Medical Problems in Pregnant Women

2012 ACCP Guideline Regarding the Pregnant Patient: A Case-Based Discussion

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Summary

The American College of Chest Physicians (ACCP) published its latest (9th edition) guidelines in February 2012. This document is a valuable reference for all clinicians. In the current article, through the analysis of three clinical cases, the authors review, describe, and analyze the most significant new information from the chapter "VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy": (1) strategies for clinicians facing the prescription of a new drug during pregnancy with little available data; (2) recommendations about indications of thromboprophylaxis for asymptomatic thrombophilias; and (3) thrombophilia screening and secondary prevention for placental complications.

Résumé

La 9^e édition des lignes directrices du American College of Chest Physicians (ACCP) (Collège américain de médecine thoracique), publiée en février 2012, est un document de référence précieux pour tous les cliniciens. À partir de trois cas cliniques, les auteurs de l'article étudient, décrivent et analysent les nouvelles données du chapitre intitulé « VTE, Thrombophilie, traitements antithrombotiques et grossesse » (MTEV, thrombophilie, traitements antithrombotiques et grossesse) : 1) stratégies à l'intention des cliniciens qui envisagent de prescrire pendant une grossesse un nouveau médicament malgré le manque de données; 2) recommandations relatives aux indications de thromboprophylaxie pour les cas de thrombophilie asymptomatique; 3) dépistage de la thrombophilie et prévention secondaire des complications placentaires.

Physicians treating pregnant women with venous thromboembolism (VTE), thrombophilia, or placental complications must make clinical decisions despite a paucity of high-quality study data. They often rely on the information published by the American College of Chest Physicians (ACCP). The newest recommendations were published in February 2012: *VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. The methodology of the ACCP 9th guideline uses structured clinical questions, and is updated to January 2010.¹

We review and discuss these recommendations as they relate to three complex cases: a pregnant patient taking new antithrombotic oral agents, the management of asymptomatic thrombophilia, and the use of secondary prophylaxis for obstetrical complications.

Case 1: Exposure to New Antithrombotic Oral Agents during Pregnancy

A 32-year-old woman, G1, who is 6 weeks pregnant, is referred in an anxious state. She had a left deep vein thrombosis 4 weeks prior and is currently on rivaroxaban. What should we tell her, and what are the maternal and fetal risks related to that medication?

Table 1. Further Resources

PubMed search

Briggs et al. (2008) *Drugs in Pregnancy and Lactation*.⁴²Grossesse et allaitement. Guide thérapeutique (2013) 2nd ed. ED du CHU Sainte-Justine¹Motherisk (Toronto) www.motherisk.orgCentre IMAGE Hôpital St-Justine (Montreal): www.chu-sainte-justine.org/Pro/micro-portails.aspx?AxelD=22

Toxnet.

DART: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC>LACTMED: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>**Background: Overview of Drug Counselling**

Organogenesis occurs from the 4th to 12th week of gestation. Although the neural tube develops early, the central nervous system will mature throughout pregnancy. When evaluating the risk of malformation with exposure to medications, clinicians must take into account the following: (1) that the baseline risk for major malformations is 2–3% in normal pregnancy; (2) that well-known teratogens are rare and cause malformations in fewer than 25% of exposed embryos; (3) the effect of all other medications, illicit drugs, alcohol, and smoking; and (4) the presence of confounding variables such as obesity, epilepsy, and congenital cardiac disease.^{1–3}

In our opinion, clinical decision making based solely on the US Food and Drug Administration (FDA) classification for medication risk in pregnancy should be discouraged. This classification can be misleading, does not always take into account new data on old drugs, and can give reassuring labels to new drugs based on animal data (and despite little human data).^{1,2,4} Table 1 includes alternative tools to determine the safety of drugs in pregnancy and lactation.

New Oral Anticoagulant Use during Pregnancy

Rivaroxaban is an anti-Xa inhibitor. There are no human safety data for its use during pregnancy. In animal models, it has been demonstrated to cross the placenta at about 20% of maternal serum concentration and is excreted in breast milk (at about 2%). In animals, it is associated with fetal toxicity, an increased prevalence of congenital malformations, and placental anomalies.^{5,6}

ACCP Recommendation

Pregnant and breastfeeding women should avoid “the use of oral direct thrombin (e.g., dabigatran) and anti-Xa (e.g., rivaroxaban, apixaban) inhibitors (Grade 1C).”¹

Discussion

We agree with the recommendation that new oral antithrombotic

Table 2. Risk of Thromboembolic Disease in Asymptomatic Thrombophilia

Thrombophilia	Estimated Absolute Risk (%) in Antepartum and Postpartum (95% CI) with Family History
Antithrombin deficiency	3.0 (0.08–15.8)
Protein C deficiency	1.7 (0.4–8.9)
Protein S deficiency	6.6 (2.2–14.7)
Factor V Leiden heterozygous	3.1 (2.1–4.6)
Prothrombin heterozygous	2.6 (0.9–5.6)
Leiden homozygous	14.0 (6.3–25.8)

Adapted from Bates et al.⁷

agents should not be prescribed to women of child-bearing age due to the lack of data,^{5,6} particularly because other therapeutic options exist.⁷ However, fewer than 50% of pregnancies are planned, and therefore the risk of exposure to these new drugs is real.^{1,2} If anticoagulant drugs are absolutely necessary, then contraception and adequate counselling are mandatory. If a patient is subsequently found to be pregnant, she should continue her antithrombotic drug temporarily and consult her physician immediately to change to a safer therapy. The risk of recurrence of a thrombotic event might be worse than the theoretical teratogenic risk.

Case Conclusion

A frank discussion concerning the absence of data in human pregnancy is essential. However, since the medication was stopped very early in pregnancy, and since true teratogens are rare, the overall risk seems low. While she is considering her options, the rivaroxaban should be stopped immediately, and low molecular weight heparin (LMWH) started at therapeutic dose. Side effects of LMWH should be discussed with the patient. The risk of bleeding is <1%.⁸ Risk of osteoporosis at therapeutic dose is probably lower than with unfractionated heparin (UFH),^{8,9} and adverse skin reactions are generally benign.^{10,11} The risk of developing heparin-induced thrombocytopenia is low for obstetrics patients (<0.1%); therefore, platelet monitoring is not recommended.^{10,12}

Case 2: Asymptomatic Thrombophilia in Pregnancy

A 28-year-old woman, G1 and 6 weeks pregnant, is seen in your office. She has a family history of VTE and is found to have a deficiency in antithrombin (AT). She has no personal history of thrombosis. What is her risk of thrombosis, and should she receive prophylaxis during the pregnancy and/or postpartum?

Background: Risk of VTE during Pregnancy in Women with Thrombophilia

Familial history of VTE is associated with two- to fourfold increased risk of VTE compared with the general population.¹³

Table 3. Summary of the ACCP 9th Guideline 2012: Thromboprophylaxis in Asymptomatic Thrombophilia

Thromboprophylaxis	No (<1 Risk%)	Postpartum (Risk ~4%)	Antepartum + Postpartum (Risk >10%)
Thrombophilia but no family history	All thrombophilias (Except Leiden homozygous or prothrombin gene mutation homozygous)	Leiden homozygous or prothrombin gene mutation homozygous	NA
Thrombophilia with family history	NA	All other thrombophilia	Leiden homozygous or prothrombin gene mutation homozygous

NA = not applicable

Adapted from Bates et al.⁷

Table 2 summarizes the estimates of absolute risk of antepartum and postpartum VTE in women with thrombophilia and a family history.^{7,14,15} The presence of factor V Leiden homozygous state is associated with the highest risk. ACCP recommendations are outlined in Table 3.

The family history and the presence of high-risk thrombophilias (factor V Leiden homozygous and prothrombin variant homozygous) warrant prophylaxis during pregnancy (grade 2B).⁷

For low-risk thrombophilias without family history, antepartum and postpartum clinical surveillance is suggested (grade 2C).⁷

Discussion

In addition to the ACCP recommendations, individual VTE risk should be taken into account when evaluating prophylaxis for these women. For example, are there other VTE risk factors such as multiple thrombophilias, obesity, immobility, varicosities, advanced maternal age, or smoking?^{14,16–23} While women with a double-heterozygous mutation are not specifically addressed in the guidelines, these patients are often treated during pregnancy and postpartum.^{16,24} Patient preference, the risk of major bleeding (which is low at <1% with prophylaxis),¹⁰ and cost of the prophylaxis should all be considered.

As antithrombin (AT) deficiency is exceedingly rare, the impact of asymptomatic carrier state in pregnancy has not been well studied. Earlier studies of AT deficiency in pregnant women suggested an incidence of up to 35% VTE in pregnancy and postpartum.^{25,26} However, these older studies had methodological flaws: a majority of events were not confirmed by objective testing, and inclusion of superficial phlebitis likely inflated the incidence. The study populations also included symptomatic women and compared pregnant women with non-pregnant women.^{25,26} A recent systematic review of asymptomatic women with AT and pregnancy (irrespective of family history) was consistent with the recommendations in the 9th ACCP guideline. In this review, 54 women with 124 pregnancies were identified with an estimated

absolute-risk of VTE of 1.63% (95% CI 0.29–9.00) in cohort studies and 0.67% (95% CI 0.16–2.80) in case-control studies.²⁷

However, several factors mean the ACCP recommendations may be inadequate. These include the severity and atypical thrombotic sites that can occur with AT deficiency; the small number of patients and pregnancies in the literature; the large confidence intervals and the low quality of the studies. Therefore, we would recommend prophylaxis.

Case Conclusion

The ACCP states that since our patient is asymptomatic for thromboembolic disease, has a family history of VTE, and does not have a high risk thrombophilia, she should not receive thromboprophylaxis in antepartum. After discussing with our patient, we would recommend prophylaxis antepartum and postpartum, since the risk of bleeding is low and our confidence in the strength of the evidence is limited.

Case 3: Thrombophilia and Placental Complications

A 29-year-old woman, G2P1, is 6 weeks pregnant. Her previous pregnancy (2 years earlier) was complicated by severe pre-eclampsia with intrauterine growth restriction (IUGR) at 30 weeks. Her obstetrician is asking you if she should be screened for thrombophilia and if she should have a secondary prophylaxis to prevent recurrence.

Thrombophilia: Background

The evidence associating thrombophilia with placental complications (recurrent first trimester losses [more than three episodes], late fetal demise, pre-eclampsia, placental abruption, and IUGR) is of low level and therefore controversial. Although initial case-control studies showed an association,¹⁴ recent prospective cohort studies²⁸ did not (Table 4).

ACCP Recommendations

For women with recurrent early pregnancy loss (three or more

Table 4. Association of Thrombophilia and Obstetrical Complications

Thrombophilia	Recurrent Loss T1	Late Loss	Pre-eclampsia	Abruptio	IUGR
FVL heterozygous ²⁸	+/-	-	-	-	-
Prothrombin gene mutation ²⁸	-	-	-	-	-
AT deficiency ¹⁴	No data	-	-	-	No data
Protein C deficiency ¹⁴	No data	-	-	-	No data
Protein S deficiency ¹⁴	No data	+	-	-	No data
APLA ²⁹⁻³¹	+	+/-	+	+/-	+/-

APLA = antiphospholipid antibodies; AT = antithrombin; FVL = factor V Leiden; IUGR = intrauterine growth restriction; + = positive association; +/- = weak association; - = no association.

Table 5. Secondary Prevention of Obstetrical Complications with LMWH

Studies	#	Inclusion Criteria	Thrombophilia	Interventions	Outcomes	NNT
Mello et al., 2005 ³⁶	80	PE and ACE GG genotype	No	Dalteparin 5,000 mg vs. open label	PE 7.3% vs. 28.2%	5
Rey et al., 2009 ³⁷	116	Severe PE <35 wk, IUGR, abruptio, fetal death	No	Dalteparin 5,000 mg vs. open label (ASA in >80%)	Severe PE, IUGR, abruptio, fetal death 5.5% vs. 23.6%	5
NOH-AP, 2010 ³⁸	160	Abruptio	No	Enoxaparin 40 mg vs. open label	PE, abruptio, IUGR, fetal death 12% vs. 31.3%	5
NOH-PE, 2011 ³⁹	224	Severe PE	No	Enoxaparin 40 mg vs. open label (ASA in 100%)	PE, abruptio, IUGR, fetal death 8.9% vs. 25%	7
FRUIT-RCT, 2012 ⁴⁰	139	Before 34 wk: severe PE or SGA	Yes	Dalteparin 5,000 mg + ASA 80 mg vs. ASA 80 mg	PE <34 wk 0% vs. 8.7% Total PE 18.6% vs. 21.7%, NS	12 32
HAPPY, 2012 ⁴¹	128	Fetal death, mild PE, severe PE, HELLP, IUGR,	No* (70 vs. 72%)	Nadroparin 3,800 IU vs. medical surveillance	PE, eclampsia, HELLP, IUGR, abruptio 21% vs. 18%, NS	

ACE GG = angiotensin I-converting enzyme GG phenotype; ASA = acetylsalicylic acid; HELLP = hemolysis, elevated liver enzymes and low platelet; IUGR = intrauterine growth restriction; NNT = number needed to treat; NS = not significant; PE = pre-eclampsia; SGA = small-for-gestational age.

*Screening for thrombophilia was done after randomization (around 60% was associated with low protein S level).

consecutive miscarriages before 10 weeks of pregnancy), screening for antiphospholipid antibodies (APLA) is recommended (grade 1B). For all other pregnancy complications, screening for inherited thrombophilia is not suggested (grade 2C).⁷

Discussion

There is no ACCP recommendation either for or against APLA screening in late pregnancy loss, pre-eclampsia, or IUGR (with concomitant APLA).²⁹⁻³¹ This may be due to insufficient proof that any current therapy changes outcome. Although controversial, our practice is to screen these women for APLA and then, if present, recommend antepartum and postpartum prophylaxis with LMWH.

The ACCP guidelines do not recommend screening for inherited thrombophilias in women with obstetrical complications. This is because there is only a weak association

at best, and LMWH efficiency does not seem to be correlated with thrombophilia status (Table 5).

Prevention of Placental Complications: Background

Aspirin (acetylsalicylic acid, or ASA) has been shown to reduce the risk of developing pre-eclampsia by 17% overall,³² and by 53% if started before 16 weeks.³³ For women at high risk, the number needed to treat (NNT) is <28.³³ High risk is defined by previous pre-eclampsia, diabetes mellitus type 1 or 2, chronic renal disease, chronic hypertension, autoimmune disease, a body mass index (BMI) ≥30, twin gestation, or a family history of pre-eclampsia.³²

LMWH use has generated a lot of interest and research in the past 10 years. Accordingly, we now have good data showing no benefit for recurrent early pregnancy losses with LMWH (outside of APLA).^{34,35} Other placental complications have often been studied together due to their common pathophysiology (see Table 5).

ACCP Recommendations

Low-dose aspirin starting in the second trimester is recommended throughout the pregnancy for women at risk of pre-eclampsia (grade 1B).

Low-dose aspirin plus prophylactic/intermediate-dose UFH or LMWH is recommended for APLA syndrome based on recurrent early pregnancy losses (grade 1B). Without APLA or thrombophilia, the recommendation is against antithrombotic prophylaxis (grade 1B).

For women with inherited thrombophilia and a history of pregnancy complications, the suggestion is not to use antithrombotic prophylaxis (grade 2C).

Discussion

Since 2010, there have been four more randomized controlled trials (therefore not available when the ACCP guidelines were written). These trials examined secondary prevention of obstetrical complication with LMWH in women with or without thrombophilia (see Table 5).^{36–41} The data are exciting, with most studies showing a reduction of severe outcomes associated with use of LMWH.

Case Conclusion

In this case, we would screen the patient only for APLA. Low-dose ASA would be recommended. Prophylactic LMWH would also be suggested, based on preliminary but accumulating evidence showing possible associated benefits. The risks, side effects, and cost of medication need to be discussed.

Conclusion

Women of child-bearing age and receiving anticoagulation treatment should also receive adequate contraception. With no human data, and uncertainty about animal studies in pregnancy and lactation, we believe that the new oral direct thrombin and anti-Xa inhibitors should be avoided.

VTE prevention in asymptomatic women with thrombophilia is still controversial. Risk assessment should take into account patient preference and other risk factors. Family history is an important consideration. Although antithrombin deficiency does not seem to be associated with a higher rate of VTE in pregnancy, we believe that cautious thromboprophylaxis is still warranted, until stronger evidence argues otherwise.

We believe that there is no indication to screen for inherited thrombophilia in placental complications. ASA is the only recommended therapy for secondary prevention of pre-eclampsia. Although the role of LMWH treatment seems to be promising, no definite recommendation can yet be made.

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