Complete Summary

GUIDELINE TITLE

Thromboprophylaxis during pregnancy, labour and after vaginal delivery.

BIBLIOGRAPHIC SOURCE(S)

Royal College of Obstetricians and Gynaecologists (RCOG). Thromboprophylaxis during pregnancy, labour and after vaginal delivery. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2004 Jan. 13 p. (Guideline; no. 37). [52 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.
- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Venous thromboembolism during pregnancy and following vaginal delivery

GUIDELINE CATEGORY

Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide guidance based on the available evidence on the prevention of venous thromboembolism (VTE) during pregnancy and following vaginal delivery.

Note: The guideline does not address thromboprophylaxis following caesarean section or the acute management of VTE in pregnancy.

TARGET POPULATION

Women at risk of venous thromboembolism during pregnancy and following vaginal delivery

INTERVENTIONS AND PRACTICES CONSIDERED

Risk Assessment

1. Assessment of risk factors for venous thromboembolism (VTE)

2. Patient history
3. Screening for inherited and acquired thrombophilia (ideally before pregnancy)

Management/Prevention

1. Thromboprophylaxis (postpartum and antenatally)
    - Low molecular weight heparin (LMWH)
    - Aspirin
    - Warfarin (postpartum only)
    - Graduated elastic compression stockings
2. Referral to hematological specialist

Considered but not recommended: dextran for thromboprophylaxis; warfarin during pregnancy

MAJOR OUTCOMES CONSIDERED

- Risk of venous thromboembolism (VTE)
- Incidence of venous thromboembolism (VTE)
- Side effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A search of Medline from 1966 to 2002 was performed to identify all relevant randomised controlled trials (RCTs), systematic reviews, and meta-analyses. The databases were searched using the relevant Medical Subject Heading (MeSH) terms including all subheadings. The principal terms used were "venous thromboembolism," "thrombosis," "pregnancy," "postpartum," "puerperium," "antenatal," and "prenatal."

In addition, current guidelines for the prevention of venous thromboembolism (VTE) in pregnancy and the puerperium were reviewed. A Cochrane review has highlighted the lack of evidence from randomised trials evaluating strategies for the prevention of VTE during pregnancy and, in general, guideline recommendations for the prevention of VTE during pregnancy are extrapolated from studies in nonpregnant women.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well-designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study

III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The recommendations were graded according to the level of evidence upon which they were based.

Grade A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)

Grade B - Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations (evidence levels IIa, IIb, III)

Grade C - Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV)

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following discussion in the Guidelines and Audit Committee, each green-top guideline is formally peer reviewed. At the same time the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) website for further peer discussion before final publication.

The names of author(s) and nominated peer reviewers are included in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Levels of evidence (**Ia-IV**) and grading of recommendations (**A-C**) are defined at the end of the "Major Recommendations" field.

Preconceptual Antenatal Risk Assessment

Risk Factors

C - All women should undergo an assessment of risk factors for venous thromboembolism (VTE) in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to hospital or develops other intercurrent problems.

See the table below for risk factors for venous thromboembolism in pregnancy and the puerperium.

Risk factors for venous thromboembolism in pregnancy and the puerperium[a]	
Pre-existing	**New onset or transient[b]**
• Previous VTE • Thrombophilia • Congenital • Antithrombin deficiency • Protein C deficiency • Protein S deficiency • Factor V Leiden • Prothrombin gene variant • Acquired (antiphospholipid syndrome) • Lupus anticoagulant • Anticardiolipin antibodies • Age over 35 years • Obesity (body mass index [BMI] >30 kg/m^2) either pre-pregnancy or in early pregnancy • Parity >4 • Gross varicose veins • Paraplegia • Sickle cell disease • Inflammatory disorders (e.g., inflammatory bowel disease) • Some medical disorders (e.g., nephrotic syndrome, certain cardiac diseases) • Myeloproliferative disorders (e.g., essential thrombocythaemia, polycythaemia vera)	• Surgical procedure in pregnancy or puerperium (e.g., evacuation of retained products of conception, postpartum sterilisation) • Hyperemesis • Dehydration • Ovarian hyperstimulation syndrome • Severe infection (e.g., pyelonephritis) • Immobility (>4 days bed rest) • Pre-eclampsia • Excessive blood loss • Long-haul travel • Prolonged labour[c] • Midcavity instrumental delivery[c] • Immobility after delivery[c]

[a] Although these are all accepted as thromboembolic risk factors, there are few data to support the degree of increased risk associated with many of them.

[b] These risk factors are potentially reversible and may develop at later stages in gestation than the initial risk assessment or may resolve; an ongoing individual risk assessment is important.

[c] Risk factors specific to postpartum VTE only

Investigation of Women with Previous VTE

B - Women with previous VTE should be screened for inherited and acquired thrombophilia ideally before pregnancy.

Thromboprophylaxis During Pregnancy and the Puerperium

Expert haematological advice or referral to a joint obstetric and haematology clinic should be sought in cases when the antenatal team is uncertain about thromboprophylaxis.

Women With a Previous VTE and No Thrombophilia

C - Women with previous VTE should be offered postpartum thromboprophylaxis with low molecular weight heparin (LMWH). It may be reasonable not to use antenatal thromboprophylaxis with heparin in women with a single previous VTE associated with a temporary risk factor that has now resolved.

C - Women with previous recurrent VTE or a previous VTE and a family history of VTE in a first-degree relative should be offered thromboprophylaxis with LMWH antenatally and for at least six weeks postpartum.

Women With a Previous VTE Who Have Inherited Thrombophilia

Expert haematological advice should be sought for women with symptomatic thrombophilia, as specific thrombophilias, particularly antithrombin (AT) deficiency, merit higher doses of LMWH (see Table 2 in the original guideline document) for thromboprophylaxis.

B - Women with previous VTE and thrombophilia should be offered thromboprophylaxis with LMWH antenatally and for at least six weeks postpartum.

Women With Inherited Thrombophilia Without Previous VTE

Women should be stratified according to the level of risk associated with their thrombophilia. Since the risk of VTE is lower in women with no history of VTE, antenatal thromboprophylaxis is not always necessary, except in those with combined defects, those homozygous for defects, or those with antithrombin deficiency. Women with antithrombin deficiency should always receive thromboprophylaxis in pregnancy and the puerperium.

Women with known inherited or acquired thrombophilia may qualify for LMWH or warfarin for six weeks following delivery, even if they were not receiving antenatal thromboprophylaxis if they have other risk factors (see table, above).

C - Women with asymptomatic inherited or acquired thrombophilia may qualify for antenatal or postnatal thromboprophylaxis, depending on the specific thrombophilia and the presence of other risk factors.

Women with Acquired Thrombophilia (Antiphospholipid Syndrome)

Women with antiphospholipid syndrome identified because of recurrent miscarriage may not require LMWH for six weeks postpartum but should receive LMWH for at least three to five days, especially if they have other risk factors.

Women Without Previous VTE or Thrombophilia

Clinical judgement is required with regard to the weighting of the above risk factors. There are circumstances where one or two risk factors alone may be sufficient to justify antenatal thromboprophylaxis with LMWH, for example, an extremely obese woman admitted to the antenatal ward.

The risk of VTE should be discussed with women at risk, and the reasons for individual recommendations explained.

Timing and Duration of Thromboprophylaxis

Antepartum

As VTE during pregnancy has an equal distribution throughout gestation, if a decision is made to initiate thromboprophylaxis antenatally, this should begin as early in pregnancy as practical. Once antenatal treatment is initiated, it should continue until delivery unless a specific risk factor is removed or disappears.

Women with ovarian hyperstimulation syndrome (OHSS) require thromboprophylaxis for at least the period of inpatient stay. Similarly, women with multiple risk factors for VTE and at risk of OHSS undergoing ovulation induction may also be considered for thromboprophylaxis. Advice for pregnant women travelling by air is available.

Postpartum

Postpartum thromboprophylaxis should be given as soon as possible after delivery, provided that there is no postpartum haemorrhage. Those with postpartum haemorrhage should be fitted with thromboembolic deterrent stockings. If the woman has been given regional analgesia, LMWH should be withheld until four hours after insertion or removal of the epidural catheter (or six hours if either insertion or removal were traumatic). The first postpartum dose can be given after insertion but before removal of the epidural catheter.

As the prothrombotic changes of pregnancy do not revert completely to normal until several weeks after delivery, postpartum thromboprophylaxis is normally continued for six weeks in high-risk women. In practice, this will mean women learning to inject themselves if they have not already commenced heparin antenatally. However, for women at lower risk, prophylaxis for three to five days is usually recommended, despite the lack of evidence in this area. Low risk includes those with two current or persisting risk factors as discussed in the table above and asymptomatic thrombophilias with low thrombotic risk (heterozygous factor V Leiden and prothrombin gene variant).The risk of VTE reduces when women are mobile postpartum but does not disappear. If the woman is discharged home early, her thromboprophylaxis should be continued at home, to complete the course of three to five days. The combined oral contraceptive pill should not be prescribed during the first three months postpartum for women with other risk factors for VTE.

Just as circumstances and risk factors can change antenatally so too may they in the puerperium. Therefore, puerperal women undergoing surgery for any reason or those who develop severe infection or who choose to travel long-haul are at increased risk of VTE even though they may have been discharged from hospital following vaginal delivery several weeks before.

B - Antenatal thromboprophylaxis should begin as early in pregnancy as practical. Postpartum prophylaxis should begin as soon as possible after delivery (but see precautions after use of regional anaesthesia).

Agents for Thromboprophylaxis

The different options for and types of treatment should be discussed with the mother.

Low Molecular Weight Heparin

B - Low molecular weight heparins are the agents of choice for antenatal thromboprophylaxis. They are as effective as and safer than unfractionated heparin in pregnancy.

See Table 2 of the original guideline document for suggested antenatal prophylactic and therapeutic doses of LMWH. Experience indicates that, provided that the woman has normal renal function, monitoring of anti-Xa levels is not required when LMWH is used for thromboprophylaxis. In antithrombin deficiency, anti-Xa monitoring is critical, higher doses of LMWH may be necessary, and these patients should be monitored by a haemostatic expert. Antithrombin concentrates may be required. Although the risk of heparin-induced thrombocytopenia is extremely low with LMWH and has never been reported in pregnancy, current guidelines still recommend checking the platelet count one week after starting LMWH.

Where antenatal thromboprophylaxis with LMWH is given to women who are normally on long-term oral anticoagulants, usually because of previous recurrent VTE and/or a thrombophilia, higher prophylactic doses or therapeutic doses of LMWH may be appropriate (see Table 2 of the original guideline document). Whether high prophylactic doses or therapeutic doses are required is controversial and there is some evidence from nonpregnant and pregnant data that the former may suffice. For postpartum thromboprophylaxis, LMWH is probably the agent of choice for women who had LMWH antenatally or for those requiring only three to five days of postpartum treatment. Experience of enoxaparin in the puerperium reports no adverse effects on the baby resulting from breastfeeding.

Low-Dose Aspirin

The use of low-dose aspirin (75 mg daily) may be appropriate in situations where the risk of VTE is increased but is not deemed high enough to warrant the use of antenatal LMWH; for example, in women with previous provoked VTE without thrombophilia. Women should be advised of the lack of evidence for benefit of aspirin use for thromboprophylaxis in pregnancy.

Warfarin

Warfarin is safe after delivery and for breastfeeding, although it requires close monitoring, frequent visits to an anticoagulant clinic, and carries an increased risk of postpartum haemorrhage and perineal haematoma compared with LMWH. It is

not appropriate for women requiring only three to five days of postpartum prophylaxis.

If the woman chooses to commence warfarin postpartum, this can usually be initiated on the second or third postnatal day. LMWH should be continued until the international normalised ratio is greater than 2.0.The dosage regimens are the same as for women converting to warfarin postpartum following an acute VTE in pregnancy.

B - Warfarin should usually be avoided during pregnancy. It is safe after delivery and during breastfeeding.

Dextran

Dextran should not be used primarily because of the risk of anaphylaxis, which has killed fetuses by causing massive histamine release and uterine hypertonus.

Graduated Elastic Compression Stockings

Graduated elastic compression stockings may be used antenatally.

Class-I thromboelastic stockings are appropriate for hospital inpatients at increased risk of VTE and may be combined with LMWH. Their use is also recommended for pregnant women travelling by air.

Definitions:

Grading of Recommendations

Grade A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)

Grade B - Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations (evidence levels IIa, IIb, III)

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Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

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III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate thromboprophylaxis in pregnant women and the prevention of venous thromboembolism (VTE) during pregnancy and following vaginal delivery

POTENTIAL HARMS

There is a potential low risk of heparin-induced thrombocytopenia following treatment with low molecular weight heparin.

CONTRAINDICATIONS

CONTRAINDICATIONS

Warfarin should be avoided if possible during pregnancy, especially between 6 and 12 weeks of gestation, because it is associated with an up to 5% risk of teratogenesis and increases the risk of miscarriage, fetal and maternal haemorrhage, neurological problems in the baby, and stillbirth.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Clinical guidelines are "systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions." Each guideline is systematically developed using a

standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of Royal College of Obstetricians & Gynaecologists (RCOG) Green-top Guidelines*.
- These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Royal College of Obstetricians and Gynaecologists (RCOG). Thromboprophylaxis during pregnancy, labour and after vaginal delivery. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2004 Jan. 13 p. (Guideline; no. 37). [52 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jan

GUIDELINE DEVELOPER(S)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

SOURCE(S) OF FUNDING

Royal College of Obstetricians and Gynaecologists

GUIDELINE COMMITTEE

Guidelines and Audit Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Guideline authors are required to complete a "declaration of interests" form.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site.

Print copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Bookshop, 27 Sussex Place, Regent's Park, London NW1 4RG; Telephone: +44 020 7772 6276; Fax, +44 020 7772 5991; e-mail: bookshop@rcog.org.uk. A listing and order form are available from the RCOG Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance for the development of RCOG green-top guidelines. Clinical Governance Advice No 1. 2000 Jan. Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site.
- Searching for evidence. Clinical Governance Advice No 3. 2001 Oct. Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 17, 2005. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection.

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