimulates angiogenesis in a dose-dependent manner via three ways: induces expression of FGF-2 by SMCs, releases FGF-2 from the extracellular matrix, where it appears to be stored in an inactive form, and acts as a co-factor in the binding of FGF-2 to its receptor[39]. Although FGF-2 is a potential mediator of heparin's effect on angiogenesis and SMC proliferation and is expressed in the lung tissue of newborn rabbits, its levels are not altered by heparin treatment[40].

Low-molecular-weight heparin (LMWH) and UFH are both effective at accelerating the normal post-natal fall in pulmonary artery pressure in rabbits. This is associated with an increase in pulmonary artery density, reduced muscularization of small pulmonary arteries, and thinning of the medial layer of muscular pulmonary arteries[40,41].

The pathological feature of pulmonary hypertension is an increased medial thickening of the pulmonary artery due to hypertrophy and hyperplasia of pulmonary artery smooth muscle cells (PASMC). Heparin inhibits PASMC growth both *in vivo* and *in vitro*[42,43], and reduces medial thickness in experimental hypoxia-induced pulmonary hypertension[44]. Dalteparin is more effective than enoxaparin in inhibiting pulmonary hypertension and vascular remodeling in hypoxic guinea pigs[45].

Since we observed that respiratory distress in the first day of life is more common in newborn infants whose mothers used LMWH and aspirin during pregnancy compared to controls (12.1% vs. 3.6%, p=0.01)[46], we performed an animal study. Lung specimens of the newborn rabbits whose mothers received heparin and/or aspirin

throughout gestation were evaluated, and pulmonary vascular thickening at the level of alveoli was determined in the heparin (with or without aspirin) groups[47]. Our findings of clinical and animal studies are contradictory to the previous studies. Maternal heparin use seems to be a predisposing factor for the development of pulmonary hypertension in the neonate. Because LWHs do not cross the placenta, their effects on fetal lungs may be due to an indirect process via affecting placental function through unknown growth factors or mediators. Another possibility is the presence of contaminants in heparin preparations.

In early 2008, the United States FDA recalled several batches of heparins due to the increased prevalence of adverse reactions and death. Fatal hypotension from anaphylactoid-type reactions was responsible for over 149 deaths all over the world. Researchers detected a heparin-like semisynthetic contaminant, namely over-sulfated chondroitin sulfate (OSCS) in significant amounts (5%-30%) that appeared to be intentional. Varying degrees of oversulfated dermatan sulfate and oversulfated heparan sulfate (HS) were also detected. LMWHs are produced using UFH, and OSCS has been found in various batches of LMWHs[48,49].

Contaminants and non-medicinal ingredients may also be another contributing factor for pulmonary hypertension development. Over-O-sulfonation of both heparin and HS increases antiproliferative activity, and 6-O-desulfonation of heparin and HS diminishes antiproliferative potency[50]. No appreciable difference is found between heparin and fully sulfated heparin. Chondroitin and dermatan sulfates actually stimulate PASMC growth, but full sulfonation made them strongly antiproliferative[51].

Benzyl alcohol, a bacteriostatic preservative, is also found at low concentration (15 mg/ml) in LMWH preparations (Clexane®). It is oxidized rapidly in healthy individuals to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. However, newborns, especially if critically ill, and preterms may not metabolize benzyl alcohol as readily as adults. High concentrations can result in toxic effects including respiratory failure, vasodilation, hypotension, convulsions, and paralysis ("fatal gasping syndrome"). The amount of benzyl alcohol at which toxicity may occur is not known. Reports in the early 1980's of 16 neonatal deaths associated with the use of saline flush solutions containing benzyl alcohol preservative led to recommendations to avoid its use in neonates[52,53]. Benzyl alcohol can cross the placenta, but its effects on fetal pulmonary vessels are unknown.

Heparin-Like Anticoagulants

These anticoagulants are used for cases of heparin allergy or heparin-induced thrombocytopenia in pregnancy.

Danaparoid: Danaparoid is a LMW heparinoid consisting of the glycosaminoglycans heparin sulfate, dermatan sulfate, and chondroitin sulfate. Like UFH and LMWH, danaparoid catalyzes the antithrombin-mediated inactivation of factor Xa. It is administered intravenously and has low placental permeability. No evidence of antifactor Xa activity has been found in the placental blood of women taking danaparoid. In published cases, no adverse fetal outcomes have been reported[54].

Fondaparinux: Fondaparinux, a selective inhibitor of factor Xa, is a pentasaccharide that mimics the active site of heparin that binds to antithrombin. Fondaparinux is administered subcutaneously. Animal studies have demonstrated no placental transfer and no harm to the fetus[55,56]. However, 10% of maternal levels have been detected in umbilical cord blood[57,58]. No adequate clinical data exist on the use of fondaparinux in pregnant and lactating women[27,58].

Recombinant hirudin: Recombinant hirudin, a direct thrombin inhibitor, is the recombinant version of the medicinal leech protein. It is administered intravenously or subcutaneously. There are two published cases of its use in pregnancy, neither with adverse fetal outcomes. Placental transfer in humans is not documented, but there is low transfer in dogs[59] and rabbits (less than 2% of maternal levels)[54].

Direct thrombin inhibitors: Several direct thrombin inhibitors (lepirudin, bivalirudin and argatroban) are labelled by the FDA as pregnancy category B drugs. Animal studies have demonstrated no evidence of impaired fertility or harm to the fetus. However, animal studies have shown that lepirudin can cross the placenta, and argatroban has been

detected in breast-milk[58]. It is not known, definitely, whether these drugs are secreted in human breast-milk. Currently, there are no adequate clinical data on the use of direct thrombin inhibitors in pregnant women. The recombinant or synthetic direct thrombin inhibitors lepirudin and bivalirudin are not allowed during pregnancy[27].

Aspirin

Aspirin is an antiplatelet drug. Platelets process prostaglandin H2 (PGH2) to produce thromboxane, which induces platelet aggregation and vasoconstriction. Aspirin selectively acetylates the hydroxyl group of one serine residue in cyclooxygenase (COX) leading to irreversible inhibition of COX, the enzyme necessary for the conversion of arachidonic acid to PGH2, the first step in the process. At high concentrations and over longer periods, aspirin acetylates a variety of proteins and nucleic acids, but at low concentrations, aspirin acetylates COX rapidly and selectively.

In many centers, aspirin is prescribed with increasing frequency to reduce the risk of maternal thrombosis and reduce the risk of miscarriage and poor pregnancy outcome. In women with either mechanical heart valves or antiphospholipid syndrome, low-dose aspirin may be used in combination with heparins[60]. In one study, aspirin alone was shown to compare favorably with aspirin plus LMWH in the treatment of women with antiphospholipid syndrome and no history of thrombosis[61]. Aspirin alone, however, is not considered sufficient to prevent thrombosis or even in women with antiphospholipid syndrome. Low-dose aspirin alone may be an acceptable alternative for the woman who has lupus, the lupus anticoagulant, or moderate-to-high levels of anticardiolipin antibodies, but no history of thrombosis or poor pregnancy outcome. In cases of low levels of anticardiolipin antibodies, because low levels are of questionable significance, no anticoagulation is required[62]. The question as to whether low-dose aspirin improves pregnancy outcomes has not been answered affirmatively.

Although aspirin crosses the placenta, it is safe in low doses of 80-150 mg per day. Large, randomized trials have demonstrated no increased risk of miscarriage, congenital anomalies, placental abruption, fetal hemorrhage, or neonatal bleeding[63-67]. However, the safety of higher doses of aspirin during the first trimester remains uncertain.

Vascular disruptions result from an interruption in the uterine, placental or fetal circulation during the critical period for organogenesis. Aspirin has been associated with an increased risk of vascular disruptions, particularly gastroschisis[68]. Kozer et al.[65], in a meta-analysis of five previously published case-control studies, found an odds ratio for gastroschisis of 2.37 (95% confidence interval [CI]: 1.44–3.88) in mothers with aspirin exposure. In a subsequent study of 206 cases and 798 controls, Werler et al.[69] found an odds ratio of 2.7 (95% CI: 1.2–5.9) for gastroschisis in mothers with aspirin exposure. It appears that aspirin exposure in the first trimester does increase the risk of gastroschisis approximately two- to three-fold[70].

As demonstrated in animal studies, COX inhibitors can cause closure of the ductus. In fact, indomethacin, a COX inhibitor, is used as a nonsurgical alternative to achieve postnatal closure of a patent ductus arteriosus. Evidence that aspirin is associated with premature closure of the ductus arteriosus includes the results of one study, which found higher salicylate levels in infants with persistent pulmonary hypertension and absence of a right-to-left shunt, indicative of premature closure of the ductus arteriosus[71], and another study which found the odds of persistent pulmonary hypertension with *in utero* aspirin exposure to be 8.09 (95% CI: 3.27–20.01)[72]. The doses of aspirin in these studies were not specified.

Premature closure of the ductus arteriosus is a rare event, occurring in only 1 in 1000 to 1 in 10,000 term deliveries. Even though randomized trials of low-dose aspirin versus placebo have included over 30,000 women, these numbers are insufficient to have detected a small increase in the incidence of premature closure of the ductus arteriosus among the fetuses or neonates born to women who were exposed to aspirin. A large increased incidence should have resulted in an increased risk of stillbirth, but the randomized trials of low-dose aspirin versus placebo have not found an increased risk of stillbirth and some studies have even found a decreased risk[67]. Therefore, the risk of premature closure of the ductus

arteriosus due to low-dose aspirin is probably small or nonexistent[73].

This may be due partly to the paradoxical effects of COX inhibitors in preterm and term infants. While COX inhibitors offer effective means to close the ductus arteriosus in near-term infants, for severely premature babies, COX inhibitors may exacerbate the problem by preventing the formation of vascular intimal cushions required for closure[74].

Other Antiplatelet Agents

Dipyridamole is a vasodilator and antiplatelet agent acting by interfering with the cyclic-AMP metabolism in the platelets. Although not more effective than aspirin, it has been approved in combination with aspirin. No data for placental transfer of dipyridamole is available, but there are numerous cases of its use in pregnancy with no adverse fetal outcomes reported. It seems that it is a safe drug in pregnancy[27].

Thienopyridine derivates (clopidogrel and ticlopidine) block the ADP-induced platelet aggregation and can be used instead of aspirin. There are no large scale data on the teratogenic effects of these agents in pregnant women, except two cases of the use of clopidogrel[75,76] and two cases of the use of ticlopidine[76,77], with no adverse fetal outcomes. Therefore, their use during pregnancy is contraindicated. Breastfeeding is also contraindicated, because their metabolites can pass to the milk[27].

The use of **abciximab**, which blocks the platelet glycoprotein IIb/IIIa receptor that allows platelet aggregation, has been reported in the treatment of one patient with an acute myocardial infarction during pregnancy with no adverse fetal outcome[78]. A small amount of abciximab was found on the fetal side of an *in vitro* placental model[79].

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