ANTIPLATELET AND ANTICOAGULANT TREATMENT CONSIDERATIONS IN PREGNANCY

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PREGNANCY IS INHERENTLY A HYPERCOAGULABLE STATE

increased levels of coagulation factors I (fibrinogen), VII, and VIII; von Willebrand factor; and factor X.

and decreased fibrinolysis, owing to increased levels of plasminogen activator inhibitors 1 and 2, as well as increased D-dimer levels

also experience decreased free protein S (a natural anticoagulant), increased acquired resistance to activated protein C

VTE

- The risk of venous thromboembolism (VTE) in pregnancy is increased five-fold and continues into the post.partum period.

ASPIRIN

- It is a nonsteroidal anti-inflammatory drug that primarily inhibits COX-1 and COX-2, which are necessary for prostaglandin synthesis, in a dose-dependent fashion. At lower doses, aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of thromboxane A2 (TXA2), which promotes platelet aggregation and is a potent vasoconstrictor.
- At higher doses, aspirin inhibits both COX-1 and COX-2, which effectively inhibits all prostaglandin production

P2Y12 INHIBITOR

- Clopidogrel is a $P2Y_{12}$ inhibitor that irreversibly inhibits platelet aggregation and activation by preventing the binding of fibrinogen to its adenosine disphosphate receptor.

P2Y12 INHIBITOR

- Ticlopidine is no longer available due to significant hematologic side effects, such as agranulocytosis, thrombotic thrombocytopenic purpura, and aplastic anemia.

THE GLYCOPROTEIN IIB/IIIA (GP IIB/IIIA) INHIBITORS

- The third class of antiplatelets are the glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, which include tirofiban, eptifibatide, and abciximab.

used in acute coronary syndrome, around the time of percutaneous coronary intervention, and are given intravenously.

there are no safety data for these agents in pregnancy

ANTICOAGULANTS

- Anticoagulants commonly used in pregnancy include vitamin K antagonists, heparin-based anticoagulants, and non-heparin anticoagulants

THE RISK OF WARFARIN EMBRYOPATHY APPEARS TO BE DOSE-DEPENDENT

- : maternal daily doses of <=5 mg/day are associated with a <3% risk of warfarin embryopathy
- compared to a >30% risk of fetal loss or embryopathy at materal doses of over 5 mg/day .

ASPIRIN AS PRIMARY PREVENTION

- bioprosthetic valves or
- a history of vascular event, such as myocardial infarction, coronary stent, or stroke
- .The most common indication for starting aspirin in pregnancy is to prevent or delay onset of preeclampsia .

ASPIRIN AS PRIMARY PREVENTION

- Guidelines in the United States recommend starting low-dose aspirin prophylaxis (81 mg/day) between 12 and 28 weeks of gestation (optimally before 16 weeks)
- European guidelines also suggest that women identified as high risk should receive aspirin prophylaxis starting at 11–14 weeks gestation but at a dose of 150 mg nightly until 36 weeks of gestation,

ASPIRIN AS PRIMARY PREVENTION

- Currently, there is no evidence for low-dose aspirin in pregnancy for women with a history of stillbirth, fetal growth restriction, preterm birth, or early pregnancy loss

CONTRAINDICATIONS TO ASPIRIN USE IN PREGNANCY

- Patients with a history of aspirin allergy or hypersensitivity to other salicylates and/or nonsteroidal anti-inflammatory drugs (NSAIDs)
- Patients with a history of nasal polyps should also avoid aspirin due to the risk of life-threatening bronchoconstriction.
- patients with asthma with a history of aspirin-induced acute bronchospasm should avoid aspirin for a similar reason.

RELATIVE CONTRAINDICATIONS TO ASPIRIN

- include history of gastrointestinal bleeding, active peptic ulcer disease, other sources of gastrointestinal or genitourinary bleeding, and severe hepatic dysfunction

MATERNAL AND FETAL RISKS OF ASPIRIN USE IN PREGNANCY

- Numerous studies have demonstrated that low-dose aspirin is not associated with an increase in antepartum or postpartum hemorrhagic complications, including placental abruption, postpartum hemorrhage, or mean blood loss during delivery, or neonatal intracranial hemorrhage .
- Aspirin has also not been associated with increased risk of congenital fetal anomalies.

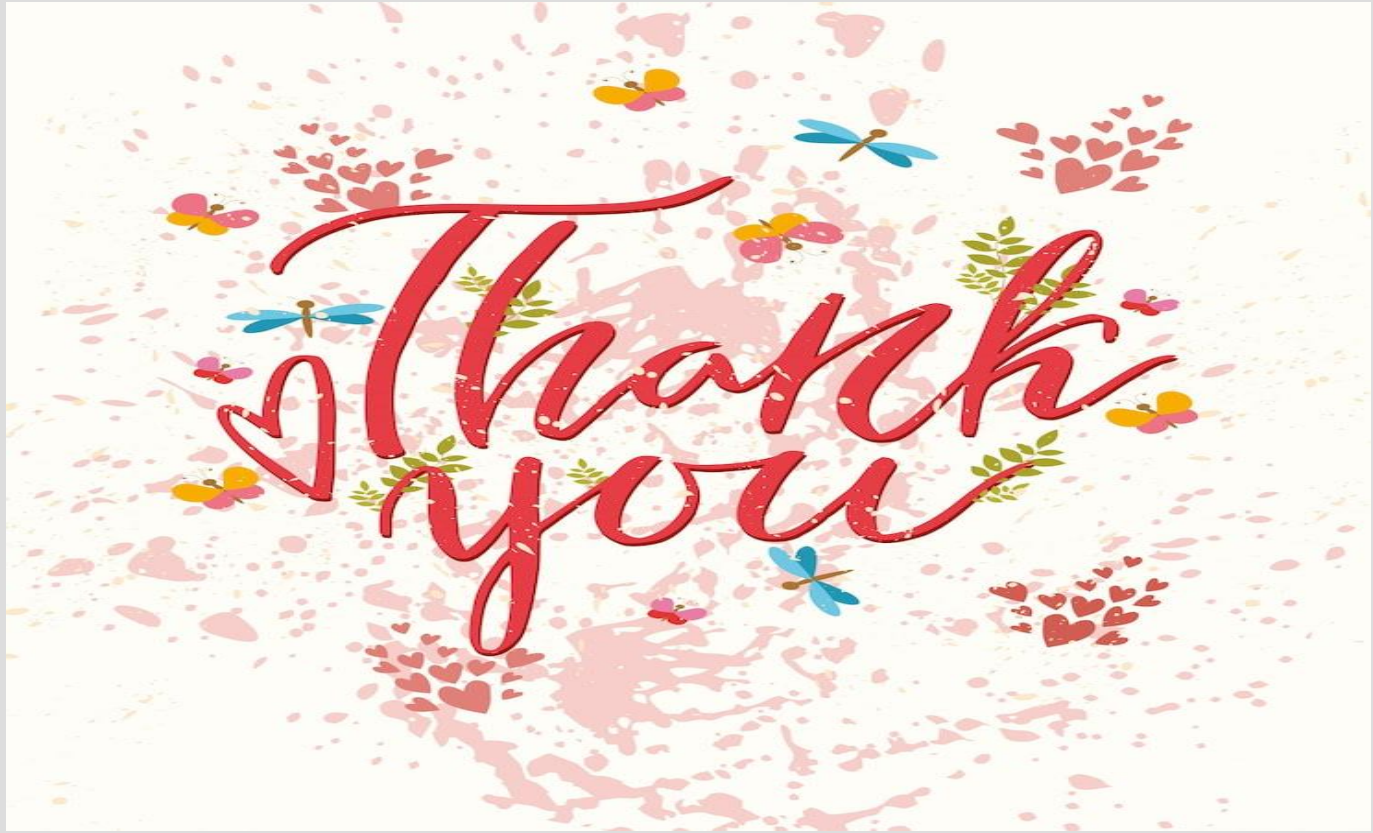
- There were a few studies that suggested a two-fold risk of gastroschisis in children of women using aspirin during pregnancy.. Furthermore, older studies suggested a relationship between in utero exposure to NSAIDs with premature closure of the ductus arteriosus and persistent pulmonary hypertension in the neonate but did not differentiate between the type and dose of NSAID exposure .these study did not find an increase in perinatal deaths from persistent pulmonary hypertension in women who used aspirin

OTHER ANTIPLATELETS

- Clopidogrel is a reasonable substitute in pregnant women with a clear indication for antiplatelet therapy who are allergic to aspirin. Clopidogrel should only be used when strictly necessary and for the shortest duration possible during pregnancy due to the lack of observational studies in humans

acute myocardial infarction.

Agent	Type of Agent	Mechanism of Action	Primary Indications in Pregnancy	Typical Dosing	Obstetric Risks
Aspirin	Antiplatelet	Inhibits COX-1 and COX-2 in dose-dependent fashion. Anti-inflammatory and anti-platelet properties [1,2,5].	1. Prevention of preeclampsia 2. Acute coronary syndrome 3. Stroke 4. ACHD: unrepaired shunt lesion, aortic coarctation, moderate to complex CHD 5. Mechanical heart valve in second and third trimesters 6. Bioprosthetic heart valve	• Preeclampsia prophylaxis: PO aspirin 81mg/day • For preeclampsia, based on US guidelines, initiate between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continue daily through delivery	• Generally considered safe in pregnancy at low dose • Contraindications: aspirin allergy, hypersensitivity to other salicylates and/or NSAIDs, history of nasal polyps, history of aspirin-induced bronchospasm • Relative contraindications: gastrointestinal bleeding, active peptic ulcer disease, other sources of gastrointestinal or genitourinary bleeding, severe hepatic dysfunction
Clopidogrel Ticagrelor Prasugrel Cangrelor	Antiplatelet	Inhibits P2Y12, which inhibits platelet aggregation and activation. Clopidogrel and prasugrel are irreversible inhibitors, while ticagrelor and prasugrel are reversible inhibitors. Clopidogrel's activity is due to its active	1. Clear indication for antiplatelet therapy but with allergy to aspirin	• PO clopidogrel 75 mg/day	• Primary risk with clopidogrel is intrapartum and postpartum hemorrhage • No safety data available for ticagrelor, prasugrel, and cangrelor use in pregnancy


Thank you

ROLE OF ANTICOAGULATION TREATMENT IN PREGNANCY

- Pregnant women are at an increased risk of both venous (~20%) and arterial (~80%) thrombosis due to the hypercoagulable state of pregnancy .

- indications for anticoagulation treatment during pregnancy, including venous thrombosis, arterial thrombosis, and mechanical valves.
- The preferred anticoagulant in pregnant women is LMWH, as intravenous UFH is logistically challenging to use.

ANTICOAGULANTS

- Vitamin K is required for γ-carboxylation of proteins, including coagulation factors II, VII, IX, and X.
- By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity

WARFARIN

- exposure to warfarin in the first trimester is associated with warfarin embryopathy, which is characterized by stippled epiphyses and nasal bone hypoplasia .
- Exposure to warfarin in the third trimester is a risk factor for fetal intracranial hemorrhage during vaginal delivery.

HEPARIN BASED ANTICOAGULANTS

- Neither UFH nor LMWH cross the placenta, and both are safe during lactation.
- They differ in that UFH preferentially inhibits factor IIa (thrombin), potentiating the effect of antithrombin, while LMWH affects mainly factor Xa and, to a lesser extent, factor IIa

NON HEPARIN BASED ANTICOAGULANTS

- Non-heparin anticoagulants include direct and indirect oral or parenteral Xa inhibitors, direct thrombin inhibitors, and heparinoids
- Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa and is recommended by theACOG for anticoagulation in the setting of HIT or heparin allergy .

HEPARIN BASED ANTICOAGULANTS

- The activated partial thromboplastin time (aPTT) is the main test used to monitor UFH. However, in the context of pregnancy, anti-Xa level is a better test, as the aPTT will be shortened due to increases in factor VIII in pregnancy.

- Pregnant patients using LMWH are recommended to have anti-Xa levels checked weekly to achieve a peak 0.7–1.2 U/mL and trough > 0.6 U/mL

HEPARIN BASED ANTICOAGULANTS

- However, concerningly, thrombotic events have still occurred in patients who achieved therapeutic peak anti-Xa levels, possibly because peak anti-Xa levels may not be adequate to ascertain therapeutic anticoagulation. Discrepancies exist between different laboratory tests designed to measure levels of anticoagulation, as divergent values of anti-Xa and aPTT have been observed.

DIRECT ORAL ANTICOAGULANTS (DOACS) **RIVAROXABAN, APIXABAN, DABIGATRAN, AND EDOXABAN**

DOACs are not approved for use in pregnancy

prevention of thrombosis in several cardiovascular contexts, including lowering stroke risk and embolism in atrial fibrillation, as well as treatment of deep vein thrombosis and pulmonary embolism treatment.

HEPARIN BASED ANTICOAGULANTS

- the challenge lies in the fact that there is no functional test for monitoring the anticoagulant effect of LMWH .
- LMWH has a longer half-life and dosing is weight-based.
- UFH is preferred in cases of severe renal insufficiency.