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GUIDELINES

European guidelines on perioperative venous thromboembolism prophylaxis

Surgery during pregnancy and the immediate postpartum period

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Thromboembolic events in the pregnant and postpartum patient remain rare but potentially fatal complications. The aim of this section was to analyse the few prospective studies addressing the issue of thromboprophylaxis following a surgical procedure during and immediately after pregnancy, as well as national guidelines, and to propose European guidelines on this specific condition. Thromboprophylaxis is broadly recommended due to the combined risks of surgery and pregnancy or the postpartum period, regardless of the mode of delivery. We recommend prophylactic thromboprophylaxis following surgery during pregnancy or the postpartum period when they imply, as a consequence, bed rest, until full mobility is recovered (Grade 1C). Similarly, thromboprophylaxis should be used in cases of perioperative infection during pregnancy or the postpartum period. Concerning thromboprophylaxis following a caesarean section, it seems avoidable only in elective procedures in low-risk patients, after a normal pregnancy, and with an early rehabilitation protocol. The duration of thromboprophylaxis following caesarean section should be at least 6 weeks for high-risk patients, and at least 7 days for the other patients requiring anticoagulation (Grade 1C).

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A synopsis of all recommendations can be found in the following accompanying article:

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Introduction

Thromboembolic events during pregnancy and the postpartum period remain rare but potentially lethal events.[1–5] For the past two decades, thrombotic risks during this period have been evaluated by numerous population-based observational studies. Diagnostic scores have been elaborated to guide clinical evaluation and prophylaxis decision-making. Because gaps persist in our knowledge of these risks, guidelines are mostly based on experts' opinions.[6] As a result, most hospitals adapt, apply and evaluate thromboprophylactic indications, doses and duration during pregnancy and the early postpartum period based on local epidemiology to minimise maternal mortality and morbidity.[7–9]

Increased thrombotic risks induced by surgery during pregnancy and the early postpartum period have not been specifically addressed. In Europe, caesarean section is the

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most frequent surgical procedure during pregnancy, with more than one million cases per year, but pregnant women also more rarely undergo a wide variety of non-obstetrical surgical procedures.[10,11] The aim of this section was to analyse the available prospective studies addressing the issue of thromboprophylaxis following a surgical procedure during pregnancy, as well as national guidelines, and to propose European guidelines on this specific condition.

Nonobstetric surgery during pregnancy and the early postpartum period

Surgery has been identified in epidemiological studies as one of the factors increasing the maternal thrombotic risk during pregnancy and the immediate postpartum period.[12,13] Both pregnancy-induced hypercoagulability and vena cava compression syndrome increase the already inherent thrombotic risk of each surgical procedure. This increase in basal thrombotic risk was demonstrated in a cohort of 2826 women with underlying malignant diseases in pregnancy.[14] Some cancers increase pregnancy-related risks of deep vein thrombosis: cervical cancer (odds ratio [OR] 8.64, 95% confidence interval [CI] [2.15 to 34.79]), ovarian cancer (OR 10.35, 95% CI [1.44 to 74.19]), Hodgkin's disease (OR 7.87, 95% CI [2.94 to 21.05]) and myeloid leukaemia (OR 20.75, 95% CI [6.61 to 65.12]). There was no increased risk of VTE among women with brain cancer, thyroid cancer, melanoma and lymphoid leukaemia.[14] Surgery may increase this risk through perioperative bed rest, inflammatory syndrome and infection.[10,15–17] More frequently in the postpartum period, deep ovarian vein thrombosis, which can occur following emergency caesarean section or genital tract injury repairs, requires both antithrombotic and antibiotic treatment.[18,19]

Caesarean section

The size of the absolute thrombotic risk for elective or emergency caesarean section in healthy young women varies among studies.[1–5,20] The frequency of symptomatic and asymptomatic deep venous thrombosis (DVT) in a low-risk caesarean section population has been evaluated in a combined clinical-epidemiological substudy.[21] A total of 59 women undergoing elective caesarean section were screened for DVT by a leg Doppler ultrasound and did not develop any DVT despite the absence of postoperative thromboprophylaxis. During the study period, caesarean section was performed in 1067 out of the 5364 live births (19.9%). Five (0.47%) of these women developed symptomatic pulmonary embolism and all of these women had additional risk factors for VTE such as obesity, twin pregnancy, a second surgical procedure or placenta praevia. The authors conclude that the risk of DVT among healthy pregnant women undergoing elective caesarean section is low and thromboprophylaxis is probably not justified. There is only one comparative prospective trial comparing two types of prophylactic-dose low molecular weight heparin (LMWH) with placebo for thromboprophylaxis after elective caesarean section in patients with one or more risk factors, as well as all emergency caesarean section.[22] A significant thrombotic events reduction was observed in the treatment groups: VTE occurred in one (0.042%) woman in the bemiparin group, two (0.085%) women in the enoxaparin group, and nine (0.384%) women in the control group ($P = 0.017$). Wound dehiscence, haematoma and separation occurred in the enoxaparin group but not in the bemiparin group.

The pharmacological profiles of the various LMWH, the mode of administration and mode of dose adjustment have been studied in small series to guide management. An Australian preliminary study, which was a small double-blind randomised controlled trial on 76 patients undergoing caesarean section, comparing dalteparin with placebo, found a 1.3% thrombotic event rate (95% CI [0.007% to 7.1%]), that is only one thrombosis, which occurred in the treatment group between 2 and 6 weeks postpartum.[23] In contrast, a multi-centre pilot study testing the feasibility of an randomized controlled trials to compare LMWH versus placebo for thromboprophylaxis after caesarean section concluded negatively because a very low recruitment rate was observed and only one out of 141 thrombotic event occurred in the treatment group.[24] A Cochrane review[20] did not find evidence in favour of systematic LMWH prophylaxis to reduce the risk of symptomatic VTE after elective caesarean section in low-risk patients (Relative risk [RR] 1.30, 95% CI [0.39 to 4.27]; four trials, 840 women). This result was consistent when considering either pulmonary embolism (RR 1.10; 95% CI [0.25 to 4.87]; four trials, 840 women) or deep vein thrombosis (RR 1.74; 95% CI [0.23 to 13.31]; four trials; 840 women).

This absence of evidence leads to a wide variation in guidelines on prophylactic strategies.[7,25] For a similar condition, LMWH thromboprophylaxis should be prescribed in only 1% of patients in the American College of Obstetrics and Gynecology guidelines, in 34.8% following the 9th recommendations of the American College of Chest Physicians and 85% for the Green Top guidelines of the Royal College of Obstetrics and Gynaecology in the United Kingdom.[25] The recent French guidelines for postpartum management,[26] based on odds ratio for each risk factor, recommend no prophylaxis for elective low risk caesarean section. Thromboprophylaxis strategies also need to take into account the anxiety induced by the treatment and the injection on patient's compliance.[27] The recent paper by Bates *et al.*[7] compares available guidelines to help patients, physicians and societies to balance VTE risks, and prevention benefits with potential side-effects such as risks of bleeding, wound haematoma, analgesic limitations and allergy at the injection sites.

What is a low-risk caesarean section?

This point has been addressed differently by national colleges and scientific bodies. Low risk is mostly defined by the negative, that is what it is not.

For example, in 2015, the Royal College of Obstetricians and Gynaecologists recommended a thromboprophylactic treatment in the postpartum period if more than one of the following minor risk factors is present[28]:

(1) Age >35 years
(2) Obesity (BMI $\geq 30\,kg\,m^{-2}$)
(3) Parity ≥ 3
(4) Smoker
(5) Elective caesarean section
(6) Family history of VTE
(7) Low-risk thrombophilia
(8) Gross varicose veins
(9) Current systemic infection
(10) Immobility, for example paraplegia, long-distance travel
(11) Current pre-eclampsia
(12) Multiple pregnancy
(13) Pre-term delivery in this pregnancy (<37+0 weeks)
(14) Stillbirth in this pregnancy
(15) Mid-cavity rotational or operative delivery
(16) Prolonged labour (>24 h)
(17) Postpartum haemorrhage > 1 l or blood transfusion

Another way to consider the problem is to define a frequency or risk threshold, as did the American college of Chest Physicians in 2012, and subsequently the *College National des Gynécologues et Obstétriciens Français* in 2015, with a 10-fold increase limit based on the multiplication of odds ratios of individual risk factors.[29] This methodology broadens the population not receiving thromboprophylaxis following a caesarean section.

Similarly, the duration of thromboprophylaxis following a caesarean section varies from one guideline to another. Most authors agree that high-risk patients should be treated for at least 6 weeks, but recommendations range from 7 days to 6 weeks for other patients, with very little evidence to tailor the duration to individual risk.

In a historical comparison of maternal adverse events following the Royal College of Obstetrics and Gynaecology guidelines' wider strategy for thromboprophylactic indications, a reduction in maternal deaths due to thromboembolism has been suggested.[30] This trend was confirmed by more recent maternal morbidity surveys.[31,32]

Recommendations

Nonobstetric surgery during pregnancy

(1) We recommend thromboprophylaxis following surgery during pregnancy or the postpartum period when they imply, as a consequence, bed rest, until full mobility is recovered (Grade 1C).
(2) We suggest that thromboprophylaxis should be used in cases of perioperative infection during pregnancy or the postpartum period (Grade 2C).

Caesarean section

(1) Thromboprophylaxis is recommended after caesarean section in all cases, except elective caesarean section in low-risk patients (Grade 1C), but there is no clear consensus on the definition of this population.
(2) The duration of thromboprophylaxis following caesarean section should be at least 6 weeks for high-risk patients, and at least 7 days for the other patients requiring anticoagulation (Grade 1C).

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References

1 Bates SM, Greer IA, Middeldorp S, *et al.*, VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141 (2 Suppl)**:e691S–e736S.
2 Nelson-Piercy C, MacCallum P, Mackillop P. RCOG Guidelines n°37a. 2015. https://www.rcog.org.uk/globalassets/.../guidelines/gtg-37b.pdf.
3 Benhamou D, Mignon A, Aya G, *et al.* Prophylaxis of thromboembolic complications in obstetrics and gynaecology. *Ann Fr Anesth Reanim* 2005; **24**:911–920.
4 Chauleur C, Gris J-C, Seffert P, *et al.* Latest developments on risk factors and prophylaxis of thromboembolic disease in obstetrics. *Gynecol Obstet Fertil* 2012; **40**:301–307.
5 Romualdi E, Dentali F, Rancan E, *et al.* Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. *J Thromb Haemost* 2013; **11**:270–281.
6 Middeldorp S. Thrombosis in women: what are the knowledge gaps in 2013? *J Thromb Haemost* 2013; **11 (Suppl 1)**:180–191.
7 Bates SM, Middeldorp S, Rodger M, *et al.* Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis* 2016; **41**:92–128.
8 Kamel H, Navi BB, Sriram N, *et al.* Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med* 2014; **370**:1307–1315.
9 Virkus RA, Løkkegaard ECL, Lidegaard Ø, *et al.* Venous thromboembolism in pregnancy and the puerperal period: a study of 1210 events. *Acta Obstet Gynecol Scand* 2013; **92**:1135–1142.
10 Van De Velde M, De Buck F. Anesthesia for nonobstetric surgery in the pregnant patient. *Minerva Anestesiol* 2007; **73**:235–240.
11 Alexander S, Blondel B, Bouvier-Colle M-H, *et al.* European perinatal health report. Health and care of pregnant women and babies in Europe in 2010. http://www.europeristat.com/reports/european-perinatal-health-report-2010.html. [Accessed 5 August 2017].
12 Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium: a register-based case-control study. *Am J Obstet Gynecol* 2008; **198**:233–240.
13 Lindqvist PG, Bremme K, Hellgren M, Working Group on Hemostatic Disorders (Hem-ARG) Swedish Society of Obstetrics and Gynecology: efficacy of obstetric thromboprophylaxis and long-term risk of recurrence of venous thromboembolism. *Acta Obstet Gynecol Scand* 2011; **90**:648–653.

14 Bleau N, Patenaude V, Abenhaim HA. Risk of venous thrombo-embolic events in pregnant patients with cancer. *J Matern Fetal Neonatal Med* 2016; **29**:380–384.
15 Reitman E, Flood P. Anaesthetic considerations for nonobstetric surgery during pregnancy. *Br J Anaesth* 2011; **107 (Suppl 1)**:i72–i78.
16 Fanzago E. Anaesthesia for non obstetric surgery in pregnant patients. *Minerva Anestesiol* 2003; **69**:416–427.
17 Cheek TG, Baird E. Anesthesia for nonobstetric surgery: maternal and fetal considerations. *Clin Obstet Gynecol* 2009; **52**:535–545.
18 Mone F, McKeown G, Adams B. Ovarian vein thrombosis in pregnancy and the puerperium: a case series. *J Obstet Gynaecol* 2015; **35**:853–854.
19 Karrasch M, Rödel J, Mühler N, *et al.* Ovarian vein thrombosis (OVT) following invasive group A Streptococcus (iGAS) puerperal sepsis associated with expression of streptococcal pyrogenic exotoxin genes speC, speG and speJ. *Eur J Obstet Gynecol Reprod Biol* 2015; **184**: 127–130.
20 Bain E, Wilson A, Tooher R, *et al.* Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane Database Syst Rev* **(2)**:2014;CD001689.
21 Jacobsen AF, Drolsum A, Klow NE, *et al.* Deep vein thrombosis after elective cesarean section. *Thromb Res* 2004; **113**:283–288.
22 Alalaf SK, Jawad RK, Muhammad PR, *et al.* Bemiparin versus enoxaparin as thromboprophylaxis following vaginal and abdominal deliveries: a prospective clinical trial. *BMC Pregnancy Childbirth* 2015; **15**:72.
23 Burrows RF, Gan ET, Gallus AS, *et al.* A randomised double-blind placebo controlled trial of low molecular weight heparin as prophylaxis in preventing venous thrombolic events after caesarean section: a pilot study. *BJOG* 2001; **108**:835–839.
24 Gates S, Brocklehurst P, Ayers S, Bowler U, Thromboprophylaxis in Pregnancy Advisory Group. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low-molecular-weight heparin. *Am J Obstet Gynecol* 2004; **191**:1296–1303.
25 Palmerola KL, D'Alton ME, Brock CO, Friedman AM. A comparison of recommendations for pharmacologic thromboembolism prophylaxis after caesarean delivery from three major guidelines. *BJOG* 2016; **123**:2157–2162.
26 Sénat MV, Sentilhes L, Battut A, *et al.* Postpartum: guidelines for clinical practice: short text. *J Gynecol Obstet Biol Reprod* 2015; **44**:1157–1166.
27 Hawkins TLA, Lange IR, Gibson PS. Compliance with a perinatal prophylaxis policy for prevention of venous thromboembolism after caesarean section. *J Obstet Gynaecol Can* 2008; **30**:1110–1117.
28 RCOG guidelines 37 a focus on the risk detection and prevention. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a April 2015 (2015). Royal College of Obstetricians and Gynaecologists. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf. Accessed 9 December 2016.
29 Fuchs F, Benhamou D. Postpartum management after cesarean delivery. Guidelines for clinical practice. *J Gynecol Obstet Biol Reprod* 2015; **44**:1111–1117.
30 Touqmatchi D, Cotzias C, Girling J. Venous thromboprophylaxis in pregnancy: the implications of changing to the 2010 RCOG guidelines. *J Obstet Gynaecol* 2012; **32**:743–746.
31 Guimicheva B, Czuprynska J, Arya R. The prevention of pregnancy-related venous thromboembolism. *Br J Haematol* 2015; **168**:163–174.
32 Guglielminotti J, Wong CA, Landau R, Li G. Temporal trends in anesthesia-related adverse events in cesarean deliveries, New York State, 2003–2012. *Anesthesiology* 2015; **123**:1013–1023.