National Institute for Health and Care Excellence

Draft for consultation

Intrapartum care for women with existing medical conditions or obstetric complications and their babies

[F] Evidence reviews for bleeding disorders

NICE guideline <TBC at publication>

Evidence reviews for women at high risk of adverse outcomes for themselves and/or their baby because of existing maternal medical conditions

September 2018

Draft for consultation

Developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Intrapartum care for women with haemostatic disorders

This evidence report contains information on 3 reviews relating to intrapartum care for women with haemostatic disorders.

- In which women with haemostatic disorders should regional anaesthesia and analgesia be avoided?
- What is the threshold level of platelet count and/or function below which plans for the birth need to be modified in women with haemostatic disorders?
- How should the third stage of labour be managed for women who are at increased risk of bleeding because of haemostatic disorders?

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Review question

In which women with haemostatic disorders should regional anaesthesia and analgesia be avoided?

Introduction

The aim of this review is to identify women with bleeding disorders who are at risk of having complications due to bleeding while having regional anaesthesia or analgesia. This is important because women with bleeding disorders who receive regional techniques for labour analgesia or anaesthesia for birth are at increased risk of developing spinal haematomas. There are also risks from avoiding or withholding regional analgesia or anaesthesia as the woman may be exposed to the (significant) risks of emergency general anaesthesia.

Summary of the protocol

See Table 1 for a summary of the population, prognostic factor and outcomes (PPO) characteristics of this review.

Table 1: Summary of the protocol (PPO) table

Population	Women in labour who have one of the following haemostatic disorders.
	Platelet dysfunction – normally thrombocytopenia
	• Spurious
	• Acquired
	  ○ Gestational
	  ○ Immune thrombocytopenic purpura (ITP)
	  ○ Haemolysis with elevated liver enzymes and low platelets (HELLP)
	  ○ Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP)
	  ○ Systemic lupus erythematosus (SLE)/antiphospholipid antibody syndrome (APS)/Evan's syndrome
	  ○ Infective, for example, human immunodeficiency virus (HIV), parvovirus
	  ○ Drug related
	  ○ Liver disease
	  ○ Disseminated intravascular coagulation (DIC)
	  ○ Myelosuppression, for example, malignancy, infection, autoimmune
	• Congenital
	  ○ Inherited platelet disorder
	  ○ TTP
	Heritable bleeding disorders

	• von Willebrand's disease (Type 1,2,3, acquired, probable) • Haemophilia A (factor VIII) carrier • Haemophilia B (factor IX) carrier • Factor XI deficiency • Factor VII deficiency • Factor XIII deficiency • Factor V deficiency • Factor X deficiency • Prothrombin deficiency • Afibrinogenemia • Dysfibrinogenemia • Hypofibrinogenemia • Fibrinogen deficiency • Combined II+VII+IX+X deficiency • Combined V+VIII deficiency • Other combined diagnoses Acquired bleeding disorders • Acquired Factor V deficiency • Acquired prothrombin deficiency • Acquired Factor XIII deficiency • Acquired deficiency (other)
Prognostic factor	Relevant factors will be limited to the following: • Platelet count • von Willebrand factor (vWF) levels • Platelet functionality test: platelet aggregation and thromboelastography (TEG)/viscoelastic methods including (ROTEM trade name) • Fibrinogen level • Factor XI level • Factor VII level • Factor IX level • Factor XIII level • Factor V level • Factor X level • Factor VIII level • Factor II level
Outcomes	For the woman: • mortality • major morbidity (such as paralysis, spinal haematoma, or spinal cord compression) • adequacy of analgesia (maternal perception of pain (pain scores), need for a top up or second technique) • need for neurological intervention (for example, neurological assessment or surgery) • women's satisfaction with labour and birth (including psychological wellbeing)

APS: antiphospholipid antibody syndrome; DIC: disseminated intravascular coagulation; HELLP: haemolysis with elevated liver enzymes and low platelets; HIV: human immunodeficiency virus; HUS: haemolytic uraemic syndrome; ITP: immune thrombocytopenic purpura; SLE: systemic lupus erythematosus; TEG: thromboelastography; TTP: thrombotic thrombocytopenic purpura; vWF: von Willebrand factor

For further details see the full review protocol in appendix A. The search strategies are presented in appendix B.

Clinical evidence

Included studies

One systematic review of case series, 1 case series study with a systematic review of previous studies, and 1 case series study that used the pooled results from the aforementioned study were included in this review (see 'Summary of clinical studies included in the evidence review').

The systematic review included studies of patients with common bleeding diseases (Choi 2009). Of the 30 studies included in the systematic review, 5 were relevant to this review and included studies among women with haemophilia (Kadir 1997) and women with von Willebrand's disease (Kadir 1998, Marrache 2007, Suddeth 2003, Varughese 2007) who underwent a neuraxial technique. Clinical outcomes were reported according to maternal platelet counts.

The two retrospective case series were among women with thrombocytopenia (Lee 2017, Levy 2018). One of the studies also included a systematic review pooling evidence from previous studies. Five other condition-specific retrospective studies were included within the broader Lee 2017 systematic review and results for these are reported by condition: women with haemolysis with elevated liver enzymes and low platelets (HELLP) syndrome (Palit 2009, Sibai 1986, Vigil-De Gracia 2001) and women with immune thrombocytopenic purpura (ITP) (Tanaka 2009, Webert 2003). The other retrospective case series (Levy 2018) reported pooled results of its primary study combined with the pooled results from Lee 2017. Clinical outcomes were reported according to maternal platelet counts.

Evidence from the studies included in the review is summarised below (see 'Quality assessment of clinical studies included in the evidence review').

Data was reported on the critical outcomes maternal major morbidity and the important outcomes need for neurological intervention. There was no evidence identified for the following outcomes for the woman: mortality (critical outcome), adequacy of analgesia and women's satisfaction with labour and birth (important outcomes). No evidence was identified for other specific population groups listed in the protocol.

See also the study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix D.

Summary of clinical studies included in the evidence review

2 Table 2 provides a brief summary of the included studies.

3 **Table 2: Summary of included studies**

Study	Population	Variables under consideration	Outcomes	Timing of the test
Choi 2009 Systematic review	5 relevant studies within a systematic review of 30 studies Women with von Willebrand disease • Varughese 2007 (N=15) • Marrache 2007 (N=9) • Suddeth 2003 (N=34) • Kadir 1997 (N=6) Women with haemophilia • Kadir 1998 (N=8)	• Type of von Willebrand's disease/ haemophilia • Number of blocks • Pre-and post-treatment coagulation variables • Treatment administered • Needle gauge/type used for the block • Difficulties noted with placement	For the woman: • Frequency of haemorrhagic complications associated with neuraxial technique with or without subsequent neurologic compromise	As part of pre-operative management
Lee 2017 Retrospective case series Systematic review (N=14 studies) (includes Palit 2009, Sibai 1986, Tanaka 2009, Vigil-De Gracia 2001 and Webert 2003)	Primary study: N=573 parturients with a platelet count <100 x 10^9/l identified from MPOG database and billing codes 3 predefined categories based on platelet count 0–49 x 10^9/l n= 15 50–69 x 10^9/l n=36 70–100 x 10^9/l n=522 Total 573 women Type of thrombocytopenia: Mixed 416/573 = type unknown Systematic review: 14 studies identified from literature search N=1402 women	Primary study: • Platelet count Systematic review: • Platelet count	Primary study For the woman: • Epidural haematoma requiring surgical decompression Systematic review For the woman: • Epidural haematoma	Within 72 hours before neuraxial technique
Levy 2018	Primary study: Sample size	Primary study: • Platelet count	Combined data For the woman:	Not reported

Study	Population	Variables under consideration	Outcomes	Timing of the test
Retrospective case series combined with data from Levy 2017 which includes primary data and systematic review data.	N=471 women with a platelet count <100 x 10^9/l of which n=308 received neuraxial blockade 3 predefined categories based on platelet count of women who received neuraxial blockade 0–49 x 10^9/l n=5 50–69 x 10^9/l n=23 70–100 x 10^9/l n=280 Type of thrombocytopenia: Gestational/unspecified 434/471 Preeclampsia/HELLP syndrome 29/471 Immune thrombocytopenic purpura 8/471 Combined with data from previous studies: N=1710 women with platelet count <100 x 10^9/l who received nauraxial blockade 0–49 x 10^9/l n=32 50–69 x 10^9/l n=112 70–100 x 10^9/l n=1566 See above Lee 2017 for more details.	Combined data: • Platelet count	• Spinal epidural haemotoma	(before birth)

1 *HELLP: haemolysis with elevated liver enzymes and low platelets; MPOG: Multicenter Perioperative Outcomes*
2 *Group*

3 See also the study evidence tables in Appendix E. No meta-analysis was undertaken for this
4 review (and so there are no forest plots in Appendix F).

Quality assessment of clinical studies included in the evidence review

6 The clinical evidence profiles for this review question are presented in Table 3, Table 4,
7 Table 5, Table 6 and Table 7. Only evidence from case series studies were included so
8 GRADE methodology was not used and there are no GRADE tables in Appendix G.

Women with thrombocytopenia

Table 3: Outcomes for women with thrombocytopenia by platelet count

Study	Number of pregnancies with outcome/total number of pregnancies (95% CI for risk of event)			Quality	Importance
	Platelet count				
	70-99 x 10^9/l	50-69 x 10^9/l	<50 x 10^9/l		
Epidural haematoma					
Levy 2018[1] Retrospective case series combined with data from previous case series studies	0/1566 (0% to 0.19%)	0/112 (0% to 2.6%)	0/32 (0% to 9%)	Very low[2,3]	Critical
Epidural haematoma requiring surgical decompression within 72 hours of neuraxial technique					
Lee 2017[1] Retrospective case series	0/522 (0% to 0.6%)	0/36 (0% to 8%)	0/15 (0% to 20%)	Very low[3]	Important

CI: confidence interval
1 No details of antenatal therapy available
2 Limited detail provided about the studies included in the combined analysis.
3 Descriptive data from a case series study.

Women with immune thrombocytopenic purpura

Table 4: Outcomes for women with immune thrombocytopenic purpura by platelet count

Study	Number of pregnancies with outcome/total number of pregnancies				Quality	Importance
	Platelet count					
	70-99 x 10^9/l	50-69 x 10^9/l	50-100 x 10^9/l	<50 x 10^9/l		
Epidural haematoma						
Tanaka 2009[1] (from Lee 2017) Case series	0/43	0/4	0/47	-	Very low[2]	Critical
Epidural haematoma						
Webert 2003[3] (from Lee 2017) Case series	-	-	0/25	0/1	Very low[2]	Critical

1 No details of antenatal therapy available.

2 Descriptive data from a case series study.
3 No details of treatment pertinent to these women are available.

Women with HELLP syndrome

Table 5: Outcomes for women with HELLP syndrome by platelet count

Study	Number of pregnancies with outcome/total number of pregnancies		Quality	Importance
	Platelet count			
	50-100 x 10^9/l	<50 x 10^9/l		
Epidural haematoma				
Palit 2009 (from Lee 2017) Case series	0/17	0/1	Very low[1]	Critical
Epidural haematoma				
Sibai 1986 (from Lee 2017) Case series	0/16	-	Very low[1]	Critical
Epidural haematoma				
Vigil de Gracia 2001 (from Lee 2017) Case series	0/28	0/5	Very low[1]	Critical

HELLP: haemolysis with elevated liver enzymes and low platelets
1 Descriptive data from a case series study.

Women with von Willebrand's disease

Table 6: Outcomes for women with von Willebrand's disease based on testing as part of pre-operative management

Study	Number of women with outcome/total number of women	Quality	Importance
Haemorrhagic complications associated with neuraxial technique with or without subsequent neurologic compromise			
Varughese 2007 (from Choi 2009) Case series	0/15	Very low[1]	Critical
Marrache 2007 (from Choi 2009) Case series	0/9	Very low[1]	Critical
Suddeth 2003 (from Choi 2009) Case series	0/34	Very low[1]	Critical

Study	Number of women with outcome/total number of women	Quality	Importance
Kadir 1998 (from Choi 2009) Case series	0/8	Very low[1]	Critical

1 *1 Descriptive data from a case series study.*

Women who are haemophilia A or B carriers

3 **Table 7: Outcomes for women who are haemophilia A or B carriers based on testing**
4 **as part of pre-operative management**

Study	Number of women with outcome/total number of women	Quality	Importance
Haemorrhagic complications associated with neuraxial technique with or without subsequent neurologic compromise			
Kadir 1997 (from Choi 2009) Case series	0/6	Very low[1]	Critical

5 *1 Descriptive data from a case series study.*

Economic evidence

Included studies

8 No economic evidence was identified for this review.

9 See the study selection flow chart in Supplement 2 (Health economics).

Excluded studies

11 No full-text copies of articles were requested for this review and so there is no excluded
12 studies list (see Supplement 2 (Health economics)).

Summary of studies included in the economic evidence review

14 No economic evidence was identified for this review (and so there are no economic evidence
15 tables in Supplement 2 (Health economics).

Economic model

17 No economic modelling was undertaken for this review because the committee agreed that
18 other topics were higher priorities for economic evaluation (see Supplement 2 (Health
19 economics).

Evidence statements

Women with thrombocytopenia

Outcomes for the woman

Major morbidity: epidural haematoma

Very low quality evidence from 1 retrospective case series combining data from previous studies (N=1710) showed that there were no events of spinal epidural haematoma in women with thrombocytopenia (with platelet count <50 x 10^9/l, 50-69 x 10^9/l and 70-99 x 10^9/l). The upper limit of the 95% CI for the risk of spinal epidural haematoma was 0.19% in women with a platelet count of 70-99 x 10^9/l, 2.6% for women with a platelet count of 50-69 x 10^9/l, and 9% for women with a platelet count of <50 x 10^9/l.

Need for neurological intervention: epidural haematoma requiring surgical decompression

Very low quality evidence from 1 retrospective study of a case series of women with thrombocytopenia (N=573) showed that there were no events of epidural haematoma requiring surgical decompression in women with thrombocytopenia (with platelet count <50 x 10^9/l, 50-69 x 10^9/l and 70-99 x 10^9/l) within 72 hours of neuraxial technique. The upper limit of the 95% CI for the risk of epidural haematoma requiring surgical decompression was 0.6% in women with a platelet count of 70-99 x 10^9/l, 8% in women with a platelet count of 50-69 x 10^9/l, and 20% in women with a platelet count of <50 x 10^9/l.

Women with immune thrombocytopenic purpura

Outcomes for the woman

Major morbidity: epidural haematoma

Very low quality evidence from 2 retrospective case series of women with immune thrombocytopenic purpura (N=94 and N=26) showed there were no events of epidural haematoma in women with platelet counts <50 x 10^9/l, 50-100 x 10^9/l, 50-69 x 10^9/l and 70-99 x 10^9/l (also presented within a systematic review of 15 case series).

Women with HELLP syndrome

Outcomes for the woman

Major morbidity: epidural haematoma

Very low quality evidence from 3 retrospective case series of women with HELLP syndrome (N=18, N=16, and N=33) showed there were no events of epidural haematoma in women with platelet counts <50 x 10^9/l and 50-100 x 10^9/l (also presented within a systematic review of 15 case series).

Women with von Willebrand's disease

Outcomes for the woman

Major morbidity: haemorrhagic complications associated with neuraxial technique

Very low quality evidence from a systematic review of case series of women with von Willebrand's disease (N=66 from 4 case series studies) showed there were no events of haemorrhagic complications associated with neuraxial technique (with or without subsequent neurologic compromise) in any of the studies.

Women with haemophilia A or B carriers

Outcomes for the woman

Major morbidity: haemorrhagic complications associated with neuraxial technique

Very low quality evidence from a systematic review of case series of women who were haemophilia A or B carriers (N=6) showed there were no events of haemorrhagic complications associated with neuraxial technique (with or without subsequent neurologic compromise).

Recommendations

F1. Discuss the balance of benefits and risks of regional analgesia and anaesthesia with women with bleeding disorders.

F2. When considering regional analgesia and anaesthesia for women with bleeding disorders, take into account:

- the overall risk of bleeding and opportunity for corrective treatment
- therapeutic and prophylactic anticoagulation
- the risk of bleeding associated with the technique to be used
- the difficulty of needle siting or insertion
- the comparative risks associated with no analgesia or non-regional analgesia
- the comparative risks of general anaesthesia.

Research recommendations

In women with thrombocytopenia, does the use of an additional assessment of bleeding risk allow the safe use of neuraxial anaesthesia?

Rationale and impact

Why the committee made the recommendations

The limited available evidence was not able to show at which level of platelet count or platelet function the risk of complications, such as epidural haematoma, starts to increase. Evidence reported no serious harm (such as epidural haematoma) from epidural or spinal

analgesia or combined spinal–epidural anaesthesia even with a platelet count below 50 x 10^9/l. Bleeding complications are more likely with epidural rather than spinal techniques (because smaller needles are used for the latter). The committee agreed that sometimes they would consider regional analgesia and anaesthesia (especially spinal techniques) for women with low platelet counts. Because serious maternal complications are so rare, the evidence did not allow a definite conclusion that there was no significant risk associated with epidural analgesia when platelet count was low. The committee decided not to set a definitive platelet threshold below which epidural or spinal analgesia should not be considered, but agreed that overall bleeding risk (including, but not limited to, platelet count) should be taken into account. Risks and benefits should be discussed with women, because the risk-benefit ratio will be highly individual and could potentially change in the intrapartum period.

Impact of the recommendations on practice

The recommendations are in line with current NHS practice.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Maternal outcomes were prioritised for this review, as effective analgesia and anaesthesia is mostly important for the woman rather than the baby.

Mortality and morbidities such as paralysis, other neurological deficit, spinal haematoma or spinal compression were identified as critical outcomes for the woman. The committee agreed that these were considered to be the most serious and long-term outcomes for women with bleeding disorders.

The need for neurological intervention was identified as an important outcome, as this is a proxy measure for the seriousness of the woman's condition which might otherwise not be recorded as major morbidity. For example, women with bleeding disorders who have a symptomatic epidural haematoma are likely to have a neurological intervention. Women's satisfaction with labour and birth or adequacy of analgesia were also regarded as important outcomes as these assess whether clinicians are able to offer adequate analgesia despite the risks posed by the underlying bleeding disorder.

The quality of the evidence

One systematic review of case series, 1 case series study with a systematic review of previous studies, and 1 case series study that used the pooled results from the aforementioned study were included in this review. The quality of the systematic reviews was assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist. The studies did not describe the eligibility criteria for inclusion explicitly. Moreover, the methodological quality assessments of the included studies in the systematic reviews was unclear and the systematic reviews did not attempt to minimise errors. Although a wide range of bleeding disorders was considered, treatment prior to labour was not reported clearly and thus, it was unclear as to whether the populations from different studies were sufficiently similar to be synthesised.

The quality of the individual case series was assessed using the Joanna Briggs Institute appraisal checklist for case series. While there were no major problems in the case series studies overall, evidence from such studies was considered to be of very low quality as it is only descriptive and non-comparative.

The committee discussed how there are a large number of different bleeding disorders which could need different management strategies. While they searched for evidence of these, they did not find evidence on most of them, and the evidence they did find was of very low quality because of small sample sizes, poor study designs, and heterogeneity in the study populations (for example, no adjustment for treatment given prior to labour).

None of the included studies reported any of the adverse events (complications) of interest in the guideline review. The upper limits of 95% CIs for the frequency of adverse events typically increased as platelet level decreased, but it was also the case that the number of women in each platelet count category decreased as the platelet count decreased and so the upper limit of each CI reflects greater uncertainty in the estimate as the platelet count decreases. For this reason the committee concluded that there was no evidence found on the platelet count or level of platelet function at which the risk of complications starts to increase.

Benefits and harms

The benefits of regional over general anaesthesia are that, for the woman, it avoids the increased risks of mortality and serious morbidity associated with general anaesthesia. However in a population of women with bleeding disorders, regional anaesthesia carries risks of bleeding into the spine causing long-term or permanent nerve damage including paralysis. The committee explained that balancing these risks and harms was not always straightforward, and that the woman should be included in discussions where risks and benefits are considered. The committee emphasised that the woman could not give informed consent for the procedure without this and therefore a strong recommendation was warranted even in the absence of evidence.

The committee used their clinical experience to recommend taking into account a list of factors to guide decision making on regional analgesia and anaesthesia. These factors could help determine whether regional blockade is more or less risky. The committee highlighted that while platelet count was important, there was no evidence to show at what platelet count regional blockade would or would not be safe. For example, the committee agreed that even with low platelet counts, regional blockade would sometimes be considered. While the committee was unable to identify a definitive list of factors that would determine whether regional blockade was or was not safe, they identified examples of factors that the anaesthesiologist might take into account and discuss with the woman. These included: considering the overall risk of bleeding; taking into consideration platelet count and the bleeding disorder at hand, and whether there is an opportunity for corrective treatment; therapeutic or prophylactic anticoagulation; techniques to be used for anaesthesia and analgesia and their associated risks of bleeding, for example, bleeding complications are more common with epidural technique compared to spinal technique because the needle is smaller in the spinal technique; difficulty of needle siting or insertion due to factors such as the woman being obese; the comparative risks of having no analgesia or having non-regional analgesia; and the risks associated with general anaesthesia.

Cost effectiveness and resource use

The committee made a qualitative assessment about cost effectiveness in the absence of any evidence to indicate the level of platelet count at which the risk of complications starts to increase.

The committee was uncertain as to whether there was a significant risk with epidural analgesia when the platelet count was low, and so they did not set a platelet threshold above which they would consider epidural or spinal analgesia to be safe and cost effective. However, they agreed that it would be cost effective to take the overall bleeding risk into account because safety and cost effectiveness are likely to be highly individualised.

The committee considered that the recommendations were in line with current practice and they did not anticipate the recommendations would have a significant resource impact for the NHS

Other factors the committee took into account

Due to the lack of good quality evidence and uncertainty of the safety of neuraxial technique in women with bleeding disorders, a research recommendation was made to evaluate the value of using an additional assessment such as thromboelastogram (TEG) to assess platelet function to guide safe decision making on offering neuraxial anaesthesia or analgesia for women with low platelet counts. See appendix L for further details.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Review question

What is the threshold level of platelet count and/or function below which plans for the birth need to be modified in women with haemostatic disorders?

Introduction

The aim of this review is to determine the threshold platelet count level and function at which labour can proceed safely without any modification. This is important because although the majority of women with bleeding disorders can undergo normal vaginal birth without serious bleeding complications, there is possibility of having excessive maternal blood loss, as well as intracranial haemorrhage, among babies of certain women during birth. Prepartum identification of these women is of importance so that they can be better prepared for labour.

Summary of the protocol

See Table 8 for a summary of the population, prognostic factor and outcomes (PPO) characteristics of this review.

Table 8: Summary of the protocol (PPO) table

Population	Women in the intrapartum period who have one of the following bleeding disorders:
	• acquired primary thrombocytopenia
	  ○ gestational thrombocytopenia
	  ○ immune thrombocytopenic purpura (ITP)
	  ○ drug-induced abnormal platelet function, for example, long-term aspirin, heparin

Prognostic factor	• Platelet count • von Willebrand factor (vWF) level • Platelet functionality tests: platelet aggregation and thromboelastography (TEG)
Outcomes	For the woman: • mortality • major morbidity (excessive/abnormal intrapartum or postpartum haemorrhage, or haematoma or wound complications (for example dehiscence, or infection)) • neuraxial haematoma For the baby:

	• perinatal mortality • major morbidity (intracranial haemorrhage)

ITP: immune thrombocytopenic purpura; TEG: thromboelastography; vWF: von Willebrand factor

For further details see the full review protocol in appendix A. The search strategies are presented in appendix B.

Clinical evidence

Included studies

Four retrospective and 1 prospective case series were included in this review (see 'Summary of clinical studies included in the evidence review'). One retrospective case series also combined data from previous studies (Payne 1997).

Of these, 2 studies were among women with gestational thrombocytopenia (Boehlen 2000, Gasparovic 2014) and reported outcomes according to maternal platelet counts. Three studies were among women with immune thrombocytopenic purpura and reported outcomes according to maternal platelet counts (Payne 1997, Tanaka 2009, Won 2005).

Evidence from the studies included in the review is summarised below (see 'Quality assessment of clinical studies included in the evidence review').

Data was reported on all the critical outcomes, maternal mortality and perinatal mortality, major morbidity for the woman or the baby, and neuraxial haematoma for the woman. No evidence was identified among women with drug-induced abnormal platelet function.

See also the study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix D.

Summary of clinical studies included in the evidence review

Table 9 provides a brief summary of the included studies.

Table 9: Summary of studies included in the evidence review

Study	Population	Variables under consideration	Outcomes	Timing of the test (platelet count)
Boehlen 2000 Prospective case series within a case control study	N=786 women with thrombocytopenia (platelet count <150 x 10^9/l) Platelet count 116-149 x 10^9/l n=621 Type of thrombocytopenia:	• Platelet count	For the woman: • Mortality • Major morbidity For the baby: • Perinatal mortality • Major morbidity	On admission to the labour ward or during a prenatal visit during the last month of pregnancy.

Study	Population	Variables under consideration	Outcomes	Timing of the test (platelet count)
	• thrombocytopenia of unknown origin n=602 • HELLP syndrome, preeclampsia, or hypertension n=17 • Other n=2 Platelet count of <116 x 10^9/l n=165 Type of thrombocytopenia: • thrombocytopenia of unknown origin n=136 • HELLP syndrome, preeclampsia, or hypertension n=19 • immune thrombocytopenic purpura n=3 • other n=7			
Gasparovic 2014 Retrospective case series	N=80 women with gestational thrombocytopenia Platelet count 50 - 100 x 10^9/l n=63 Severe group <50 x 10^9/l n=17	• Platelet count	For the woman: • Maternal morbidities For the baby: • Perinatal mortality • Major morbidity	After 24 weeks of gestation
Payne 1997 Retrospective case series combined with data from a review of 17 studies	Primary study: N=41 women (55 pregnancies, 55 babies) with immune thrombocytopenic purpura Combined data: N=601 babies of women with	• Immune thrombocytopenic purpura (exact platelet counts not reported)	For the baby: • Major morbidity	Not reported.

Study	Population	Variables under consideration	Outcomes	Timing of the test (platelet count)
	autoimmune thrombocytopenia from 18 studies/reports			
Tanaka 2009 Retrospective case series	N=75 women with thrombocytopenia Type of thrombocytopenia: • immune n=49 • gestational n=20 • other n=6	• Platelet count	For the woman: • Major morbidity	On the day of anaesthesia
Won 2005 Retrospective case series	N=30 women (31 pregnancies) with chronic immune thrombocytopenic purpura Platelet counts >100 x 10^9/l n=3 50-100 x 10^9/l n=17 20-50 x 10^9/l n=9 <20 x 10^9/l n=2	• Platelet count	For the woman: • Mortality • Major morbidity For the baby: • Perinatal mortality • Major morbidity	Before and during pregnancy (from diagnosis of pregnancy to delivery 1 week ago) and at delivery (from delivery 1 week ago to the time of delivery)

1 *HELLP: haemolysis with elevated liver enzymes and low platelets*

2 See also the study evidence tables in Appendix E. No meta-analysis was undertaken for this
3 review (and so there are no forest plots in Appendix F).

Quality assessment of clinical studies included in the evidence review

5 Only evidence from case series studies were included so GRADE methodology was not used
6 and there are no GRADE tables in appendix G.

Women with gestational thrombocytopenia

8 **Table 10: Outcomes for women with gestational thrombocytopenia by platelet count**

Study	Number of women or babies with outcome/total number of women or babies				Quality	Importance
	Platelet count					
	116-149 x 10^9/l	<116 x 10^9/l	50-100 x 10^9/l	<50 x 10^9/l		

Mortality						
Boehlen 2000 Prospective case series	0/621	0/165	-	-	Very low[1]	Critical
Major morbidity: Bleeding complication						
Boehlen 2000 Prospective case series	0/621	0/165	-	-	Very low[1]	Critical
Major morbidity: DIC, severe maternal postpartum bleeding, or peripartal hysterectomy						
Gasparovic 2014 Retrospective case series	-	-	0/63	0/17	Very low[1]	Critical

1 *DIC: disseminated intravascular coagulation*
2 *1 Descriptive data from a case series study.*

3 **Table 11: Outcomes for babies of women with gestational thrombocytopenia by**
4 **maternal platelet count**

	Number of women or babies with outcome/total number of women or babies					
	Platelet count					
Study	**116-149 x 10^9/l**	**<116 x 10^9/l**	**50-100 x 10^9/l**	**<50 x 10^9/l**	**Quality**	**Importance**
Perinatal mortality						
Boehlen 2000 Prospective case series	0/577	-	-	-	Very low[1]	Critical
Gasparovic 2014 Retrospective case series	-	-	0/63	0/17	Very low[1]	Critical
Major morbidity						
Boehlen 2000 Prospective case series	0/577	-	-	-	Very low[1]	Critical
Major morbidity: Neonatal bleeding						
Gasparovic 2014 Retrospective case series	-	-	0/63	0/17	Very low[1]	Critical

5 *1 Descriptive data from a case series study.*

Women with immune thrombocytopenic purpura

Table 12: Outcomes for women with immune thrombocytopenic purpura by platelet count

Study	Number of women or babies with outcomes/total number of women or babies					Quality	Importance
	Platelet count						
	>100 x 10^9/l	50-100 x 10^9/l	20-50 x 10^9/l	<20 x 10^9/l	<100 x 10^9/l		
Mortality							
Won 2005 Retrospective case series	0/3	0/17	0/9	1/2[1]	-	Very low[2]	Critical
Major morbidity: Gastric ulcer bleeding							
Won 2005 Retrospective case series	0/3	0/17	0/9	1/2[3]	-	Very low[2]	Critical
Major morbidity: Anaesthetic complications							
Tanaka 2009 Retrospective case series	-	-	-	-	0/75	Very low[2]	Critical

1 Cause of death acute pulmonary oedema after caesarean section.
2 Descriptive data from a case series study.
3 Gastric ulcer bleeding during birth (the woman died later due to pulmonary oedema after caesarean section).

Table 13: Outcomes for babies of women with immune thrombocytopenic purpura by maternal platelet count

Study	Number of women or babies with outcomes/total number of women or babies					Quality	Importance
	Platelet count						
	>100 x 10^9/l	50-100 x 10^9/l	20-50 x 10^9/l	<20 x 10^9/l	Not reported		
Perinatal mortality							
Won 2005 Retrospective case series	0[1]	0[1]	0[1]	1[1,2]	-	Very low[3]	Critical
Major morbidity							
Won 2005 Retrospective case series	0[1]	0[1]	0[1]	0[1]	-	Very low[3]	Critical
Major morbidity: Neonatal intracranial haemorrhage							

Study	Number of women or babies with outcomes/total number of women or babies					Quality	Importance
	Platelet count						
	>100 x 10^9/l	50-100 x 10^9/l	20-50 x 10^9/l	<20 x 10^9/l	Not reported		
Payne 1997 Data from 18 studies of immune thrombocytopenic purpura in pregnancy between 1973 and 1997 (including Payne 1997)	-	-	-	-	6/601	Very low[3]	Critical

1 A total of 28 live births (2 intrauterine deaths occurred) but not reported how many live births per each platelet groups.
2 Respiratory failure, born at 27 weeks gestation.
3 Descriptive data from a case series study.

Economic evidence

Included studies

No economic evidence was identified for this review.

See the study selection flow chart in Supplement 2 (Health economics).

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list (see Supplement 2 (Health economics)).

Summary of studies included in the economic evidence review

No economic evidence was identified for this review (and so there are no economic evidence tables in Supplement 2 (Health economics).

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation (see Supplement 2 (Health economics).

Evidence statements

Women with gestational thrombocytopenia

Outcomes for the woman

Mortality

Very low quality evidence from 1 prospective case series among women with gestational thrombocytopenia (N=786) diagnosed on admission to labour ward or in the last antenatal month reported that there were no maternal deaths in women with a platelet count of 116-149 x 10^9/l (n=621) or <116 x 10^9/l (n=165).

Major morbidity: Bleeding complications

Very low quality evidence from 1 prospective case series among women with gestational thrombocytopenia (N=786) diagnosed on admission to labour ward or in the last antenatal month reported that there were no maternal bleeding complications in women with a platelet count of 116-149 x 10^9/l (n=621) or <116 x 10^9/l (n=165).

Major morbidity: disseminated intravascular coagulation (DIC), severe maternal postpartum bleeding, peripartum hysterectomy

Very low quality evidence from 1 retrospective case series among women with gestational thrombocytopenia (N=80) diagnosed after 24 weeks of gestation reported that there were no maternal morbidity events such as DIC, severe maternal postpartum bleeding or peripartal hysterectomy in women with platelet counts of 50-100 x 10^9/l (n=63) or <50 x 10^9/l (n=17).

Outcomes for the baby

Perinatal mortality

Very low quality evidence from 1 prospective case series among women with gestational thrombocytopenia (N=786) diagnosed on admission to the labour ward or in the last antenatal month reported that there were no perinatal deaths of babies born to women with a platelet count of 116-149 x 10^9/l (n=577).

Very low quality evidence from one retrospective case series among women with gestational thrombocytopenia (N=80) diagnosed after 24 weeks of gestation reported that there were no fetal or neonatal deaths of babies born to women with platelet counts of 50-100 x 10^9/l (n=63) or <50 x 10^9/l (n=17).

Major morbidity

Very low quality evidence from one prospective case series among women with gestational thrombocytopenia (N=786) diagnosed on admission to labour ward or in the last antenatal month reported that there was no major neonatal morbidity of babies born to women with a platelet count of 116-149 x 10^9/l (n=577).

Major morbidity: Neonatal bleeding

Very low quality evidence from one retrospective case series among women with gestational thrombocytopenia (N=80) diagnosed after 24 weeks of gestation reported that there were no

neonatal bleeding events of babies born to women with platelet counts of 50-100 x 10^9/l (n=63) or <50 x 10^9/l (n=17).

Women with immune thrombocytopenic purpura

Outcomes for the woman

Mortality

Very low quality evidence from 1 retrospective case series among women with immune thrombocytopenic purpura (N=31 pregnancies) reported one intrapartum maternal death out of two woman with a platelet count of <20 x 10^9/l. The woman developed a gastrointestinal bleed during caesarean section and subsequently died due to pulmonary oedema. There was no maternal deaths in women with platelet counts of >100 x 10^9/l (n=3) or 50-100 x 10^9/l (n=17) or 20-50 x 10^9/l (n=9).

Major morbidity: Gastrointestinal bleeding

Very low quality evidence from 1 retrospective case series among women with immune thrombocytopenic purpura (N=31 pregnancies) reported 1 event of gastrointestinal bleed out of 2 women with a platelet count of <20 x 10^9/l. The bleeding occurred during caesarean section and the woman subsequently died due to pulmonary oedema. There was no gastrointestinal bleeding in women with platelet counts of >100 x 10^9/l (n=3), or 50-100 x 10^9/l (n=17), or 20-50 x 10^9/l (n=9).

Major morbidity: Anaesthetic complications

Very low quality evidence from 1 retrospective case series among women with immune thrombocytopenic purpura (N=75 women) on the day of anaesthesia reported that there were no serious anaesthesia-related complication events in women who had a platelet count of <100 × 10^9/l.

Outcomes for the baby

Perinatal mortality

Very low quality evidence from 1 retrospective case series among women with immune thrombocytopenic purpura (N=29) reported 1 neonatal death due to respiratory failure. This baby was 27 gestational weeks old and was born to 1 out of 2 women with a platelet count of <20 x 10^9/l. The woman developed a gastrointestinal bleed during caesarean section and subsequently died due to pulmonary oedema. There was no perinatal death reported for the babies of all women who had a platelet count of >20 × 10^9/l.

Major morbidity

Very low quality evidence from 1 retrospective case series among women with immune thrombocytopenic purpura (N=28) reported no neonatal morbidity events in any of the platelet count groups.

Major morbidity: Neonatal intracranial haemorrhage

Very low quality evidence from a review of 18 studies between 1973 and 1997 among women with immune thrombocytopenic purpura identified 6 neonatal intracranial haemorrhages in 601 babies.

Recommendations

F3. For woman with known immune thrombocytopenic purpura, before admission for birth:

- plan birth in an obstetric-led unit with a neonatal unit that routinely provides high-dependency care
- assume the baby will be at risk of bleeding irrespective of the woman's platelet count
- consider monitoring maternal platelet count weekly from 36 weeks, and if the platelet count is below 50:
  - discuss and agree a plan for intrapartum management with the multidisciplinary team, including a haematologist
  - consider giving steroids or intravenous immunoglobulin to raise the maternal platelet count.

F4. For women with known immune thrombocytopenic purpura, on admission for birth:

- measure maternal platelet count
- manage intrapartum care according to Table 14.

F5. For women with immune thrombocytopenic purpura or suspected immune thrombocytopenic purpura, take the following precautions to reduce the risk of bleeding for the baby:

- do not use ventouse
- do not carry out fetal blood sampling
- use fetal scalp electrodes with caution
- use mid-cavity or rotational forceps with caution
- bear in mind that a caesarean section may not protect the baby from bleeding
- inform the neonatal team of the imminent birth of a baby at risk
- measure the platelet count in the umbilical cord blood at birth.

F6. For women with gestational thrombocytopenia (presenting for the first time in pregnancy (without pre-eclampsia and HELLP syndrome, and otherwise well), or with an uncertain diagnosis of immune thrombocytopenic purpura, modify the birth plan based on maternal platelet count, using Table 14 as a guide.

Table 14: Modifying the birth plan according to platelet count in women with thrombocytopenia

	Maternal risk	Fetal and neonatal risk
Platelet count above 80 × 109/l	Treat the woman as healthy for the purpose of considering regional analgesia and anaesthesia	If the woman has IPT or suspected IPT, assume the baby is at risk of bleeding and take precautions as outlined in recommendation **Error! Reference source not found.** If the woman has gestational thrombocytopenia, assume the baby has a normal risk of bleeding
Platelet count 50 to 80 × 109/l	Take into account clinical history, the woman's preferences and anaesthetic expertise before considering regional analgesia and anaesthesia	
Platelet count below 50 × 109/l	Avoid regional analgesia and anaesthesia under most circumstances	

Rationale and impact

Why the committee made the recommendations

No evidence was identified on platelet count and level of platelet function at which risks for either the woman or her baby would increase. Therefore the committee made recommendations based on their knowledge and expertise. Women with gestational thrombocytopenia are generally considered at low risk of bleeding complications during birth whereas women with immune thrombocytopenic purpura are regarded as high risk. So the committee recommended significant changes to the birth plan only if the woman had immune thrombocytopenic purpura, or gestational thrombocytopenia with a low platelet count.

Women with immune thrombocytopenic purpura may have a low platelet count and high risk of bleeding whilst the baby has a normal platelet count and low risk of bleeding. Conversely, a woman with immune thrombocytopenic purpura may have a normal platelet count and a baby with a low platelet count and high risk of bleeding. In other words, for women with immune thrombocytopenic purpura the bleeding risk of the woman does not correspond to the bleeding risk of the baby. Consequently if the woman has immune thrombocytopenic purpura, it is safest to treat the baby as being at high risk of bleeding, and modify the birth plan to reduce the bleeding risk to the baby wherever possible, for example, by not carrying out any fetal blood sampling.

Women with gestational thrombocytopenia do not have an alloantibody that affects the fetal platelet count. Gestational thrombocytopenia therefore only puts the woman at risk of bleeding, and not her baby.

Impact of the recommendations on practice

Women with immune thrombocytopenic purpura are at high risk of bleeding and so should give birth in an obstetric unit with a neonatal unit that routinely provides high dependency care. However, the committee were aware that this does not always happen in practice, and

so the recommendation could create more demand for high dependency neonatal units. However, this might be offset by women at lower risk (for example, with gestational thrombocytopenia and a high platelet count) not being referred to these units.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Maternal and neonatal outcomes were prioritised for the review because a bleed in either the woman or the baby can have serious consequences for that person.

Maternal mortality, maternal morbidities (such as excessive or abnormal intrapartum or postpartum haemorrhage or haematoma or wound complications), maternal neuraxial haematoma, perinatal mortality and major neonatal morbidity, including intracranial haemorrhage, were rated as critical outcomes, as these were considered to be detrimental for pregnant women with thrombocytopenia which the committee considered should be avoided at all cost.

The quality of the evidence

The evidence search identified case series of variable sample sizes (range 15 to 786). The quality of each study was assessed using the Joanna Briggs Institute appraisal checklist for case series and none of the studies was considered to have reported comprehensively. The most common omissions were lack of information about how the platelet count was assessed, lack of follow-up data, and lack of description of the setting in order to assess if it was applicable to the UK setting. In one study (Boehlen 2000), although the sample size was 786, the study authors did not report clearly on the inclusion criteria for cases. In another study (Payne 1997), although most of the information was reported (apart from the lack of information on the above 3 points), the sample size was 55. Overall, the evidence was of very low quality.

Benefits and harms

The committee considered gestational thrombocytopenia and immune thrombocytopenic purpura (meaning immune destruction of platelets leading to thrombocytopaenia and purpura) to be the haemostatic disorders of most relevance in this guideline because these are the two most commonly encountered bleeding disorders in clinical practice. The committee's view was that it is important to exclude other serious pregnancy-related thrombocytopenia such as pre-eclampsia or antiphospholipid syndrome. The committee was aware of other guidelines for the management of bleeding disorders, such as the Royal College of Obstetricians and Gynaecologists (RCOG) guideline on management of inherited bleeding disorders in pregnancy (Green-top Guideline No. 71). See the section on 'Other factors the committee took into account'.

The committee explained that based on their expertise, if the woman has known immune thrombocytopenic purpura before birth then intrapartum care should be modified to accommodate this. For example, the woman should be referred to a maternity unit that can offer high dependency care. The committee justified the strong recommendation as there was a risk of maternal death if the woman bled without adequate clinical support. For this reason, the committee also recommended that if the maternal platelet count is below 50 x

10^9/l before admission for birth, an intrapartum management plan should be agreed with a multidisciplinary team that include a haematologist. The committee recommended monitoring the woman's platelet count to identify whether her condition is changing (for example, in response to treatment of the condition). The committee explained that monitoring the woman's platelet count at 36 weeks of gestation is part of standard clinical practice, and that the recommendation is 'weak' because starting at 36 weeks of gestation is based on clinical consensus rather than evidence.

The committee agreed that if the platelet count is below 50 x 10^9/l after 36 weeks of gestation then epidural and spinal analgesia should be avoided in most circumstances. Thirty-six weeks was selected because this is almost term and, therefore, the beginning of the period when labour is likely to start. The platelet count threshold of 50 x 10^9/l was selected as the threshold on the basis of clinical consensus as being the lowest count at which an anaesthetist would usually consider regional analgesia. The committee discussed the use of steroids or intravenous immunoglobulin to increase the platelet count. Because of lack of evidence there was uncertainty about its effectiveness in preventing adverse outcomes, however, the committee recommended considering steroids or intravenous immunoglobulin for women with a platelet count less than 50 x 10^9/l to increase the count before admission for birth.

The committee agreed that once the woman with known immune thrombocytopenic purpura presented on admission, the maternal platelet count should be measured on admission to determine the actual platelet count as this will inform the overall risk of bleeding. They suggested that the intrapartum care should be modified according to the platelet count as detailed below. It was also noted by the committee that the bleeding risk of the woman does not correspond to the bleeding risk of the baby as it is possible that the woman with a normal platelet count could have a baby with a low platelet count with a high risk of bleeding. For example, if the woman is known to have immune thrombocytopenic purpura before birth, she might have received treatment during pregnancy to increase the platelet counts and thus, the platelet count of the woman could not be a reliable indicator of the bleeding risk of the baby. Therefore, it was agreed to always treat the baby as high risk when the woman has immune thrombocytopenic purpura (either known or suspected) and to modify the birth accordingly to reduce the risk of bleeding.

The committee highlighted the fact that maternal platelet counts do not reflect babies' platelet counts in immune thrombocytopenic purpura. Therefore, they decided to make a separate recommendation for the neonatal management of babies born to these women. The committee explained that using ventouse or fetal blood sampling in labour can expose babies to a high risk of bleeding and thus, these procedures should be avoided for babies of women with bleeding disorders. The committee justified the strong recommendations on the grounds that if the baby has a low platelet count then a bleed could be fatal, and there are other ways of achieving the same outcome without exposing the baby to the same risks. The committee also recommended being aware of the risks involved in using fetal scalp electrodes, mid-cavity forceps or rotational forceps. The committee could not make strong recommendations here as the link between these procedures and bleeding risk was less clear and available substitutes not always clinically appropriate. The committee added that caesarean section may not protect the baby from bleeding; the common misconception that caesarean section would protect the baby in this way which might lead to a woman agreeing to a surgical procedure unnecessarily.

As part of management for babies born to women with thrombocytopenia, the committee recommended informing the neonatal team of the imminent birth of a baby at risk and taking umbilical cord blood to provide information on the baby's platelet count to help guide further management. The committee noted that subsequent management for a baby at risk was beyond the scope of this guideline, and it is already covered in other NICE guidance, for example intrapartum care for healthy women and babies (CG190).

The strength of the recommendations was justified as the risk to women and babies of not carrying out these actions was high, and the cost of carrying out such actions was negligible. The committee believed there would be a benefit to undertaking the actions and they were aware that sometimes important handover procedures such as those described could be overlooked in the period immediately after a high-risk birth because various clinical parameters in the women require checking.

The committee explained that the recommendations were intended to allow for as much individual consideration of the woman's condition as possible, but that there would be occasions when the recommendations would be inappropriate (for example, when a woman with no antenatal care presents in labour with gestational thrombocytopenia or when the diagnosis of immune thrombocytopenic purpura is uncertain). For these situations, the committee used their clinical experience to suggest the following guidelines to follow based on platelet count alone while considering regional analgesia or anaesthesia. They suggested on the basis of their experience a 3-tier cut-off system where risk was: known to be high; known to be low; and unknown. They discussed how different clinicians might choose to manage in different ways:

Platelet count >80 x 10^9/l

In the experience of the committee, a woman with a platelet count above 80 x 10^9/l would not need her birth plan to be modified in the absence of any other risk factors. Thus, the committee suggested to treat the woman as 'healthy' when considering regional analgesia or anaesthesia. The committee explained how a woman with immune thrombocytopenic purpura with a high platelet count could still possibly have a baby with a low platelet count and so platelet count was no guide in determining risk for these babies, but a woman with gestational thrombocytopenia and a high platelet count was also likely to have a baby with a high platelet count, and therefore the risk to the baby would be minimal.

Platelet count 50-80 x 10^9/l

In the experience of the committee, a woman with a platelet count between 50 and 80 x 10^9/l may or may not need her birth plan modified depending on other risk factors. The woman's history, preferences and the level of expertise of the anaesthetist should be considered before deciding whether or not to use regional analgesia or anaesthesia. The committee explained that the balance of benefits and risks would shift somewhere between a platelet count of 50 and 80 x 10^9/l, but that in the absence of evidence they were unsure where that would be. However the committee explained that the changes in management required to avoid bleeding risk in the baby were relatively minor and that it would be prudent to assume the baby was at risk of bleeding even at relatively high platelet counts. However, in the case of gestational thrombocytopenia, the bleeding risk in the baby was assumed to be normal because only the woman is at risk of bleeding as women with gestational thrombocytopenia do not have an alloantibody that affects the fetal platelet count.

Platelet count <50 x 10^9/l

In the experience of the committee, a woman with a platelet count below 50 x 10^9/l would almost always need her intrapartum care to be modified; the woman and the baby would be at high risk of bleeding if the woman had immune thrombocytopenic purpura. Babies of women with gestational thrombocytopenia were assumed to have normal bleeding risk because they do not have an alloantibody that affects the fetal platelet count and so only the woman is at risk of bleeding. The committee explained that regional anaesthesia and analgesia could still be considered under certain rare circumstances, for example, for a woman who was otherwise healthy and well and where the anaesthetist was experienced in caring for women with low platelet counts. However, the committee agreed that in general regional anaesthesia and analgesia should be avoided in this group.

Cost effectiveness and resource use

No clinical evidence was identified for this review and therefore the committee made a qualitative assessment of cost effectiveness.

The committee considered that some women would have a high risk of bleeding and others would have a low risk and that it would be cost effective to make separate recommendations to reflect this. The committee considered that no significant changes to the birth plan would be required if the woman had gestational thrombocytopenia. For women with immune thrombocytopenic purpura, both the woman and the baby can have a high risk of bleeding and therefore the committee reasoned that it would be cost effective to modify the birth plan to minimise the risks. The committee was generally of the view that the cost of the recommendations was minor in comparison to the potential harms from not following the recommendations.

The committee considered that there is variation in practice and that not all women with immune thrombocytopenic purpura give birth in an obstetric unit with a neonatal unit that routinely provides high dependency care. Therefore they recognised that the recommendation could lead to more women requiring high dependency care. However, they thought this might be offset by women at lower risk not being referred to such units. Given the small prevalence of these conditions the committee did not think their recommendations would have a significant cost impact or saving for the NHS.

Other factors the committee took into account

During protocol drafting, the committee limited the scope of this review to focus on bleeding disorders of greatest relevance during labour and birth. They agreed that it was not possible to consider every possible bleeding disorder in this guideline. They identified gestational thrombocytopenia and immune thrombocytopenic purpura as relatively common bleeding disorders in pregnancy and for which there might be evidence available to guide recommendations. The committee was aware that limiting the review to these bleeding disorders might result in there being little evidence to interpret with regard to platelet function. On the other hand, they recognised the difficulty of having a dynamic test (that would detect platelet size, shape etc.) during labour and so reasoned that platelet count would be an appropriate parameter to consider in developing recommendations. The committee was aware of existing and comprehensive guidance such as the RCOG management of inherited bleeding disorders in pregnancy (Green-top Guideline No. 71) which healthcare professionals could consult for bleeding disorders not covered in the guideline.

The committee discussed how a research recommendation on gestational thrombocytopenia might be relevant in light of the limited evidence identified in this review. However, gestational thrombocytopenia is generally considered to be a low-risk condition and so the committee agreed it would be unlikely to have a significant impact on practice. A research recommendation on immune thrombocytopenic purpura would be probably be less relevant, as it would be difficult to design a clinical trial based on clinical equipoise. Consequently the committee did not make any research recommendations related to management of bleeding disorders in pregnancy.

Intrapartum care for women with haemostatic disorders – third stage of labour

Review question

How should the third stage of labour be managed for women who are at increased risk of bleeding because of haemostatic disorders?

Introduction

The aim of this review is to determine how the third stage of labour should be managed for women who are at increased risk of postpartum haemorrhage because of haemostatic disorders.

Summary of the protocol

See Table 15 for a summary of the population, intervention, comparison, and outcomes (PICO) characteristics of this review.

Table 15: Summary of the protocol (PICO) table

Population	Women in labour who have one of the haemostatic disorders below.
	
	Platelet dysfunction – normally thrombocytopenia
	• Spurious
	• Acquired
	  ○ Gestational
	  ○ Immune thrombocytopenic purpura (ITP)
	  ○ Haemolysis with elevated liver enzymes and low platelets (HELLP)
	  ○ Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP)
	  ○ Systemic lupus erythematosus (SLE)/antiphospholipid antibody syndrome (APS)/Evan's syndrome
	  ○ Infective, for example, human immunodeficiency virus (HIV), parvovirus
	  ○ Drug related
	  ○ Liver disease
	  ○ Disseminated intravascular coagulation (DIC)
	  ○ Myelosuppression e.g. malignancy, infection, autoimmune
	• Congenital
	  ○ Inherited platelet disorder
	  ○ TTP
	
	Heritable bleeding disorders
	• von Willebrand's disease (Type 1,2,3, acquired, probable)
	• Haemophilia A (factor VIII) carrier

	• Haemophilia B (factor IX) carrier • Factor XI deficiency • Factor VII deficiency • Factor XIII deficiency • Factor V deficiency • Factor X deficiency • Prothrombin deficiency • Afibrinogenemia • Dysfibrinogenemia • Hypofibrinogenemia • Fibrinogen deficiency • Combined II+VII+IX+X deficiency • Combined V+VIII deficiency • Other combined diagnoses Acquired bleeding disorders • Acquired Factor V deficiency • Acquired prothrombin deficiency • Acquired Factor XIII deficiency • Acquired deficiency (other)

Intervention	<u>Intervention 1</u>
	Active management plus appropriate haemostatic therapy
	• Haemostatic therapy would include:
	  ○ desmopressin infusion (tradename DDAVP)
	  ○ improving clot stability by antifibrinolytic drugs, for example, tranexamic acid
	  ○ transfusion
	  - platelet transfusion
	  - fresh frozen plasma transfusion
	  ○ coagulation factor replacement therapy (with factor concentrates such as plasma factor concentrates or recombinant factors)
	
	<u>Intervention 2</u>
	Active management plus additional obstetric interventions plus appropriate haemostatic therapy
	• Additional obstetric interventions would include:
	  ○ brace suture
	  ○ intrauterine balloon
	  ○ interventional radiological vascular occlusion
	  ○ ligation of internal iliac vessels

Comparison	<u>Comparison 1a (to be compared with intervention 1)</u> Active management (alone) with no additional haemostatic therapy <u>Comparison 1b (to be compared with intervention 1)</u> Active management plus additional obstetric interventions with no additional haemostatic therapy

	Comparison 2 (to be compared with intervention 2) Active management plus additional obstetric interventions with no additional haemostatic therapy
Outcomes	For the woman: • mortality • major morbidity (major or severe primary postpartum haemorrhage (defined as blood loss >1000 ml within 24 hours of the birth) or secondary postpartum haemorrhage (defined as abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally)) • further intervention such as surgery, brace suture, intrauterine balloon, cell salvage, hysterectomy, major blood vessel ligation, or interventional radiology • admission to a high dependency unit (HDU) or intensive treatment unit (ITU) • blood transfusion • women's satisfaction with labour or birth (including psychological wellbeing) • breastfeeding

APS: antiphospholipid antibody syndrome; DIC: disseminated intravascular coagulation; HDU: high dependency unit; HELLP: haemolysis with elevated liver enzymes and low platelets; HIV: human immunodeficiency virus; HUS: haemolytic uraemic syndrome; ITP: immune thrombocytopenic purpura; ITU: intensive therapy unit; SLE: systemic lupus erythematosus; TTP: thrombotic thrombocytopenic purpura

For further details see the full review protocol in appendix A. The search strategies are presented in appendix B.

Clinical evidence

Included studies

Three retrospective cohort studies and 1 case series study were included in this review (see 'Summary of clinical studies included in the evidence review').

Of the 3 retrospective cohort studies, 1 study compared heparin to supportive treatment in women with HELLP syndrome (Detti 2005). One study compared tranexamic acid, tranexamic acid plus desmopressin (tradename DDAVP), tranexamic acid plus clotting factor concentrate (CFC), and any haemostatic therapy to no additional haemostatic therapy in women with von Willebrand's disease (Govorov 2016). One study compared tranexamic acid to no tranexamic acid in women haemostatic disorders (76% with von Willebrand's disease, 18% haemophilia A carriers) (Hawke 2015).

Although the protocol did not consider non-comparative studies, 1 case series study was exceptionally included as this was a UK national audit of pregnant women with severe immune thrombocytopenic purpura (Care 2018). In this study, the women received antenatal treatment such as steroids, intravenous immunoglobulin, or both, and the clinical outcomes are reported descriptively according to treatment received.

Evidence from the studies included in the review is summarised below (see 'Quality assessment of clinical studies included in the evidence review').

Data was reported on the critical outcomes maternal mortality, major morbidity (such as postpartum haemorrhage) and need for further intervention (such as surgery), and the important outcomes admission to a high dependency unit or intensive treatment unit and blood transfusion. There was no evidence identified for the following outcomes for the

woman: women's satisfaction with labour or birth (important outcome) and breastfeeding (outcome of limited importance). No evidence was identified for other population groups specified in the protocol. No evidence was identified comparing additional obstetric interventions with haemostatic therapy to additional obstetric interventions without additional haemostatic therapy (comparison 2).

See also the study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix D.

Summary of clinical studies included in the evidence review

Table 16 provides a summary of the included studies.

Table 16: Summary of included studies

Study	Population	Intervention/Comparison	Outcomes
Care 2018 Prospective case series (national audit study UKOSS) UK	N=107 women with severe thrombocytopenia (platelet count <50 x 10^9/l)	• Steroids (n=38) • IVIG (n=17) • Steroids plus IVIG (n=28) • Other (n=2) • No treatment (n=22)	For the woman: • Mortality • Postpartum haemorrhage • Hysterectomy for postpartum haemorrhage • ICU admission
Detti 2005 Retrospective cohort study Italy and USA	N=32 women with HELLP syndrome	• Heparin (women in Italy) (n=16) • Supportive treatment only (women in USA) (n=16)	For the woman: • Postpartum haemorrhage • DIC • Hysterectomy • Exploratory laparotomy • Dialysis • Plasmapheresis • Platelet transfusion • Fresh frozen plasma transfusion • Red blood cell transfusion
Govorov 2016 Retrospective cohort study Sweden	N=34 women (59 pregnancies) with von Willebrand Disease	• Tranexamic acid (prophylactic IV or oral tranexamic acid 8 hourly up to median 10 days) (n=9) • Tranexamic acid plus desmopressin (n=12) • Tranexamic acid plus CFC (n=22)	For the woman: • Primary postpartum haemorrhage • Secondary postpartum haemorrhage • Blood transfusion

Study	Population	Intervention/Comparison	Outcomes
		• No haemostatic therapy (women who were diagnosed after birth) (n=16)	
Hawke 2016 Retrospective cohort study Canada	N=33 women (62 pregnancies) with inherited bleeding disorders Type of bleeding disorder: • von Willebrand Disease n=47 • Haemophilia A carrier n=11 • Factor X deficiency n=2 • Platelet function disorder n=2	• Tranexamic acid on discharge (n=36 pregnancies) • No tranexamic acid (n=26 pregnancies)	For the woman: • Excessive delayed postpartum bleeding

CFC: clotting factor concentrate; DIC: disseminated intravascular coagulation; HELLP: haemolysis with elevated liver enzymes and low platelets; ICU: intensive care unit; IV: intravenous; IVIG: intravascular immunoglobulin; UKOSS: UK Obstetric Surveillance System

See also the study evidence tables in Appendix E. No meta-analysis was undertaken for this review (and so there are no forest plots in Appendix F).

Quality assessment of clinical studies included in the evidence review

Table 17 presents descriptive evidence from a case series study. GRADE methodology was not used for case series evidence.

For comparative evidence where GRADE methodology has been used, see appendix G for full clinical evidence profiles.

Women with immune thrombocytopenic purpura

Table 17: Outcomes for women with severe immune thrombocytopenic purpura who underwent caesarean birth by type of treatment received

Study	Number of outcomes/total number of births Type of intervention No treatment	Steroids	IVIG	Steroids + IVIG	Quality	Importance
Mortality						
Care 2018 Prospective case series	0/22	0/38	0/17	0/28	Very low[1]	Critical
Postpartum haemorrhage (blood loss of ≥ 500 ml in first 24 hours after birth)						
Care 2018 Prospective case series	10/22	17/38	9/17	18/28	Very low[1]	Critical
Hysterectomy for postpartum haemorrhage						
Care 2018 Prospective case series	0/22	0/38	0/17	0/28	Very low[1]	Critical
ICU admission						
Care 2018 Prospective case series	0/22	0/38	0/17	0/28	Very low[1]	Important

ICU: intensive care unit; IVIG: intravenous immunoglobulin
1 Descriptive data from a case series study.

Women with HELLP syndrome

The clinical evidence profiles for this review question are presented in Appendix G.

Women with von Willebrand Disease

The clinical evidence profiles for this review question are presented in Appendix G.

Economic evidence

Included studies

No economic evidence was identified for this review.

See the study selection flow chart in Supplement 2 (Health economics).

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list (see Supplement 2 (Health economics).

Summary of studies included in the economic evidence review

No economic evidence was identified for this review (and so there are no economic evidence tables in Supplement 2 (Health economics).

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation (see Supplement 2 (Health economics).

Evidence statements

Women with immune thrombocytopenic purpura

Outcomes for the woman

Mortality

Very low quality evidence from 1 study of prospective case series of women with severe immune thrombocytopenic purpura (N=105) reported that there were no mortality in women with or without any antenatal haemostatic treatment (steroids, IVIG, or steroids plus IVIG).

Major morbidity: Primary postpartum haemorrhage

Very low quality evidence from 1 study of prospective case series of women with severe immune thrombocytopenic purpura (N=105) reported that 10 out of 22 (45%) women who did not receive any antenatal haemostatic treatment, 17 out of 38 (45%) women who received steroid therapy, 9 out of 17 (53%) women who received IVIG, and 18 out of 28 (64%) women who received steroids and IVIG had primary postpartum haemorrhage (blood loss of ≥500 ml within 24 hours after birth).

Further intervention: Hysterectomy

Very low quality evidence from 1 study of prospective case series of women with severe immune thrombocytopenic purpura (N=105) reported that there were no events of hysterectomy for postpartum haemorrhage in women with or without any antenatal haemostatic treatment (steroids, IVIG, or steroids plus IVIG).

Maternal admission to a high-dependency unit or intensive care unit

Very low quality evidence from 1 study of prospective case series of women with severe immune thrombocytopenic purpura (N=105) reported that there were no events of maternal admission to an intensive care unit in women with or without any antenatal haemostatic treatment (steroids, IVIG, or steroids plus IVIG).

Women with HELLP syndrome

Comparison: Heparin versus supportive treatment

Outcomes for the woman

Major morbidity: Postpartum haemorrhage (undefined)

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) showed that there was no clinically important difference in the risk of postpartum haemorrhage between women receiving heparin and those who did not.

Major morbidity: Disseminated intravascular coagulation (DIC)

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) reported a clinically important higher number of women with disseminated intravascular coagulation (DIC) in the group of women receiving heparin in comparison with those who did not.

Further intervention: Hysterectomy

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) showed that there was no clinically important difference in the risk of hysterectomy between women receiving heparin and those who did not.

Further intervention: Exploratory laparotomy

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) showed that there was no clinically important difference in the risk of exploratory laparotomy between women receiving heparin and those who did not.

Further intervention: Dialysis

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) showed that there was no clinically important difference in the risk of dialysis between women receiving heparin and those who did not.

Further intervention: Plasmapheresis

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) showed that there was no clinically important difference in the risk of plasmapheresis between women receiving heparin and those who did not.

Blood transfusion: Platelet transfusion

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) suggested a clinically important decrease in the need for platelet transfusion in the group of women receiving heparin in comparison with those who did not.

Blood transfusion: Fresh frozen plasma transfusion

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) suggested a clinically important increase in the need for fresh frozen plasma (FFP) transfusion in the group of women receiving heparin in comparison with those who did not.

Blood transfusion: Red blood cell transfusion

Very low quality evidence from 1 retrospective cohort study among women with HELLP syndrome (N=32) suggested a clinically important increase in the need for red blood cell

(RBC) transfusion in the group of women receiving heparin in comparison with those who did not.

Women with von Willebrand disease

Comparison: Tranexamic acid versus no haemostatic therapy

Outcomes for the woman

Major morbidity: Primary postpartum haemorrhage (blood loss of any degree in first 24 hours of birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=25) suggested that there was no clinically important difference in the risk of primary postpartum haemorrhage between women treated with tranexamic acid and women without any treatment.

Major morbidity: Major or severe primary postpartum haemorrhage (blood loss of more than 1000ml within 24 hours after birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=25) suggested that there was no clinically important difference in the risk of severe primary postpartum haemorrhage (blood loss of more than 1000 ml) between women treated with tranexamic acid and women without any treatment.

Major morbidity: Secondary postpartum haemorrhage (abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=25) reported that there was no clinically important difference in the risk of secondary postpartum haemorrhage between women receiving tranexamic acid alone and women without any treatment.

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=62) showed that there may be a clinically important beneficial effect in the risk of secondary postpartum haemorrhage in the group of women receiving tranexamic acid at discharge in comparison with women without any haemostatic therapy, however, there is an uncertainty around the estimate.

Blood transfusion

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=25) suggested that there was no clinically important difference in the risk of necessitating blood transfusion in women who received tranxenamic acid and women who did not receive any treatment.

Comparison: Tranexamic acid plus desmopressin versus no haemostatic therapy

Outcomes for the woman

Major morbidity: Primary postpartum haemorrhage (blood loss of any degree in first 24 hours of birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=28) suggested that there was no clinically important difference in the risk of primary postpartum haemorrhage between women treated with tranexamic acid plus desmopressin and women without any treatment.

Major morbidity: Major or severe primary postpartum haemorrhage (blood loss of more than 1000ml within 24 hours after birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=28) suggested that there was no clinically important difference in the risk of severe primary postpartum haemorrhage (blood loss of more than 1000 ml) between women treated with tranexamic acid plus desmopressin and women without any treatment.

Major morbidity: Secondary postpartum haemorrhage (abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=28) reported that there was no clinically important difference in the risk of secondary postpartum haemorrhage between women treated with tranexamic acid plus desmopressin and women without any treatment.

Blood transfusion

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=28) suggested that there was no clinically important difference in the risk of necessitating blood transfusion in women who received tranxenamic acid plus desmopressin and women who did not receive any treatment.

Comparison: Tranexamic acid plus clotting factor concentrate versus no haemostatic therapy

Outcomes for the woman

Major morbidity: Primary postpartum haemorrhage (blood loss of any degree in first 24 hours of birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=38) suggested that there was no clinically important difference in the risk of primary postpartum haemorrhage between women treated with tranexamic acid plus clotting factor concentrate and women without any treatment.

Major morbidity: Major or severe primary postpartum haemorrhage (blood loss of more than 1000ml within 24 hours after birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=38) suggested that there was no clinically important difference in the risk of severe primary postpartum haemorrhage (blood loss of more than 1000 ml) between women treated with tranexamic acid plus clotting factor concentrate and women without any treatment.

Major morbidity: Secondary postpartum haemorrhage (abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=38) reported that there may be a clinically important harmful effect in women receiving tranexamic acid plus clotting factor concentrate in comparison with women without any treatment for the risk of secondary postpartum haemorrhage, however, there is uncertainty around the estimate.

Blood transfusion

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=38) suggested that there was no clinically important difference in the risk of necessitating blood transfusion in women who received tranxenamic acid plus clotting factor concentrate and women who did not receive any treatment.

Comparison: Any haemostatic therapy versus no haemostatic therapy

Outcomes for the woman

Major morbidity: Primary postpartum haemorrhage (blood loss of any degree in first 24 hours of birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=59) suggested that there was no clinically important difference in the risk of primary postpartum haemorrhage between women treated with tranexamic acid plus or minus desmopressin or clotting factor concentrate and women without any treatment.

Major morbidity: Major or severe primary postpartum haemorrhage (blood loss of more than 1000ml within 24 hours after birth)

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=59) suggested that there was no clinically important difference in the risk of severe primary postpartum haemorrhage (blood loss of more than 1000 ml) between women treated with tranexamic acid plus or minus desmopressin or clotting factor concentrate and women without any treatment.

Major morbidity: Secondary postpartum haemorrhage (abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally)

Low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=59) showed a clinically important beneficial effect in women receiving tranexamic acid plus desmopressin or clotting factor concentrate for the risk of reduction in secondary postpartum haemorrhage in comparison with women without any treatment.

Blood transfusion

Very low quality evidence from 1 retrospective cohort study among women with von Willebrand disease (N=59) suggested that there may be a clinically important beneficial effect in women who received tranxenamic acid plus or minus desmopressin or clotting factor in comparison with women who did not receive any treatment for decreased number of women necessitating blood transfusion.

Recommendations

F7. Be aware that women with bleeding disorders are at increased risk of primary and secondary postpartum haemorrhage.

F8. Offer active management rather than physiological management of the third stage of labour for women with bleeding disorders, in line with the NICE guideline on intrapartum care for healthy women and babies.

F9. Consider giving uterotonics intravenously for women with bleeding disorders if there are concerns about giving these by intramuscular injection.

Postpartum management for women with bleeding disorders

F10. Offer individualised postpartum monitoring and management as discussed with a senior haematologist for women with bleeding disorders, to include:

- estimation of blood loss
- obstetric complications
- haematological parameters.

F11. Be aware that non-steroidal anti-inflammatory drugs can add to the risk of bleeding.

F12. Before discharge from hospital, inform women with bleeding disorders of the risk of secondary bleeding postpartum and how to access care.

Rationale and impact

Why the committee made the recommendations

The committee decided to make recommendations based on their knowledge and experience as the evidence was very limited. A number of bleeding disorders can affect the third stage of labour but evidence was not found for all these conditions. In addition, it was not always possible to tell whether an outcome was linked to a treatment or a specific condition because conditions were sometimes grouped together according to severity. Therefore, the committee was unable to use clinical evidence to inform the recommendations and instead based them on their clinical expertise.

The risk to a woman's life from postpartum haemorrhage is greater if she has a bleeding disorder. To reduce postpartum haemorrhage, the committee recommended active management of labour (rather than physiological management), which includes intramuscular oxytocin, early clamping of the cord and controlled cord traction, as described in NICE guideline on intrapartum care for healthy women and babies (CG190).

Women with bleeding disorders may need some adjustments to active management of labour. For example, there may be risks associated with intramuscular injections in these women. These considerations will need oversight from a senior haematologist, more frequent and possibly extended monitoring, and discussion of any changes in clinical condition.

Impact of the recommendations on practice

These recommendations should lead to fewer attempts at physiological management of the third stage in women with bleeding disorders, with fewer postpartum haemorrhages and reduced maternal morbidity. The recommendations will apply to a small number of women, so implementing them is unlikely to cause staffing or resource issues for hospitals.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Maternal outcomes were prioritised as this review is about management of third stage of labour.

The committee identified 3 outcomes of critical importance for the woman. These were mortality, major morbidities (such as postpartum haemorrhage), and further interventions (such as surgery or interventional radiology). The committee considered these to be the most serious and long-term outcomes for women with bleeding disorders and they agreed that the effectiveness of third stage interventions should be evaluated with reference to these outcomes.

Maternal admission to a high-dependency unit or intensive therapy unit, maternal blood transfusion and women's satisfaction with labour and birth were regarded as important outcomes because they reflect indirectly the seriousness of the woman's bleeding condition. For example, women with bleeding disorders who have a severe postpartum haemorrhage are likely to be admitted to the intensive therapy unit.

The quality of the evidence

There were 3 retrospective cohort studies and 1 UK national study of prospective case series included. Although comparative studies were initially prioritised, a case series study was exceptionally included as this was a UK national audit for pregnant women with severe immune thrombocytopenic purpura.

Risk of bias of each study was assessed using either the Newcastle-Ottawa assessment scales (cohort studies) or the Joanna Briggs Institute appraisal checklist (case series). None of the cohort studies controlled adequately for confounders; for example, in one study women were allocated to different treatment options depending on disease severity rather than disease subtype, making it difficult to determine whether poor outcomes were due to specific treatment options or different disease subtypes. The sample size of the studies ranged from 12 to 62, which the committee regarded as being too small to adequately assess a rare maternal outcome such as death due to severe postpartum haemorrhage. Thus, the evidence was of very low quality by GRADE assessment. Although the UKOSS case series was assessed as a comprehensive report and regarded as having a low risk of bias, the overall quality was considered to be very low as it was a non-comparative study.

Benefits and harms

Based on their clinical expertise, the committee agreed women with haematological conditions were more likely to have a primary and secondary postpartum haemorrhage. The committee explained that it was important for everyone in the woman's care team – including the woman herself – to be aware of this, so that early signs and symptoms of a potential haemorrhage were not overlooked.

The committee explained that for almost all haematological conditions it was important to avoid postpartum haemorrhage, since the risk to the woman's life would be much greater if she had a haematological condition. Consequently the committee recommended active

(rather than physiological) management of labour, which would include intramuscular syntocinon, early clamping of the cord and controlled cord traction as described in the NICE guideline on intrapartum care for healthy women and babies (CG190). The committee justified a strong recommendation here since they included a cross-reference to other strong recommendations. They agreed that women with haematological conditions should not be regarded as 'healthy' on the basis of the procedure for active management of labour being similar to that used for healthy woman and babies.

The committee was aware that the NICE guideline on intrapartum care for healthy women and babies described active management as involving oxytocin by intramuscular injection. They described how this might not always be suitable for women who could bleed seriously from an injection site (although usually it would be). For example, this could include women at risk of intramuscular haematoma. Consequently they added to the existing recommendations to take account of this particular characteristic, otherwise postpartum duration of stay might be extended and there might be a requirement for more intensive haematological monitoring postpartum.

Consequently the committee recommended more intensive monitoring for this group of women. The justification for this is that more intensive monitoring is more likely to identify a symptom or sign of a haemorrhage before this becomes too severe to manage without significant risk to the woman. The committee justified a strong recommendation in favour of close monitoring on the grounds that the risk of not monitoring in this group of women was significant and potentially fatal, and they provided examples of what the monitoring should include based on factors that could predict a haemorrhage. However, this list was not intended to be exhaustive, and so the committee was unable to make a strong recommendation about exactly how the monitoring should be conducted.

The committee explained that the complexity of haematological conditions and the need for an individualised approach meant that expertise in haematological conditions in pregnancy would be needed to provide safe advice to the woman on the management of bleeding risk in the third stage of labour. They therefore justified a strong recommendation on the grounds that without a senior haematologist there could be avoidable harm to the woman.

The committee was aware from its knowledge and experience that steroids increase postpartum bleeding risk. If such circumstances, it would be important that the care team was made aware of this increased risk, especially the endocrinologist who may not have expertise in the management of haematological conditions.

The committee could not make recommendations on the management of postpartum haemorrhage risk more than 24 hours after birth (see the 'Other factors the committee took into account'). However in order to emphasise that the risk would continue during this period, they made a strong recommendation on providing information for the woman on how to recognise the need for care in a potential postpartum haemorrhage situation and where to seek care in such circumstances.

Cost effectiveness and resource use

The evidence was very limited and the committee made a qualitative assessment of cost effectiveness.

The committee noted that the risk of dying from postpartum haemorrhage is greater if the woman has a bleeding disorder. Therefore, they considered it would be cost effective to

recommend active management of the third stage of labour as opposed to physiological management. As women with bleeding disorders may need some adjustments to active management of labour the committee considered that more extensive monitoring and oversight from a senior haematologist would also be cost effective.

The committee thought that the recommendations should lead to fewer attempts at physiological management of the third stage in women with bleeding disorders, and consequently fewer postpartum haemorrhages and reduced maternal morbidity. However, as the recommendations apply only to a small number of women, they did not think there would be a significant resource impact for the NHS.

Other factors the committee took into account

The committee discussed how the phrase 'postpartum haemorrhage' might be slightly misleading in the context of this guideline, which focuses on the intrapartum period. However, the guideline scope covers the immediate postpartum period (up to 24 hours after the birth), and therefore in this period when there is particularly high risk of serious bleeding the bleed would usually be referred to as a postpartum haemorrhage. Later bleeding would also be referred to as postpartum haemorrhage but this was beyond the scope of the guideline.

The committee explained that a research recommendation in this area would be difficult to implement because most clinicians were in equipoise on the management of the third stage of labour for women with bleeding disorders. In addition, the critical outcomes in the review protocol are fortunately rare and therefore trial recruitment would be difficult and probably require multinational collaboration. For these reasons the question was not prioritised for a research recommendation.

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Appendices

Appendix A – Review protocols

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Item	Details	Working notes
Area in the scope	Women at high risk of adverse outcomes for themselves and/or their baby because of existing maternal medical conditions – intrapartum care for women with haemostatic disorders – use of regional anaesthesia and analgesia	
Review question in the scope	When should regional anaesthesia and analgesia be avoided in women with haemostatic disorders and what investigations can help in this decision making?	
Review question for the guideline	In which women with haemostatic disorders should regional anaesthesia and analgesia be avoided?	
Objective	The aim of this review is to identify women with haemostatic disorders who are at risk of having complications due to bleeding while having regional anaesthesia or analgesia. This is important because women with haemostatic disorders who receive regional techniques for labour analgesia or anaesthesia for birth are at increased risk of developing spinal haematomas. There are also risks from avoiding or withholding regional analgesia or anaesthesia as the woman may be exposed to the (significant) risks of emergency general anaesthesia	

Population and directness	Women in labour who have one of the following haemostatic disorders.
	
	Platelet dysfunction – normally thrombocytopenia
	• Spurious
	• Acquired
	  ○ Gestational
	  ○ ITP
	  ○ HELLP
	  ○ HUS/TTP
	  ○ SLE/APS/Evan's syndrome
	  ○ Infective e.g. HIV, parvovirus
	  ○ Drug related
	  ○ Liver disease
	  ○ DIC
	  ○ Myelosuppression, for example, malignancy, infection, autoimmune	

Item	Details	Working notes

	• Congenital
	  ○ Inherited platelet disorder
	  ○ TTP
	
	Heritable bleeding disorders
	• von Willebrand's disease (Type 1,2,3, acquired, probable)
	• Haemophilia A (factor VIII) carrier
	• Haemophilia B (factor IX) carrier
	• Factor XI deficiency
	• Factor VII deficiency
	• Factor XIII deficiency
	• Factor V deficiency
	• Factor X deficiency
	• Prothrombin deficiency
	• Afibrinogenemia
	• Dysfibrinogenemia
	• Hypofibrinogenemia
	• Fibrinogen deficiency
	• Combined II+VII+IX+X deficiency
	• Combined V+VIII deficiency
	• Other combined diagnoses
	
	Acquired bleeding disorders
	• Acquired Factor V deficiency
	• Acquired prothrombin deficiency
	• Acquired Factor XIII deficiency
	• Acquired deficiency (other)	

Prognostic test or intervention	Relevant factors will be limited to the following. • Platelet count • von Willebrand factor (vWF) levels • Platelet functionality test: platelet aggregation and thromboelastography (TEG)/viscoelastic methods including (ROTEM trade name) • Fibrinogen level • Factor XI level • Factor VII level • Factor IX level • Factor XIII level • Factor V level • Factor X level • Factor VIII level • Factor II level	

Item	Details	Working notes
Comparison	Threshold or level of the relevant coagulation factor or platelets or vWF at which a women undergoes birth without experiencing any major adverse outcome (as defined in the Outcomes section below)	

Outcomes	Critical outcomes:
	• for the woman:
	  ○ mortality
	  ○ major morbidity (such as paralysis, spinal haematoma, or spinal cord compression)
	
	Important outcomes:
	• for the woman:
	  ○ adequacy of analgesia (maternal perception of pain (pain scores), need for a top up or second technique)
	  ○ need for neurological intervention (for example, neurological assessment or surgery)
	  ○ women's satisfaction with labour and birth (including psychological wellbeing)	

Importance of outcomes	Preliminary classification of the outcomes for decision making: • critical (up to 3 outcomes) • important but not critical (up to 3 outcomes) • of limited importance (1 outcome)	
Setting	All settings	
Stratified, subgroup and adjusted analyses	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: • type of bleeding disorders (as defined in Population and directness above) • type of bleeding/clotting test abnormality • type of factor deficiency • levels of platelet counts • other co-existing/pre-existing medical conditions (for example, hypertension, or renal disease) These subgroup factors will be used as confounding factors when data from observational studies are analysed	
Language	English	
Study design	• Published full-text papers only • Systematic reviews • RCTs	

Item	Details	Working notes
	• Only if RCTs unavailable or there is limited data to inform decision making with a minimum sample size of 15 women in each group: ○ prospective or retrospective comparative cohort studies ○ case series studies • Prospective study designs will be prioritised over retrospective study designs • Conference abstracts will not be considered	
Search strategy	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies	
Review strategy	Appraisal of methodological quality: • the methodological quality of each study will be assessed using checklists recommended in the NICE guidelines manual 2014 (for example, AMSTAR or ROBIS for systematic reviews, and Cochrane RoB tool for RCTs) and the quality of the evidence for each outcome (that is, across studies) will be assessed using GRADE • if studies report only p-values, this information will be recorded in GRADE tables without an assessment of imprecision Synthesis of data: • meta-analysis will be conducted where appropriate • default MIDs will be used; 0.8 and 1.25 for dichotomous outcomes; 0.5 times the SD of the measurement in the control arm (or median score across control arms if multiple studies are included) for continuous outcomes • for continuous data, change scores will be used in preference to final scores for data from non-RCT studies; final and change scores will not be pooled; if any study reports both, the method used in the majority of studies will be adopted	Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies will be resolved through discussion between the first and second reviewers or by reference to a third person. This review question was not prioritised for health economic analysis and so no formal dual weeding, study selection (inclusion/exclusion) or data extraction into evidence tables will be undertaken. However, internal (NGA) quality assurance processes will include consideration of the outcomes of weeding, study selection and data extraction and the committee will review the results of study selection and data extraction

Item	Details	Working notes
Equalities	Equalities considerations will be considered systematically in relation to the available evidence and draft recommendations. The guideline scope includes women with cognitive or physical disability as populations for whom there may be equalities issues. Women who have received no antenatal care will be considered as a subgroup for all systematic reviews performed within the medical conditions work stream and a specific question has been included in the obstetric complications work stream for this population	
Notes/additional information	NICE guideline intrapartum care for healthy women and babies (CG190): Intravenous and intramuscular opioids 1.8.12 Ensure that pethidine, diamorphine or other opioids are available in all birth settings. Inform the woman that these will provide limited pain relief during labour and may have significant side effects for both her (drowsiness, nausea and vomiting) and her baby (short-term respiratory depression and drowsiness which may last several days). [2007] 1.8.13 Inform the woman that pethidine, diamorphine or other opioids may interfere with breastfeeding. [2007] 1.8.14 If an intravenous or intramuscular opioid is used, also administer an antiemetic. [2007] 1.8.15 Women should not enter water (a birthing pool or bath) within 2 hours of opioid administration or if they feel drowsy. [2007] 1.9 Pain relief in labour: regional analgesia Information about regional analgesia 1.9.1 If a woman is contemplating regional analgesia, talk with her about the risks and benefits and the implications for her labour, including the arrangements and time involved for transfer of care to an obstetric unit if she is at home or in a midwifery unit (follow the general principles for transfer of care described in section 1.6). [2007, amended 2014] 1.9.2 Provide information about epidural analgesia, including the following: ○ It is available only in obstetric units. ○ It provides more effective pain relief than opioids. ○ It is not associated with long-term backache.	

Item	Details	Working notes
	○ It is not associated with a longer first stage of labour or an increased chance of a caesarean birth. ○ It is associated with a longer second stage of labour and an increased chance of vaginal instrumental birth. ○ It will be accompanied by a more intensive level of monitoring and intravenous access, and so mobility may be reduced. [2007, amended 2014] Timing of regional analgesia 1.9.3 If a woman in labour asks for regional analgesia, comply with her request. This includes women in severe pain in the latent first stage of labour. [2007] Care and observations for women with regional analgesia 1.9.4 Always secure intravenous access before starting regional analgesia. [2007] 1.9.5 Preloading and maintenance fluid infusion need not be administered routinely before establishing low-dose epidural analgesia and combined spinal–epidural analgesia. [2007] 1.9.6 Undertake the following additional observations for women with regional analgesia: ○ During establishment of regional analgesia or after further boluses (10 ml or more of low-dose solutions), measure blood pressure every 5 minutes for 15 minutes. ○ If the woman is not pain-free 30 minutes after each administration of local anaesthetic/opioid solution, recall the anaesthetist. ○ Assess the level of the sensory block hourly. [2007] 1.9.7 Encourage women with regional analgesia to move and adopt whatever upright positions they find comfortable throughout labour. [2007] 1.9.8 Once established, continue regional analgesia until after completion of the third stage of labour and any necessary perineal repair. [2007] 1.9.9 Upon confirmation of full cervical dilatation in a woman with regional analgesia, unless the woman has an urge to push or the baby's head is visible, pushing should be delayed for at least 1 hour and longer if the woman wishes, after which	

Item	Details	Working notes
	actively encourage her to push during contractions. [2007] 1.9.10 After diagnosis of full dilatation in a woman with regional analgesia, agree a plan with the woman in order to ensure that birth will have occurred within 4 hours regardless of parity. [2007] 1.9.11 Do not routinely use oxytocin in the second stage of labour for women with regional analgesia. [2007] 1.9.12 Perform continuous cardiotocography for at least 30 minutes during establishment of regional analgesia and after administration of each further bolus of 10 ml or more. [2007, amended 2014] Establishing and maintaining regional analgesia 1.9.13 Use either epidural or combined spinal–epidural analgesia for establishing regional analgesia in labour. [2007] 1.9.14 If rapid analgesia is required, use combined spinal–epidural analgesia. [2007] 1.9.15 Establish combined spinal–epidural analgesia with bupivacaine and fentanyl. [2007] 1.9.16 Establish epidural analgesia with a low-concentration local anaesthetic and opioid solution with, for example, 10–15 ml of 0.0625–0.1% bupivacaine with 1–2 micrograms per ml fentanyl. The initial dose of local anaesthetic plus opioid is essentially a test dose, so administer cautiously to ensure that inadvertent intrathecal injection has not occurred. [2007] 1.9.17 Use low-concentration local anaesthetic and opioid solutions (0.0625–0.1% bupivacaine or equivalent combined with 2.0 micrograms per ml fentanyl) for maintaining epidural analgesia in labour. [2007] 1.9.18 Do not use high concentrations of local anaesthetic solutions (0.25% or above of bupivacaine or equivalent) routinely for either establishing or maintaining epidural analgesia. [2007] 1.9.19 Either patient-controlled epidural analgesia or intermittent bolus given by healthcare professionals are the preferred modes of administration for maintenance of epidural analgesia. [2007]	
Key papers	1. Lefkou, E. and Junt, B.J. (2015) Bleeding disorders in pregnancy. Obstetrics, Gynaecology and Reproductive Medicine. 25(11):314-320.	

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; APS: antiphospholipid antibody syndrome; CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CG: clinical guideline; DARE: Database of Abstracts of Reviews of Effects; DIC: disseminated intravascular coagulation; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HELLP: haemolysis with elevated liver enzymes and low platelets; HIV: human immunodeficiency virus; HTA: Health Technology Assessment; HUS: Haemolytic Uraemic Syndrome; ITP: immune thrombocytopenic purpura; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation; SLE: systemic lupus erythematosis; TTP: thrombotic thrombocytopenic purpura; vWF: von Willebrand factor

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Item	Details	Working notes
Area in the scope	Women at high risk of adverse outcomes for themselves and/or their baby because of existing maternal medical conditions – intrapartum care for women with haemostatic disorders – thresholds for platelet count and/or function requiring plans for the birth to be modified	
Review question in the scope	What is the threshold level of platelet count and/or function below which plans for the birth need to be modified in women with haemostatic disorders?	
Review question for the guideline	What is the threshold level of platelet count and/or function below which plans for the birth need to be modified in women with haemostatic disorders?	
Objective	The aim of this review is to determine the threshold platelet count level and function at which labour can proceed safely without any modification. This is important because although the majority of women with bleeding disorders can undergo normal vaginal birth without serious bleeding complications, there is possibility of having excessive maternal blood loss, as well as intracranial haemorrhage, among babies of certain women during birth. Prepartum identification of these women is of importance so that they can be better prepared for labour	

Population and directness	Women in the intrapartum period who have one of the following bleeding disorders:
	• acquired primary thrombocytopenia
	  ○ gestational thrombocytopenia
	  ○ ITP
	  ○ drug-induced abnormal platelet function, for example, long-term aspirin, heparin	

Prognostic factor	• Platelet count • vWF level • Platelet functionality tests: platelet aggregation and thromboelastography (TEG)	
Reference standard	Data allowing, the intention is to compare different threshold values of the prognostic tests (for example, by plotting them on a graph) and either seeing which	

Item	Details	Working notes
	thresholds lead to poor outcomes or extrapolating this information using statistical methods	

Outcomes	Critical outcomes:
	• for the woman:
	  ○ mortality
	  ○ major morbidity (excessive/abnormal intrapartum or postpartum haemorrhage, or haematoma or wound complications (for example dehiscence, or infection))
	  ○ neuraxial haematoma
	• for the baby:
	  ○ perinatal mortality
	  ○ major morbidity (intracranial haemorrhage)	

Importance of outcomes	Preliminary classification of the outcomes for decision making: • critical (up to 3 outcomes) • important but not critical (up to 3 outcomes) • of limited importance (1 outcome)	
Setting	All settings	
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • type of bleeding disorders (as specified above) • different levels of platelet count • different levels of other platelet functionality (for example, vWF, aggregation and TEG) • timing of the test and/or modification of care	
Language	English	

Study design	• Published full-text papers only
	• Systematic reviews
	• RCTs
	• Only if RCTs unavailable or there is limited data to inform decision making with minimum sample size of studies of 25 women in each group:
	  ○ prospective or retrospective comparative cohort studies
	  ○ case series studies
	• Prospective study designs will be prioritised over retrospective study designs
	• Conference abstracts will not be considered	

Search strategy	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used.	

Item	Details	Working notes
	See appendix B for full strategies	
Review strategy	Appraisal of methodological quality: • the methodological quality of each study will be assessed using checklists recommended in the NICE guidelines manual 2014 (for example, AMSTAR or ROBIS for systematic reviews, and Cochrane RoB tool for RCTs) and the quality of the evidence for each outcome (that is, across studies) will be assessed using GRADE • if studies report only p-values, this information will be recorded in GRADE tables without an assessment of imprecision Synthesis of data: • meta-analysis will be conducted where appropriate • default MIDs will be used; 0.8 and 1.25 for dichotomous outcomes; 0.5 times the SD of the measurement in the control arm (or median score across control arms if multiple studies are included) for continuous outcomes • for continuous data, change scores will be used in preference to final scores for data from non-RCT studies; final and change scores will not be pooled; if any study reports both, the method used in the majority of studies will be adopted	Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies will be resolved through discussion between the first and second reviewers or by reference to a third person. This review question was not prioritised for health economic analysis and so no formal dual weeding, study selection (inclusion/exclusion) or data extraction into evidence tables will be undertaken. However, internal (NGA) quality assurance processes will include consideration of the outcomes of weeding, study selection and data extraction and the committee will review the results of study selection and data extraction
Equalities	Equalities considerations will be considered systematically in relation to the available evidence and draft recommendations.	

Item	Details	Working notes
	The guideline scope includes women with cognitive or physical disability as populations for whom there may be equalities issues. Women who have received no antenatal care will be considered as a subgroup for all systematic reviews performed within the medical conditions work stream and a specific question has been included in the obstetric complications work stream for this population	
Notes/additional information	Management of **von Willebrand disease**: a guideline from the UK Haemophilia Centre Doctors' Organisation "In type 1vWD treatment is not usually needed for delivery. If required, the treatment options are the same as in the non-pregnant although all drugs should be given with caution in pregnancy. If DDAVP is used then prolonged administration should be avoided and the patient monitored closely for water retention (Grade C, level IV) DDAVP should be avoided in women with preeclampsia (Grade C, level IV). In type 2 vWD treatment will be required if an episiotomy is performed to assist delivery, a perineal tear occurs or for other operative delivery (Grade C, level IV). Women with type 3 vWD require treatment for all types of delivery (Grade C, level IV)." Guideline for the diagnosis and management of the rare coagulation disorders **Combined factor V and VIII deficiency** "For delivery in women with FV activity <0.2IU/ml in the third trimester, consider SD-FFP 15-25 ml/kg once in established labour or before caesarean section to achieve FV activity 0.2-0.4 IU/ml. Consider further SD-FFP 10ml/kg once every 12 hour to maintain FV activity >0.2IU/ml for at least 3-day. Consider additional rFVIII if the FVIII activity is <0.5IU/ml in the third trimester (2C)." Medical and Scientific Advisory Council (MASAC) guidelines for perinatal management of women with bleeding disorders and carries of **haemophilia A and B** "While the majority of infants of haemophilia carriers can be safely delivered vaginally, the outcome of labour cannot be predicted, and a spontaneous (non-operative) vaginal delivery cannot be guaranteed. A vaginal delivery may be associated with abnormal labour. Therefore, obstetricians caring for women who are carriers of haemophilia should discuss with the woman the maternal and fetal risks of a vaginal delivery versus a planned caesarean delivery; the option of a planned caesarean delivery should be recommended when an affected or potentially affected infant is anticipated. (Grade B, Level III). In women who elect vaginal delivery, forceps and vacuum extraction, interventions that triple the risk of intracranial haemorrhage in affected infants, should be avoided, as should fetal scalp electrodes during labour.	

Item	Details	Working notes
	Society of obstetricians and gynaecologists of Canada (SOGC) guidelines on women with **inherited bleeding disorders** "Vacuum extraction, forceps, fetal scalp electrodes, and fetal scalp blood sampling should be avoided if the fetus is known or thought to be at risk of a congenital bleeding disorder. A caesarean section should be performed for obstetrical indications only. (II-2C) "The risk of early and late postpartum haemorrhage is increased in women with bleeding disorders. Women with inherited bleeding disorders should be advised about the possibility of excessive postpartum bleeding and instructed to report this immediately (III-B)." Factor VII deficiency "For delivery in women with FVII activity < 0.2 IU/ml in the third trimester, who require caesarean delivery or who have a history of bleeding, consider rFVIIIa 15-30ug/kg every 4-6 hour for at least 3 days. For all other women with F7D, consider rFVIIa 15-30ug/kg only in response to abnormal bleeding (2C)."	
Key papers	None identified by the committee	

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; DDAVP: tradename for desmopressin; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; ITP: immune thrombocytopenic purpura; MASAC: Medical and Scientific Advisory Council; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RCOG: Royal College of Obstetricians and Gynaecologists; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation; SD-FFP: solvent detergent frech frozen plasma; SOGC: Society of Obstetricians and Gynaecologists of Canada; TEG: thromboelastography; vWD: von Willebrand's disease; vWF: von Willebrand factor

Intrapartum care for women with haemostatic disorders – third stage of labour

Item	Details	Working notes
Area in the scope	Women at high risk of adverse outcomes for themselves and/or their baby because of existing maternal medical conditions – intrapartum care for women with haemostatic disorders – management of the third stage of labour	
Review question in the scope	How should the third stage of labour be managed for women who are at increased risk of haemorrhage because of haemostatic disorders?	
Review question for the guideline	How should the third stage of labour be managed for women who are at increased risk of bleeding because of haemostatic disorders?	
Objective	The aim of this review is to determine how the third stage of labour should be managed for women who are at increased risk of postpartum haemorrhage because of haemostatic disorders	

Population and directness	Women in labour who have one of the haemostatic disorders below.
	
	Platelet dysfunction – normally thrombocytopenia
	• Spurious
	• Acquired
	  ○ Gestational
	  ○ ITP
	  ○ HELLP
	  ○ HUS/TTP
	  ○ SLE/APS/Evan's syndrome
	  ○ Infective e.g. HIV, parvovirus
	  ○ Drug related
	  ○ Liver disease
	  ○ DIC
	  ○ Myelosuppression e.g. malignancy, infection, autoimmune
	• Congenital
	  ○ Inherited platelet disorder
	  ○ TTP
	
	Heritable bleeding disorders
	• von Willebrand's disease (Type 1,2,3, acquired, probable)
	• Haemophilia A (factor VIII) carrier
	• Haemophilia B (factor IX) carrier
	• Factor XI deficiency
	• Factor VII deficiency
		•

Item	Details	Working notes
	• Factor XIII deficiency • Factor V deficiency • Factor X deficiency • Prothrombin deficiency • Afibrinogenemia • Dysfibrinogenemia • Hypofibrinogenemia • Fibrinogen Deficiency • Combined II+Vii+IX+X Deficiency • Combined V+VIII Deficiency • Other combined diagnoses Acquired bleeding disorders • Acquired Factor V deficiency • Acquired prothrombin deficiency • Acquired Factor XIII deficiency • Acquired deficiency (other)	

Intervention	Intervention 1
	Active management plus appropriate haemostatic therapy
	• Haemostatic therapy would include:
	  ○ desmopressin infusion (tradename DDAVP)
	  ○ improving clot stability by antifibrinolytic drugs, for example, tranexamic acid
	  ○ transfusion
	  - platelet transfusion
	  - fresh frozen plasma transfusion
	  ○ coagulation factor replacement therapy (with factor concentrates such as plasma factor concentrates or recombinant factors)
	
	Intervention 2
	Active management plus additional obstetric interventions plus appropriate haemostatic therapy
	• Additional obstetric interventions would include:
	  - brace suture
	  - intrauterine balloon
	  - interventional radiological vascular occlusion
	  - ligation of internal iliac vessels	

Comparison	Comparison 1a (to be compared with intervention 1) Active management (alone) with no additional haemostatic therapy Comparison 1b (to be compared with intervention 1)	

Item	Details	Working notes
	Active management plus additional obstetric interventions with no additional haemostatic therapy Comparison 2 (to be compared with intervention 2) Active management plus additional obstetric interventions with no additional haemostatic therapy	

Outcomes	Critical outcomes:
	• for the woman:
	  ○ mortality
	  ○ major morbidity (major or severe primary postpartum haemorrhage (defined as blood loss >1000 ml within 24 hours of the birth) or secondary postpartum haemorrhage (defined as abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally))
	  ○ further intervention such as surgery, brace suture, intrauterine balloon, cell salvage, hysterectomy, major blood vessel ligation, or interventional radiology
	
	Important outcomes:
	• for the woman:
	  ○ admission to a high dependency unit (HDU) or intensive treatment unit (ITU)
	  ○ blood transfusion
	  ○ women's satisfaction with labour or birth (including psychological wellbeing)
	
	Outcomes of limited importance:
	• for the woman:
	  ○ breastfeeding	

Importance of outcomes	Preliminary classification of the outcomes for decision making: • critical (up to 3 outcomes) • important but not critical (up to 3 outcomes) • of limited importance (1 outcome)	
Setting	All settings	
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately if data are available: • women who had no antenatal care • women whose conditions are not well controlled • women with preterm labour In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: • type of condition	

Item	Details	Working notes
	• factor levels during the last trimester of pregnancy • factor levels postpartum • maternal age • parity Potential confounders: • vaginal birth or caesarean section • women who are newly diagnosed in pregnancy or labour • factor levels during the last trimester of pregnancy • factor levels postpartum • type of condition • maternal age • parity	
Language	English	
Study design	• Published full-text papers only • Systematic reviews • RCTs • Only if RCTs unavailable or there is limited data to inform decision making: ○ prospective or retrospective comparative observational studies (including cohort and case-control studies) • Prospective study designs will be prioritised over retrospective study designs • Conference abstracts will not be considered	
Search strategy	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies	
Review strategy	Appraisal of methodological quality: • the methodological quality of each study will be assessed using checklists recommended in the NICE guidelines manual 2014 (for example, AMSTAR or ROBIS for systematic reviews, and Cochrane RoB tool for RCTs) and the quality of the evidence for each outcome (that is, across studies) will be assessed using GRADE • if studies report only p-values, this information will be recorded in GRADE tables without an assessment of imprecision	Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies will be resolved through

Item	Details	Working notes
	Synthesis of data: • meta-analysis will be conducted where appropriate • default MIDs will be used; 0.8 and 1.25 for dichotomous outcomes; 0.5 times the SD of the measurement in the control arm (or median score across control arms if multiple studies are included) for continuous outcomes • for continuous data, change scores will be used in preference to final scores for data from non-RCT studies; final and change scores will not be pooled; if any study reports both, the method used in the majority of studies will be adopted	discussion between the first and second reviewers or by reference to a third person. This review question was not prioritised for health economic analysis and so no formal dual weeding, study selection (inclusion/exclusion) or data extraction into evidence tables will be undertaken. However, internal (NGA) quality assurance processes will include consideration of the outcomes of weeding, study selection and data extraction and the committee will review the results of study selection and data extraction
Equalities	Equalities considerations will be considered systematically in relation to the available evidence and draft recommendations. The guideline scope includes women with cognitive or physical disability as populations for whom there may be equalities issues. Women who have received no antenatal care will be considered as a subgroup for all systematic reviews performed within the medical conditions work stream and a specific question has been included in the obstetric complications work stream for this population	
Notes/additional information	NICE guideline on intrapartum care for healthy women and babies (CG190) NICE guideline on blood transfusion (NG24) NICE guideline on preterm labour and birth (NG25) Royal College of Obstetricians and Gynaecologists. Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No.52. 2011	
Key papers	Lee CA, Chi C, Pavord SR, Bolton-Maggs PH, Pollard D, Hinchcliffe-Wood A, Kadir RA; UK Haemophilia Centre Doctors' Organization. The obstetric and gynaecological management of women with inherited bleeding disorders – review with guidelines produced by	

Item	Details	Working notes
	a taskforce of UK Haemophilia Centre Doctors Organization. Haemophilia. 2006 12: 301-336 Huq FY, Kadir RA. Management of pregnancy, labour and delivery in women with inherited bleeding disorders. Haemophilia. 2011 Jul;17 Suppl 1:20-30. doi: 10.1111/j.1365-2516.2011.02561.x. Demers C, Derzko C, David M, Douglas J. Gynaecological and obstetric management of women with inherited bleeding disorders. J Obstet Gynaecol Can 2005;27:707–18. Italian Association of Haemophilia Centres. Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Register relevant to clinical practice.BJOG 2003;110:311–14. Chi C, Kadir Rezan. Review: Management of women with inherited bleeding disorders in pregnancy. The Obstetrician & Gynaecologist. 2007;9:27-33 James, Steer, Weiner, Gonik, Crowther, Robson. High Risk Pregnancy: Management Options. Expertconsult.com. Elsevier Saunders 2011. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Surveillance of maternal deaths in the UK 2011-13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2015. Anorlu RI, Maholwana B, Hofmeyr GJ. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD004737. doi: 10.1002/14651858.CD004737.pub2.1 Methods of delivering the placenta at caesarean section. Morales M., Ceysens G., Jastrow N., Viardot C., Faron G., Vial Y., Kirkpatrick C., Irion O., Boulvain M. Spontaneous delivery or manual removal of the placenta during caesarean section: a randomised controlled trial. BJOG: An International Journal of Obstetrics and Gynaecology. 2004. Vol. 111, pp. 908-912	

Item	Details	Working notes
	Kaima A. Frass, Postpartum hemorrhage is related to the hemoglobin levels at labor: Observational study. Alexandria Journal of Medicine. Volume 51, Issue 4, December 2015, Pages 333–337. doi:10.1016/j.ajme.2014.12.002 Health and Social Care Information Centre. Hospital Episode Statistics: NHS Maternity Statistics – 2012-13. 2013. URL: http://www.hscic.gov.uk/catalogue/PUB12744/nhs-mate-eng-2012-13-summ-repo-rep.pdf Healthcare Improvement Scotland. Scottish Confidential Audit of Severe Maternal Morbidity: reducing avoidable harm. 9th Annual Report. 2013. URL: http://www.scottishpatientsafetyprogramme.scot.nhs.uk/Media/Docs/MCQIC/Maternity%20Care/2013-08-09%20Final%209th%20annual%20SCASMM%20report.pdf	

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; APS: antiphospholipid antibody syndrome; CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CG: clinical guideline; DARE: Database of Abstracts of Reviews of Effects; DIC: disseminated intravascular coagulation; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HDU: high dependency unit; HELLP: haemolysis with elevated liver enzymes and low platelets; HIV: human immunodeficiency virus; HTA: Health Technology Assessment; HUS: haemolytic uraemic syndrome; ITP: immune thrombocytopenic purpura; ITU: intensive therapy unit; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation; SLE: systemic lupus erythematosis; TTP: thrombotic thrombocytopenic purpura; UKHDO: United Kingdom Haemophilia Centre Doctors' Organisation

Appendix B – Literature search strategies

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Database: Medline; Medline Epub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	PREGNANCY/
2	PERIPARTUM PERIOD/
3	PARTURITION/
4	exp LABOR, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	DELIVERY, OBSTETRIC/
7	pregnan$.ti,ab.
8	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
9	((during or giving or give) adj3 birth?).ti,ab.
10	or/1-9
11	exp BLOOD PLATELET DISORDERS/

#	Searches
12	(Blood Platelet Disorder? Or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab.
13	HELLP SYNDROME/
14	HELLP.ti,ab.
15	HEMOLYTIC-UREMIC SYNDROME/
16	76nrolment76 uremic syndrome.ti,ab.
17	LUPUS ERYTHEMATOSUS, SYSTEMIC/
18	systemic lupus erythematosus.ti,ab.
19	ANTIPHOSPHOLIPID SYNDROME/
20	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
21	Evans syndrome.ti,ab.
22	(Platelet adj3 (Disorder? Or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
23	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab.
24	exp HEMORRHAGIC DISORDERS/
25	(Hemorrhagic Disorder? Or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? Or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? Adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? Or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? Or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab.
26	exp BLOOD COAGULATION DISORDERS, INHERITED/
27	((Blood Coagulation Disorder? Adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
28	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
29	or/11-28
30	ANALGESIA, EPIDURAL/
31	INJECTIONS, EPIDURAL/
32	((Spinal$ or spinous$) adj5 analges$).ti,ab.
33	epidural$.ti,ab.
34	CSE.ti,ab.
35	((central$ or regional$) adj5 neuraxial$ adj5 block$).ti,ab.
36	(neuraxial$ adj5 analges$).ti,ab.
37	or/30-36
38	ANALGESIA, PATIENT-CONTROLLED/
39	(patient? Adj3 control$ adj3 analges$).ti,ab.
40	ANALGESIA, OBSTETRICAL/
41	(obstetric$ adj3 analges$).ti,ab.
42	or/38-41
43	exp ANESTHESIA, CONDUCTION/
44	((nerve or ganglion or plexus) adj3 block$).ti,ab.
45	(an?esthe$ adj5 (conduction or region$ or caudal$ or local$ or spinal$)).ti,ab.
46	epidural$.ti,ab.

#	Searches
47	CSE.ti,ab.
48	((nerve or ganglion or plexus or neuraxial$) adj5 block$).ti,ab.
49	(neuraxial$ adj5 an?esthe$).ti,ab.
50	or/43-49
51	ANESTHESIA, OBSTETRICAL/
52	(an?esthe$ adj5 (obstetric$ or gyn?ecolog$)).ti,ab.
53	or/51-52
54	37 or 42 or 50 or 53
55	BLOOD COAGULATION TESTS/
56	exp PLATELET FUNCTION TESTS/
57	(platelet? Adj3 (count$ or number?)).ti,ab.
58	(platelet? Adj3 function$ adj3 test$).ti,ab.
59	PLATELET AGGREGATION/
60	(platelet? Adj3 aggregat$).ti,ab.
61	THROMBELASTOGRAPHY/
62	thromb?elasto$.ti,ab.
63	TEG.ti,ab.
64	viscoelastic$.ti,ab.
65	rotem.ti,ab.
66	((von Willebrand? Or vwf or Fibrinogen or Factor XI or Factor VII or Factor IX or Factor XIII or Factor V or Factor X or Factor VIII or Factor II) adj5 level?).ti,ab.
67	or/55-66
68	SEVERITY OF ILLNESS INDEX/
69	REFERENCE STANDARDS/
70	REFERENCE VALUES/
71	(grade? Or grading).ti,ab.
72	severit$.ti,ab.
73	classif$.ti,ab.
74	(index$ or indices).ti,ab.
75	degree?.ti,ab.
76	threshold?.ti,ab.
77	(define? Or defining).ti,ab.
78	criteri$.ti,ab.
79	cut off?.ti,ab.
80	parameter?.ti,ab.
81	below.ti,ab.
82	minimal.ti,ab.
83	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
84	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
85	(reference adj3 (standard? Or value? Or range?)).ti,ab.
86	or/68-85
87	77nrolment77e77te$.ti,ab.
88	((no or avoid$) adj3 (analges$ or an?esthe$)).ti,ab.
89	ANALGESIA, EPIDURAL/ct [Contraindications]
90	INJECTIONS, EPIDURAL/ct [Contraindications]
91	ANALGESIA, PATIENT-CONTROLLED/ct [Contraindications]
92	ANALGESIA, OBSTETRICAL/ct [Contraindications]
93	or/89-92
94	ANALGESIA, EPIDURAL/ae [Adverse Effects]
95	INJECTIONS, EPIDURAL/ae [Adverse Effects]
96	ANALGESIA, PATIENT-CONTROLLED/ae [Adverse Effects]

#	Searches
97	ANALGESIA, OBSTETRICAL/ae [Adverse Effects]
98	or/94-97
99	exp ANESTHESIA, CONDUCTION/ct [Contraindications]
100	ANESTHESIA, OBSTETRICAL/ct [Contraindications]
101	or/99-100
102	exp ANESTHESIA, CONDUCTION/ae [Adverse Effects]
103	ANESTHESIA, OBSTETRICAL/ae [Adverse Effects]
104	or/102-103
105	93 or 98 or 101 or 104
106	10 and 29 and 54 and 67
107	10 and 54 and 67 and 86
108	29 and 54 and 67 and 86
109	10 and 29 and 54 and 87
110	10 and 29 and 88
111	10 and 29 and 105
112	or/106-111
113	limit 112 to 78nrolme language
114	LETTER/
115	EDITORIAL/
116	NEWS/
117	exp HISTORICAL ARTICLE/
118	ANECDOTES AS TOPIC/
119	COMMENT/
120	CASE REPORT/
121	(letter or comment*).ti.
122	or/114-121
123	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
124	122 not 123
125	ANIMALS/ not HUMANS/
126	exp ANIMALS, LABORATORY/
127	exp ANIMAL EXPERIMENTATION/
128	exp MODELS, ANIMAL/
129	exp RODENTIA/
130	(rat or rats or mouse or mice).ti.
131	or/124-130
132	113 not 131

Database: Cochrane Central Register of Controlled Trials

#	Searches
1	PREGNANCY/
2	PERIPARTUM PERIOD/
3	PARTURITION/
4	exp LABOR, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	DELIVERY, OBSTETRIC/
7	pregnan$.ti,ab,kw.
8	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab,kw.
9	((during or giving or give) adj3 birth?).ti,ab.
10	or/1-9
11	exp BLOOD PLATELET DISORDERS/

#	Searches
12	(Blood Platelet Disorder? Or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab,kw.
13	HELLP SYNDROME/
14	HELLP.ti,ab.
15	HEMOLYTIC-UREMIC SYNDROME/
16	79nrolment79 uremic syndrome.ti,ab,kw.
17	LUPUS ERYTHEMATOSUS, SYSTEMIC/
18	systemic lupus erythematosus.ti,ab,kw.
19	ANTIPHOSPHOLIPID SYNDROME/
20	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
21	Evans syndrome.ti,ab,kw.
22	(Platelet adj3 (Disorder? Or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
23	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab,kw.
24	exp HEMORRHAGIC DISORDERS/
25	(Hemorrhagic Disorder? Or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? Or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? Adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? Or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? Or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab,kw.
26	exp BLOOD COAGULATION DISORDERS, INHERITED/
27	((Blood Coagulation Disorder? Adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
28	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
29	or/11-28
30	ANALGESIA, EPIDURAL/
31	INJECTIONS, EPIDURAL/
32	((Spinal$ or spinous$) adj5 analges$).ti,ab.
33	epidural$.ti,ab,kw.
34	CSE.ti,ab.
35	((central$ or regional$) adj5 neuraxial$ adj5 block$).ti,ab.
36	(neuraxial$ adj5 analges$).ti,ab.
37	or/30-36
38	ANALGESIA, PATIENT-CONTROLLED/
39	(patient? Adj3 control$ adj3 analges$).ti,ab.
40	ANALGESIA, OBSTETRICAL/
41	(obstetric$ adj3 analges$).ti,ab.
42	or/38-41
43	exp ANESTHESIA, CONDUCTION/
44	((nerve or ganglion or plexus) adj3 block$).ti,ab.
45	(an?esthe$ adj5 (conduction or region$ or caudal$ or local$ or spinal$)).ti,ab.
46	epidural$.ti,ab,kw.

#	Searches
47	CSE.ti,ab.
48	((nerve or ganglion or plexus or neuraxial$) adj5 block$).ti,ab.
49	(neuraxial$ adj5 an?esthe$).ti,ab.
50	or/43-49
51	ANESTHESIA, OBSTETRICAL/
52	(an?esthe$ adj5 (obstetric$ or gyn?ecolog$)).ti,ab.
53	or/51-52
54	37 or 42 or 50 or 53
55	BLOOD COAGULATION TESTS/
56	exp PLATELET FUNCTION TESTS/
57	(platelet? Adj3 (count$ or number?)).ti,ab.
58	(platelet? Adj3 function$ adj3 test$).ti,ab.
59	PLATELET AGGREGATION/
60	(platelet? Adj3 aggregat$).ti,ab.
61	THROMBELASTOGRAPHY/
62	thromb?elasto$.ti,ab,kw.
63	TEG.ti,ab.
64	viscoelastic$.ti,ab,kw.
65	rotem.ti,ab.
66	((von Willebrand? Or vwf or Fibrinogen or Factor XI or Factor VII or Factor IX or Factor XIII or Factor V or Factor X or Factor VIII or Factor II) adj5 level?).ti,ab.
67	or/55-66
68	SEVERITY OF ILLNESS INDEX/
69	REFERENCE STANDARDS/
70	REFERENCE VALUES/
71	(grade? Or grading).ti,ab.
72	severit$.ti,ab.
73	classif$.ti,ab.
74	(index$ or indices).ti,ab.
75	degree?.ti,ab.
76	threshold?.ti,ab.
77	(define? Or defining).ti,ab.
78	criteri$.ti,ab.
79	cut off?.ti,ab.
80	parameter?.ti,ab.
81	below.ti,ab.
82	minimal.ti,ab.
83	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
84	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
85	(reference adj3 (standard? Or value? Or range?)).ti,ab.
86	or/68-85
87	80nrolment80e80te$.ti,ab.
88	((no or avoid$) adj3 (analges$ or an?esthe$)).ti,ab.
89	ANALGESIA, EPIDURAL/ct [Contraindications]
90	INJECTIONS, EPIDURAL/ct [Contraindications]
91	ANALGESIA, PATIENT-CONTROLLED/ct [Contraindications]
92	ANALGESIA, OBSTETRICAL/ct [Contraindications]
93	or/89-92
94	ANALGESIA, EPIDURAL/ae [Adverse Effects]
95	INJECTIONS, EPIDURAL/ae [Adverse Effects]
96	ANALGESIA, PATIENT-CONTROLLED/ae [Adverse Effects]

#	Searches
97	ANALGESIA, OBSTETRICAL/ae [Adverse Effects]
98	or/94-97
99	exp ANESTHESIA, CONDUCTION/ct [Contraindications]
100	ANESTHESIA, OBSTETRICAL/ct [Contraindications]
101	or/99-100
102	exp ANESTHESIA, CONDUCTION/ae [Adverse Effects]
103	ANESTHESIA, OBSTETRICAL/ae [Adverse Effects]
104	or/102-103
105	93 or 98 or 101 or 104
106	10 and 29 and 54 and 67
107	10 and 54 and 67 and 86
108	29 and 54 and 67 and 86
109	10 and 29 and 54 and 87
110	10 and 29 and 88
111	10 and 29 and 105
112	or/106-111

Database: Cochrane Database of Systematic Reviews

#	Searches
1	PREGNANCY.kw.
2	PERIPARTUM PERIOD.kw.
3	PARTURITION.kw.
4	LABOR, OBSTETRIC.kw.
5	OBSTETRIC LABOR, PREMATURE.kw.
6	DELIVERY, OBSTETRIC.kw.
7	pregnan$.ti,ab.
8	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
9	((during or giving or give) adj3 birth?).ti,ab.
10	or/1-9
11	BLOOD PLATELET DISORDERS.kw.
12	(Blood Platelet Disorder? Or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab.
13	HELLP SYNDROME.kw.
14	HELLP.ti,ab.
15	HEMOLYTIC-UREMIC SYNDROME.kw.
16	81nrolment81 uremic syndrome.ti,ab.
17	LUPUS ERYTHEMATOSUS, SYSTEMIC.kw.
18	systemic lupus erythematosus.ti,ab.
19	ANTIPHOSPHOLIPID SYNDROME.kw.
20	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
21	Evans syndrome.ti,ab.
22	(Platelet adj3 (Disorder? Or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
23	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab.
24	HEMORRHAGIC DISORDERS.kw.
25	(Hemorrhagic Disorder? Or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or

#	Searches
	Hemostatic Disorder? Or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? Adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? Or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? Or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab.
26	BLOOD COAGULATION DISORDERS, INHERITED.kw.
27	((Blood Coagulation Disorder? Adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
28	PREGNANCY COMPLICATIONS, HEMATOLOGIC.kw.
29	or/11-28
30	ANALGESIA, EPIDURAL.kw.
31	INJECTIONS, EPIDURAL.kw.
32	((Spinal$ or spinous$) adj5 analges$).ti,ab.
33	epidural$.ti,ab.
34	CSE.ti,ab.
35	((central$ or regional$) adj5 neuraxial$ adj5 block$).ti,ab.
36	(neuraxial$ adj5 analges$).ti,ab.
37	or/30-36
38	ANALGESIA, PATIENT-CONTROLLED.kw.
39	(patient? Adj3 control$ adj3 analges$).ti,ab.
40	ANALGESIA, OBSTETRICAL.kw.
41	(obstetric$ adj3 analges$).ti,ab.
42	or/38-41
43	ANESTHESIA, CONDUCTION.kw.
44	((nerve or ganglion or plexus) adj3 block$).ti,ab.
45	(an?esthe$ adj5 (conduction or region$ or caudal$ or local$ or spinal$)).ti,ab.
46	epidural$.ti,ab.
47	CSE.ti,ab.
48	((nerve or ganglion or plexus or neuraxial$) adj5 block$).ti,ab.
49	(neuraxial$ adj5 an?esthe$).ti,ab.
50	or/43-49
51	ANESTHESIA, OBSTETRICAL.kw.
52	(an?esthe$ adj5 (obstetric$ or gyn?ecolog$)).ti,ab.
53	or/51-52
54	37 or 42 or 50 or 53
55	BLOOD COAGULATION TESTS.kw.
56	PLATELET FUNCTION TESTS.kw.
57	(platelet? Adj3 (count$ or number?)).ti,ab.
58	(platelet? Adj3 function$ adj3 test$).ti,ab.
59	PLATELET AGGREGATION.kw.
60	(platelet? Adj3 aggregat$).ti,ab.
61	THROMBELASTOGRAPHY.kw.
62	thromb?elasto$.ti,ab.
63	TEG.ti,ab.
64	viscoelastic$.ti,ab.
65	rotem.ti,ab.

#	Searches
66	((von Willebrand? Or vwf or Fibrinogen or Factor XI or Factor VII or Factor IX or Factor XIII or Factor V or Factor X or Factor VIII or Factor II) adj5 level?).ti,ab.
67	or/55-66
68	SEVERITY OF ILLNESS INDEX.kw.
69	REFERENCE STANDARDS.kw.
70	REFERENCE VALUES.kw.
71	(grade? Or grading).ti,ab.
72	severit$.ti,ab.
73	classif$.ti,ab.
74	(index$ or indices).ti,ab.
75	degree?.ti,ab.
76	threshold?.ti,ab.
77	(define? Or defining).ti,ab.
78	criteri$.ti,ab.
79	cut off?.ti,ab.
80	parameter?.ti,ab.
81	below.ti,ab.
82	minimal.ti,ab.
83	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
84	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
85	(reference adj3 (standard? Or value? Or range?)).ti,ab.
86	or/68-85
87	83nrolment83e83te$.ti,ab.
88	((no or avoid$) adj3 (analges$ or an?esthe$)).ti,ab.
89	10 and 29 and 54 and 67
90	10 and 54 and 67 and 86
91	29 and 54 and 67 and 86
92	10 and 29 and 54 and 87
93	10 and 29 and 88
94	or/89-93

Database: Database of Abstracts of Reviews of Effects

#	Searches
1	PREGNANCY.kw.
2	PERIPARTUM PERIOD.kw.
3	PARTURITION.kw.
4	LABOR, OBSTETRIC.kw.
5	OBSTETRIC LABOR, PREMATURE.kw.
6	DELIVERY, OBSTETRIC.kw.
7	pregnan$.tw,tx.
8	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).tw,tx.
9	((during or giving or give) adj3 birth?).tw,tx.
10	or/1-9
11	BLOOD PLATELET DISORDERS.kw.
12	(Blood Platelet Disorder? Or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).tw,tx.
13	HELLP SYNDROME.kw.
14	HELLP.tw,tx.

#	Searches
15	HEMOLYTIC-UREMIC SYNDROME.kw.
16	84nrolment84 uremic syndrome.tw,tx.
17	LUPUS ERYTHEMATOSUS, SYSTEMIC.kw.
18	systemic lupus erythematosus.tw,tx.
19	ANTIPHOSPHOLIPID SYNDROME.kw.
20	((antiphospholipid or anti-phospholipid) adj3 syndrome?).tw,tx.
21	Evans syndrome.tw,tx.
22	(Platelet adj3 (Disorder? Or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).tw,tx.
23	(Bone marrow suppression or myelotoxic$ or myelosuppression).tw,tx.
24	HEMORRHAGIC DISORDERS.kw.
25	(Hemorrhagic Disorder? Or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? Or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? Adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? Or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? Or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).tw,tx.
26	BLOOD COAGULATION DISORDERS, INHERITED.kw.
27	((Blood Coagulation Disorder? Adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).tw,tx.
28	PREGNANCY COMPLICATIONS, HEMATOLOGIC.kw.
29	or/11-28
30	ANALGESIA, EPIDURAL.kw.
31	INJECTIONS, EPIDURAL.kw.
32	((Spinal$ or spinous$) adj5 analges$).tw,tx.
33	epidural$.tw,tx.
34	CSE.tw,tx.
35	((central$ or regional$) adj5 neuraxial$ adj5 block$).tw,tx.
36	(neuraxial$ adj5 analges$).tw,tx.
37	or/30-36
38	ANALGESIA, PATIENT-CONTROLLED.kw.
39	(patient? Adj3 control$ adj3 analges$).tw,tx.
40	ANALGESIA, OBSTETRICAL.kw.
41	(obstetric$ adj3 analges$).tw,tx.
42	or/38-41
43	ANESTHESIA, CONDUCTION.kw.
44	((nerve or ganglion or plexus) adj3 block$).tw,tx.
45	(an?esthe$ adj5 (conduction or region$ or caudal$ or local$ or spinal$)).tw,tx.
46	epidural$.tw,tx.
47	CSE.tw,tx.
48	((nerve or ganglion or plexus or neuraxial$) adj5 block$).tw,tx.
49	(neuraxial$ adj5 an?esthe$).tw,tx.
50	or/43-49
51	ANESTHESIA, OBSTETRICAL.kw.
52	(an?esthe$ adj5 (obstetric$ or gyn?ecolog$)).tw,tx.

#	Searches
53	or/51-52
54	37 or 42 or 50 or 53
55	BLOOD COAGULATION TESTS.kw.
56	PLATELET FUNCTION TESTS.kw.
57	(platelet? Adj3 (count$ or number?)).tw,tx.
58	(platelet? Adj3 function$ adj3 test$).tw,tx.
59	PLATELET AGGREGATION.kw.
60	(platelet? Adj3 aggregat$).tw,tx.
61	THROMBELASTOGRAPHY.kw.
62	thromb?elasto$.tw,tx.
63	TEG.tw,tx.
64	viscoelastic$.tw,tx.
65	rotem.tw,tx.
66	((von Willebrand? Or vwf or Fibrinogen or Factor XI or Factor VII or Factor IX or Factor XIII or Factor V or Factor X or Factor VIII or Factor II) adj5 level?).tw,tx.
67	or/55-66
68	SEVERITY OF ILLNESS INDEX.kw.
69	REFERENCE STANDARDS.kw.
70	REFERENCE VALUES.kw.
71	(grade? Or grading).tw,tx.
72	severit$.tw,tx.
73	classif$.tw,tx.
74	(index$ or indices).tw,tx.
75	degree?.tw,tx.
76	threshold?.tw,tx.
77	(define? Or defining).tw,tx.
78	criteri$.tw,tx.
79	cut off?.tw,tx.
80	parameter?.tw,tx.
81	below.tw,tx.
82	minimal.tw,tx.
83	((low$ or decreas$ or abnormal$) adj5 level?).tw,tx.
84	((low$ or decreas$ or abnormal$) adj5 count?).tw,tx.
85	(reference adj3 (standard? Or value? Or range?)).tw,tx.
86	or/68-85
87	85nrolment85e85te$.tw,tx.
88	((no or avoid$) adj3 (analges$ or an?esthe$)).tw,tx.
89	10 and 29 and 54 and 67
90	10 and 54 and 67 and 86
91	29 and 54 and 67 and 86
92	10 and 29 and 54 and 87
93	10 and 29 and 88
94	or/89-93

Database: Health Technology Assessment

#	Searches
1	PREGNANCY/
2	PERIPARTUM PERIOD/
3	PARTURITION/
4	exp LABOR, OBSTETRIC/

#	Searches
5	OBSTETRIC LABOR, PREMATURE/
6	DELIVERY, OBSTETRIC/
7	pregnan$.tw.
8	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).tw.
9	((during or giving or give) adj3 birth?).tw.
10	or/1-9
11	exp BLOOD PLATELET DISORDERS/
12	(Blood Platelet Disorder? Or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).tw.
13	HELLP SYNDROME/
14	HELLP.tw.
15	HEMOLYTIC-UREMIC SYNDROME/
16	86nrolment86 uremic syndrome.tw.
17	LUPUS ERYTHEMATOSUS, SYSTEMIC/
18	systemic lupus erythematosus.tw.
19	ANTIPHOSPHOLIPID SYNDROME/
20	((antiphospholipid or anti-phospholipid) adj3 syndrome?).tw.
21	Evans syndrome.tw.
22	(Platelet adj3 (Disorder? Or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).tw.
23	(Bone marrow suppression or myelotoxic$ or myelosuppression).tw.
24	exp HEMORRHAGIC DISORDERS/
25	(Hemorrhagic Disorder? Or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? Or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? Adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? Or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? Or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).tw.
26	exp BLOOD COAGULATION DISORDERS, INHERITED/
27	((Blood Coagulation Disorder? Adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).tw.
28	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
29	or/11-28
30	ANALGESIA, EPIDURAL/
31	INJECTIONS, EPIDURAL/
32	((Spinal$ or spinous$) adj5 analges$).tw.
33	epidural$.tw.
34	CSE.tw.
35	((central$ or regional$) adj5 neuraxial$ adj5 block$).tw.
36	(neuraxial$ adj5 analges$).tw.
37	or/30-36
38	ANALGESIA, PATIENT-CONTROLLED/
39	(patient? Adj3 control$ adj3 analges$).tw.

#	Searches
40	ANALGESIA, OBSTETRICAL/
41	(obstetric$ adj3 analges$).tw.
42	or/38-41
43	exp ANESTHESIA, CONDUCTION/
44	((nerve or ganglion or plexus) adj3 block$).tw.
45	(an?esthe$ adj5 (conduction or region$ or caudal$ or local$ or spinal$)).tw.
46	epidural$.tw.
47	CSE.tw.
48	((nerve or ganglion or plexus or neuraxial$) adj5 block$).tw.
49	(neuraxial$ adj5 an?esthe$).tw.
50	or/43-49
51	ANESTHESIA, OBSTETRICAL/
52	(an?esthe$ adj5 (obstetric$ or gyn?ecolog$)).tw.
53	or/51-52
54	37 or 42 or 50 or 53
55	BLOOD COAGULATION TESTS/
56	exp PLATELET FUNCTION TESTS/
57	(platelet? Adj3 (count$ or number?)).tw.
58	(platelet? Adj3 function$ adj3 test$).tw.
59	PLATELET AGGREGATION/
60	(platelet? Adj3 aggregat$).tw.
61	THROMBELASTOGRAPHY/
62	thromb?elasto$.tw.
63	TEG.tw.
64	viscoelastic$.tw.
65	rotem.tw.
66	((von Willebrand? Or vwf or Fibrinogen or Factor XI or Factor VII or Factor IX or Factor XIII or Factor V or Factor X or Factor VIII or Factor II) adj5 level?).tw.
67	or/55-66
68	SEVERITY OF ILLNESS INDEX/
69	REFERENCE STANDARDS/
70	REFERENCE VALUES/
71	(grade? Or grading).tw.
72	severit$.tw.
73	classif$.tw.
74	(index$ or indices).tw.
75	degree?.tw.
76	threshold?.tw.
77	(define? Or defining).tw.
78	criteri$.tw.
79	cut off?.tw.
80	parameter?.tw.
81	below.tw.
82	minimal.tw.
83	((low$ or decreas$ or abnormal$) adj5 level?).tw.
84	((low$ or decreas$ or abnormal$) adj5 count?).tw.
85	(reference adj3 (standard? Or value? Or range?)).tw.
86	or/68-85
87	87nrolment87e87te$.tw.
88	((no or avoid$) adj3 (analges$ or an?esthe$)).tw.
89	ANALGESIA, EPIDURAL/ct [Contraindications]

#	Searches
90	INJECTIONS, EPIDURAL/ct [Contraindications]
91	ANALGESIA, PATIENT-CONTROLLED/ct [Contraindications]
92	ANALGESIA, OBSTETRICAL/ct [Contraindications]
93	or/89-92
94	ANALGESIA, EPIDURAL/ae [Adverse Effects]
95	INJECTIONS, EPIDURAL/ae [Adverse Effects]
96	ANALGESIA, PATIENT-CONTROLLED/ae [Adverse Effects]
97	ANALGESIA, OBSTETRICAL/ae [Adverse Effects]
98	or/94-97
99	exp ANESTHESIA, CONDUCTION/ct [Contraindications]
100	ANESTHESIA, OBSTETRICAL/ct [Contraindications]
101	or/99-100
102	exp ANESTHESIA, CONDUCTION/ae [Adverse Effects]
103	ANESTHESIA, OBSTETRICAL/ae [Adverse Effects]
104	or/102-103
105	93 or 98 or 101 or 104
106	10 and 29 and 54 and 67
107	10 and 54 and 67 and 86
108	29 and 54 and 67 and 86
109	10 and 29 and 54 and 87
110	10 and 29 and 88
111	10 and 29 and 105
112	or/106-111

Database: Embase

#	Searches
1	*PREGNANCY/
2	*PERINATAL PERIOD/
3	exp *BIRTH/
4	exp *LABOR/
5	*PREMATURE LABOR/
6	*OBSTETRIC DELIVERY/
7	*INTRAPARTUM CARE/
8	pregnan$.ti,ab.
9	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
10	((during or giving or give) adj3 birth?).ti,ab.
11	or/1-10
12	exp *THROMBOCYTE DISORDER/
13	(Blood Platelet Disorder? Or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab.
14	*HELLP SYNDROME/
15	HELLP.ti,ab.
16	*HEMOLYTIC UREMIC SYNDROME/
17	88nrolment88 uremic syndrome.ti,ab.
18	*SYSTEMIC LUPUS ERYTHEMATOSUS/
19	systemic lupus erythematosus.ti,ab.
20	*ANTIPHOSPHOLIPID SYNDROME/
21	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.

#	Searches
22	Evans syndrome.ti,ab.
23	(Platelet adj3 (Disorder? Or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
24	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab.
25	*BLEEDING DISORDER/
26	*BLOOD CLOTTING DISORDER/
27	*ACTIVATED PROTEIN C RESISTANCE/
28	exp *BLOOD CLOTTING FACTOR DEFICIENCY/
29	*DISSEMINATED INTRAVASCULAR CLOTTING/
30	(Hemorrhagic Disorder? Or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? Or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? Adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? Or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? Or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab.
31	((Blood Coagulation Disorder? Adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
32	or/12-31
33	EPIDURAL ANALGESIA/
34	EPIDURAL DRUG ADMINISTRATION/
35	((Spinal$ or spinous$) adj5 analges$).ti,ab.
36	epidural$.ti,ab.
37	CSE.ti,ab.
38	((central$ or regional$) adj5 neuraxial$ adj5 block$).ti,ab.
39	(neuraxial$ adj5 analges$).ti,ab.
40	or/33-39
41	PATIENT CONTROLLED ANALGESIA/
42	(patient? Adj3 control$ adj3 analges$).ti,ab.
43	OBSTETRIC ANALGESIA/
44	(obstetric$ adj3 analges$).ti,ab.
45	or/41-44
46	exp EPIDURAL ANESTHESIA/
47	exp LOCAL ANESTHESIA/
48	exp REGIONAL ANESTHESIA/
49	exp SPINAL ANESTHESIA/
50	((nerve or ganglion or plexus) adj3 block$).ti,ab.
51	(an?esthe$ adj5 (conduction or region$ or caudal$ or local$ or spinal$)).ti,ab.
52	epidural$.ti,ab.
53	CSE.ti,ab.
54	((nerve or ganglion or plexus or neuraxial$) adj5 block$).ti,ab.
55	(neuraxial$ adj5 an?esthe$).ti,ab.
56	or/46-55
57	OBSTETRIC ANESTHESIA/
58	(an?esthe$ adj5 (obstetric$ or gyn?ecolog$)).ti,ab.
59	or/57-58

#	Searches
60	40 or 45 or 56 or 59
61	BLOOD CLOTTING TEST/
62	THROMBOCYTE COUNT/
63	(platelet? Adj3 (count$ or number?)).ti,ab.
64	exp BLOOD CLOTTING PARAMETERS/
65	(platelet? Adj3 function$ adj3 test$).ti,ab.
66	THROMBOCYTE AGGREGATION/
67	(platelet? Adj3 aggregat$).ti,ab.
68	THROMBELASTOGRAPHY/
69	thromb?elasto$.ti,ab.
70	TEG.ti,ab.
71	viscoelastic$.ti,ab.
72	rotem.ti,ab.
73	((von Willebrand? Or vwf or Fibrinogen or Factor XI or Factor VII or Factor IX or Factor XIII or Factor V or Factor X or Factor VIII or Factor II) adj5 level?).ti,ab.
74	or/61-73
75	“SEVERITY OF ILLNESS INDEX”/
76	STANDARD/
77	REFERENCE VALUES/
78	ANALYTICAL PARAMETERS/
79	(grade? Or grading).ti,ab.
80	severit$.ti,ab.
81	classif$.ti,ab.
82	(index$ or indices).ti,ab.
83	degree?.ti,ab.
84	threshold?.ti,ab.
85	(define? Or defining).ti,ab.
86	criteri$.ti,ab.
87	cut off?.ti,ab.
88	parameter?.ti,ab.
89	below.ti,ab.
90	minimal.ti,ab.
91	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
92	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
93	(reference adj3 (standard? Or value? Or range?)).ti,ab.
94	or/75-93
95	TREATMENT CONTRAINDICATION/
96	90nrolment90e90te$.ti,ab.
97	or/95-96
98	((no or avoid$) adj3 (analges$ or an?esthe$)).ti,ab.
99	EPIDURAL DRUG ADMINISTRATION/ae [Adverse Drug Reaction]
100	PATIENT CONTROLLED ANALGESIA/ae [Adverse Drug Reaction]
101	OBSTETRIC ANALGESIA/ae [Adverse Drug Reaction]
102	or/99-101
103	exp EPIDURAL ANESTHESIA/ae [Adverse Drug Reaction]
104	exp LOCAL ANESTHESIA/ae [Adverse Drug Reaction]
105	exp REGIONAL ANESTHESIA/ae [Adverse Drug Reaction]
106	exp SPINAL ANESTHESIA/ae [Adverse Drug Reaction]
107	OBSTETRIC ANESTHESIA/ae [Adverse Drug Reaction]
108	or/103-107
109	102 or 108

#	Searches
110	11 and 32 and 60 and 74
111	11 and 60 and 74 and 94
112	32 and 60 and 74 and 94
113	11 and 32 and 60 and 97
114	11 and 32 and 98
115	11 and 32 and 109
116	or/110-115
117	limit 116 to 91nrolme language
118	letter.pt. or LETTER/
119	note.pt.
120	editorial.pt.
121	CASE REPORT/ or CASE STUDY/
122	(letter or comment*).ti.
123	or/118-122
124	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
125	123 not 124
126	ANIMAL/ not HUMAN/
127	NONHUMAN/
128	exp ANIMAL EXPERIMENT/
129	exp EXPERIMENTAL ANIMAL/
130	ANIMAL MODEL/
131	exp RODENT/
132	(rat or rats or mouse or mice).ti.
133	or/125-132
134	117 not 133

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Database: Medline; Medline Epub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	PREGNANCY/
2	PERIPARTUM PERIOD/
3	PARTURITION/
4	exp LABOR, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	pregnan$.ti,ab.
7	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
8	((during or giving or give) adj3 birth?).ti,ab.
9	or/1-8
10	exp THROMBOCYTOPENIA/
11	thrombocytopeni$.ti,ab.
12	TCP.ti,ab.
13	werlhof$ disease.ti,ab.

#	Searches
14	ITP.ti,ab.
15	or/10-14
16	(platelet? Adj5 function$ adj5 (abnormal$ or defect$ or impair$)).ti,ab.
17	(platelet? Adj5 dysfunction$).ti,ab.
18	or/16-17
19	PHARMACEUTICAL PREPARATIONS/
20	drug?.ti,ab.
21	ASPIRIN/
22	aspirin?.mp.
23	exp HEPARIN/
24	heparin?.mp.
25	or/19-24
26	18 and 25
27	BLOOD PLATELET DISORDERS/ci, de, dt [Chemically Induced, Drug Effects, Drug Therapy]
28	or/26-27
29	15 or 28
30	PLATELET COUNT/
31	(platelet? Adj5 (count$ or number?)).ti,ab.
32	((von Willebrand factor or vwf) adj5 (test$ or level? Or antigen? Or activit$)).ti,ab.
33	PLATELET FUNCTION TESTS/
34	(platelet? Adj5 function$ adj5 test$).ti,ab.
35	PLATELET AGGREGATION/
36	(platelet? Adj5 aggregat$).ti,ab.
37	THROMBELASTOGRAPHY/
38	thromboelastograph$.ti,ab.
39	TEG.ti,ab.
40	or/30-39
41	SEVERITY OF ILLNESS INDEX/
42	REFERENCE STANDARDS/
43	REFERENCE VALUES/
44	(grade? Or grading).ti,ab.
45	severit$.ti,ab.
46	classif$.ti,ab.
47	(index$ or indices).ti,ab.
48	degree?.ti,ab.
49	threshold?.ti,ab.
50	(define? Or defining).ti,ab.
51	criteri$.ti,ab.
52	cut off?.ti,ab.
53	parameter?.ti,ab.

#	Searches
54	below.ti,ab.
55	minimal.ti,ab.
56	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
57	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
58	(reference adj3 (standard? Or value? Or range?)).ti,ab.
59	or/41-58
60	plateletcrit.ti,ab.
61	PCT.ti,ab.
62	platelet distribution width?.ti,ab.
63	PDW.ti,ab.
64	mean platelet volume?.ti,ab.
65	MPV.ti,ab.
66	or/60-65
67	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
68	exp *THROMBOCYTOPENIA/di [Diagnosis]
69	exp *THROMBOCYTOPENIA/et [Etiology]
70	((manag$ or plan$ or identif$ or diagnos$ or etiolog$ or 93nrolment$) adj5 thrombocytopeni$ adj5 (pregnan$ or labo?r or childbirth or partu$ or intra?part$ or peri?part$)).ti,ab.
71	9 and 29 and 40 and 59
72	9 and 29 and 66
73	40 and 59 and 67
74	9 and (40 or 59) and 68
75	9 and (40 or 59) and 69
76	or/70-75
77	limit 76 to 93nrolme language
78	LETTER/
79	EDITORIAL/
80	NEWS/
81	exp HISTORICAL ARTICLE/
82	ANECDOTES AS TOPIC/
83	COMMENT/
84	CASE REPORT/
85	(letter or comment*).ti.
86	or/78-85
87	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
88	86 not 87
89	ANIMALS/ not HUMANS/
90	exp ANIMALS, LABORATORY/
91	exp ANIMAL EXPERIMENTATION/
92	exp MODELS, ANIMAL/
93	exp RODENTIA/

#	Searches
94	(rat or rats or mouse or mice).ti.
95	or/88-94
96	77 not 95

Database: Cochrane Central Register of Controlled Trials

#	Searches
1	PREGNANCY/
2	PERIPARTUM PERIOD/
3	PARTURITION/
4	exp LABOR, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	pregnan$.ti,ab,kw.
7	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab,kw.
8	((during or giving or give) adj3 birth?).ti,ab.
9	or/1-8
10	exp THROMBOCYTOPENIA/
11	thrombocytopeni$.ti,ab,kw.
12	TCP.ti,ab.
13	werlhof$ disease.ti,ab,kw.
14	ITP.ti,ab.
15	or/10-14
16	(platelet? Adj5 function$ adj5 (abnormal$ or defect$ or impair$)).ti,ab.
17	(platelet? Adj5 dysfunction$).ti,ab.
18	or/16-17
19	PHARMACEUTICAL PREPARATIONS/
20	drug?.ti,ab.
21	ASPIRIN/
22	aspirin?.mp.
23	exp HEPARIN/
24	heparin?.mp.
25	or/19-24
26	18 and 25
27	BLOOD PLATELET DISORDERS/ci, de, dt [Chemically Induced, Drug Effects, Drug Therapy]
28	or/26-27
29	15 or 28
30	PLATELET COUNT/
31	(platelet? Adj5 (count$ or number?)).ti,ab.
32	((von Willebrand factor or vwf) adj5 (test$ or level? Or antigen? Or activit$)).ti,ab.
33	PLATELET FUNCTION TESTS/
34	(platelet? Adj5 function$ adj5 test$).ti,ab.

#	Searches
35	PLATELET AGGREGATION/
36	(platelet? Adj5 aggregat$).ti,ab.
37	THROMBELASTOGRAPHY/
38	thromboelastograph$.ti,ab,kw.
39	TEG.ti,ab.
40	or/30-39
41	SEVERITY OF ILLNESS INDEX/
42	REFERENCE STANDARDS/
43	REFERENCE VALUES/
44	(grade? Or grading).ti,ab.
45	severit$.ti,ab.
46	classif$.ti,ab.
47	(index$ or indices).ti,ab.
48	degree?.ti,ab.
49	threshold?.ti,ab.
50	(define? Or defining).ti,ab.
51	criteri$.ti,ab.
52	cut off?.ti,ab.
53	parameter?.ti,ab.
54	below.ti,ab.
55	minimal.ti,ab.
56	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
57	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
58	(reference adj3 (standard? Or value? Or range?)).ti,ab.
59	or/41-58
60	plateletcrit.ti,ab.
61	PCT.ti,ab.
62	platelet distribution width?.ti,ab.
63	PDW.ti,ab.
64	mean platelet volume?.ti,ab.
65	MPV.ti,ab.
66	or/60-65
67	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
68	exp *THROMBOCYTOPENIA/di [Diagnosis]
69	exp *THROMBOCYTOPENIA/et [Etiology]
70	((manag$ or plan$ or identif$ or diagnos$ or etiolog$ or 95nrolment$) adj5 thrombocytopeni$ adj5 (pregnan$ or labo?r or childbirth or partu$ or intra?part$ or peri?part$)).ti,ab.
71	9 and 29 and 40 and 59
72	9 and 29 and 66
73	40 and 59 and 67
74	9 and (40 or 59) and 68

#	Searches
75	9 and (40 or 59) and 69
76	or/70-75

Database: Cochrane Database of Systematic Reviews

#	Searches
1	PREGNANCY.kw.
2	PERIPARTUM PERIOD.kw.
3	PARTURITION.kw.
4	LABOR, OBSTETRIC.kw.
5	OBSTETRIC LABOR, PREMATURE.kw.
6	pregnan$.ti,ab.
7	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
8	((during or giving or give) adj3 birth?).ti,ab.
9	or/1-8
10	THROMBOCYTOPENIA.kw.
11	thrombocytopeni$.ti,ab.
12	TCP.ti,ab.
13	werlhof$ disease.ti,ab.
14	ITP.ti,ab.
15	or/10-14
16	(platelet? Adj5 function$ adj5 (abnormal$ or defect$ or impair$)).ti,ab.
17	(platelet? Adj5 dysfunction$).ti,ab.
18	or/16-17
19	PHARMACEUTICAL PREPARATIONS.kw.
20	drug?.ti,ab.
21	ASPIRIN.kw.
22	aspirin?.mp.
23	HEPARIN.kw.
24	heparin?.mp.
25	or/19-24
26	18 and 25
27	15 or 26
28	PLATELET COUNT.kw.
29	(platelet? Adj5 (count$ or number?)).ti,ab.
30	((von Willebrand factor or vwf) adj5 (test$ or level? Or antigen? Or activit$)).ti,ab.
31	PLATELET FUNCTION TESTS.kw.
32	(platelet? Adj5 function$ adj5 test$).ti,ab.
33	PLATELET AGGREGATION.kw.
34	(platelet? Adj5 aggregat$).ti,ab.
35	THROMBELASTOGRAPHY.kw.

#	Searches
36	thromboelastograph$.ti,ab.
37	TEG.ti,ab.
38	or/28-37
39	SEVERITY OF ILLNESS INDEX.kw.
40	REFERENCE STANDARDS.kw.
41	REFERENCE VALUES.kw.
42	(grade? Or grading).ti,ab.
43	severit$.ti,ab.
44	classif$.ti,ab.
45	(index$ or indices).ti,ab.
46	degree?.ti,ab.
47	threshold?.ti,ab.
48	(define? Or defining).ti,ab.
49	criteri$.ti,ab.
50	cut off?.ti,ab.
51	parameter?.ti,ab.
52	below.ti,ab.
53	minimal.ti,ab.
54	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
55	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
56	(reference adj3 (standard? Or value? Or range?)).ti,ab.
57	or/39-56
58	plateletcrit.ti,ab.
59	PCT.ti,ab.
60	platelet distribution width?.ti,ab.
61	PDW.ti,ab.
62	mean platelet volume?.ti,ab.
63	MPV.ti,ab.
64	or/58-63
65	PREGNANCY COMPLICATIONS, HEMATOLOGIC.kw.
66	((manag$ or plan$ or identif$ or diagnos$ or etiolog$ or 97nrolment$) adj5 thrombocytopeni$ adj5 (pregnan$ or labo?r or childbirth or partu$ or intra?part$ or peri?part$)).ti,ab.
67	9 and 27 and 38 and 57
68	9 and 27 and 64
69	38 and 57 and 65
70	or/66-69

Database: Database of Abstracts of Reviews of Effects

#	Searches
1	PREGNANCY.kw.
2	PERIPARTUM PERIOD.kw.

#	Searches
3	PARTURITION.kw.
4	LABOR, OBSTETRIC.kw.
5	OBSTETRIC LABOR, PREMATURE.kw.
6	pregnan$.tw,tx.
7	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).tw,tx.
8	((during or giving or give) adj3 birth?).tw,tx.
9	or/1-8
10	THROMBOCYTOPENIA.kw.
11	thrombocytopeni$.tw,tx.
12	TCP.tw,tx.
13	werlhof$ disease.tw,tx.
14	ITP.tw,tx.
15	or/10-14
16	(platelet? Adj5 function$ adj5 (abnormal$ or defect$ or impair$)).tw,tx.
17	(platelet? Adj5 dysfunction$).tw,tx.
18	or/16-17
19	PHARMACEUTICAL PREPARATIONS.kw.
20	drug?.tw,tx.
21	ASPIRIN.kw.
22	aspirin?.mp.
23	HEPARIN.kw.
24	heparin?.mp.
25	or/19-24
26	18 and 25
27	15 or 26
28	PLATELET COUNT.kw.
29	(platelet? Adj5 (count$ or number?)).tw,tx.
30	((von Willebrand factor or vwf) adj5 (test$ or level? Or antigen? Or activit$)).tw,tx.
31	PLATELET FUNCTION TESTS.kw.
32	(platelet? Adj5 function$ adj5 test$).tw,tx.
33	PLATELET AGGREGATION.kw.
34	(platelet? Adj5 aggregat$).tw,tx.
35	THROMBELASTOGRAPHY.kw.
36	thromboelastograph$.tw,tx.
37	TEG.tw,tx.
38	or/28-37
39	SEVERITY OF ILLNESS INDEX.kw.
40	REFERENCE STANDARDS.kw.
41	REFERENCE VALUES.kw.
42	(grade? Or grading).tw,tx.

#	Searches
43	severit$.tw,tx.
44	classif$.tw,tx.
45	(index$ or indices).tw,tx.
46	degree?.tw,tx.
47	threshold?.tw,tx.
48	(define? Or defining).tw,tx.
49	criteri$.tw,tx.
50	cut off?.tw,tx.
51	parameter?.tw,tx.
52	below.tw,tx.
53	minimal.tw,tx.
54	((low$ or decreas$ or abnormal$) adj5 level?).tw,tx.
55	((low$ or decreas$ or abnormal$) adj5 count?).tw,tx.
56	(reference adj3 (standard? Or value? Or range?)).tw,tx.
57	or/39-56
58	plateletcrit.tw,tx.
59	PCT.tw,tx.
60	platelet distribution width?.tw,tx.
61	PDW.tw,tx.
62	mean platelet volume?.tw,tx.
63	MPV.tw,tx.
64	or/58-63
65	PREGNANCY COMPLICATIONS, HEMATOLOGIC.kw.
66	((manag$ or plan$ or identif$ or diagnos$ or etiolog$ or 99nrolment$) adj5 thrombocytopeni$ adj5 (pregnan$ or labo?r or childbirth or partu$ or intra?part$ or peri?part$)).tw,tx.
67	9 and 27 and 38 and 57
68	9 and 27 and 64
69	38 and 57 and 65
70	or/66-69

Database: Health Technology Assessment

#	Searches
1	PREGNANCY/
2	PERIPARTUM PERIOD/
3	PARTURITION/
4	exp LABOR, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	pregnan$.tw.
7	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).tw.
8	((during or giving or give) adj3 birth?).tw.
9	or/1-8

#	Searches
10	exp THROMBOCYTOPENIA/
11	thrombocytopeni$.tw.
12	TCP.tw.
13	werlhof$ disease.tw.
14	ITP.tw.
15	or/10-14
16	(platelet? Adj5 function$ adj5 (abnormal$ or defect$ or impair$)).tw.
17	(platelet? Adj5 dysfunction$).tw.
18	or/16-17
19	PHARMACEUTICAL PREPARATIONS/
20	drug?.tw.
21	ASPIRIN/
22	aspirin?.mp.
23	exp HEPARIN/
24	heparin?.mp.
25	or/19-24
26	18 and 25
27	BLOOD PLATELET DISORDERS/ci, de, dt [Chemically Induced, Drug Effects, Drug Therapy]
28	or/26-27
29	15 or 28
30	PLATELET COUNT/
31	(platelet? Adj5 (count$ or number?)).tw.
32	((von Willebrand factor or vwf) adj5 (test$ or level? Or antigen? Or activit$)).tw.
33	PLATELET FUNCTION TESTS/
34	(platelet? Adj5 function$ adj5 test$).tw.
35	PLATELET AGGREGATION/
36	(platelet? Adj5 aggregat$).tw.
37	THROMBELASTOGRAPHY/
38	thromboelastograph$.tw.
39	TEG.tw.
40	or/30-39
41	SEVERITY OF ILLNESS INDEX/
42	REFERENCE STANDARDS/
43	REFERENCE VALUES/
44	(grade? Or grading).tw.
45	severit$.tw.
46	classif$.tw.
47	(index$ or indices).tw.
48	degree?.tw.
49	threshold?.tw.

#	Searches
50	(define? Or defining).tw.
51	criteri$.tw.
52	cut off?.tw.
53	parameter?.tw.
54	below.tw.
55	minimal.tw.
56	((low$ or decreas$ or abnormal$) adj5 level?).tw.
57	((low$ or decreas$ or abnormal$) adj5 count?).tw.
58	(reference adj3 (standard? Or value? Or range?)).tw.
59	or/41-58
60	plateletcrit.tw.
61	PCT.tw.
62	platelet distribution width?.tw.
63	PDW.tw.
64	mean platelet volume?.tw.
65	MPV.tw.
66	or/60-65
67	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
68	exp *THROMBOCYTOPENIA/di [Diagnosis]
69	exp *THROMBOCYTOPENIA/et [Etiology]
70	((manag$ or plan$ or identif$ or diagnos$ or etiolog$ or 101nrolment$) adj5 thrombocytopeni$ adj5 (pregnan$ or labo?r or childbirth or partu$ or intra?part$ or peri?part$)).tw.
71	9 and 29 and 40 and 59
72	9 and 29 and 66
73	40 and 59 and 67
74	9 and (40 or 59) and 68
75	9 and (40 or 59) and 69
76	or/70-75

Database: Embase

#	Searches
1	*PREGNANCY/
2	*PERINATAL PERIOD/
3	exp *BIRTH/
4	exp *LABOR/
5	*PREMATURE LABOR/
6	*INTRAPARTUM CARE/
7	pregnan$.ti,ab.
8	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
9	((during or giving or give) adj3 birth?).ti,ab.
10	or/1-9

#	Searches
11	exp *THROMBOCYTOPENIA/
12	thrombocytopeni$.ti,ab.
13	TCP.ti,ab.
14	werlhof$ disease.ti,ab.
15	ITP.ti,ab.
16	or/11-15
17	(platelet? Adj5 function$ adj5 (abnormal$ or defect$ or impair$)).ti,ab.
18	(platelet? Adj5 dysfunction$).ti,ab.
19	or/17-18
20	DRUG/
21	drug?.ti,ab.
22	ACETYLSALICYLIC ACID/
23	aspirin?.mp.
24	HEPARIN/
25	heparin?.mp.
26	or/20-25
27	19 and 26
28	THROMBOCYTE DISORDER/dr, dt [Drug Resistance, Drug Therapy]
29	or/27-28
30	16 or 29
31	THROMBOCYTE COUNT/
32	(platelet? Adj5 (count$ or number?)).ti,ab.
33	((von Willebrand factor or vwf) adj5 (test$ or level? Or antigen? Or activit$)).ti,ab.
34	BLOOD CLOTTING PARAMETERS/
35	(platelet? Adj5 function$ adj5 test$).ti,ab.
36	THROMBOCYTE AGGREGATION/
37	(platelet? Adj5 aggregat$).ti,ab.
38	THROMBOELASTOGRAPHY/
39	Thromb?elastogra$.ti,ab.
40	TEG.ti,ab.
41	or/31-40
42	“SEVERITY OF ILLNESS INDEX”/
43	STANDARD/
44	REFERENCE VALUE/
45	ANALYTICAL PARAMETERS/
46	(grade? Or grading).ti,ab.
47	severit$.ti,ab.
48	classif$.ti,ab.
49	(index$ or indices).ti,ab.
50	degree?.ti,ab.

#	Searches
51	threshold?.ti,ab.
52	(define? Or defining).ti,ab.
53	criteri$.ti,ab.
54	cut off?.ti,ab.
55	parameter?.ti,ab.
56	below.ti,ab.
57	minimal.ti,ab.
58	((low$ or decreas$ or abnormal$) adj5 level?).ti,ab.
59	((low$ or decreas$ or abnormal$) adj5 count?).ti,ab.
60	(reference adj3 (standard? Or value? Or range?)).ti,ab.
61	or/42-60
62	plateletcrit.ti,ab.
63	PCT.ti,ab.
64	platelet distribution width?.ti,ab.
65	PDW.ti,ab.
66	mean platelet volume?.ti,ab.
67	MPV.ti,ab.
68	or/62-67
69	exp *THROMBOCYTOPENIA/di [Diagnosis]
70	exp *THROMBOCYTOPENIA/et [Etiology]
71	((manag$ or plan$ or identif$ or diagnos$ or etiolog$ or 103nrolment$) adj5 thrombocytopeni$ adj5 (pregnan$ or labo?r or childbirth or partu$ or intra?part$ or peri?part$)).ti,ab.
72	10 and 30 and 41 and 61
73	10 and 30 and 68
74	10 and (41 or 61) and 69
75	10 and (41 or 61) and 70
76	or/71-75
77	limit 76 to 103nrolme language
78	letter.pt. or LETTER/
79	note.pt.
80	editorial.pt.
81	CASE REPORT/ or CASE STUDY/
82	(letter or comment*).ti.
83	or/78-82
84	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
85	83 not 84
86	ANIMAL/ not HUMAN/
87	NONHUMAN/
88	exp ANIMAL EXPERIMENT/
89	exp EXPERIMENTAL ANIMAL/
90	ANIMAL MODEL/

#	Searches
91	exp RODENT/
92	(rat or rats or mouse or mice).ti.
93	or/85-92
94	77 not 93

1
2

Intrapartum care for women with haemostatic disorders – third stage of labour

Database: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	exp BLOOD PLATELET DISORDERS/
2	(Blood Platelet Disorder? or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab.
3	HELLP SYNDROME/
4	HELLP.ti,ab.
5	HEMOLYTIC-UREMIC SYNDROME/
6	hemolytic uremic syndrome.ti,ab.
7	LUPUS ERYTHEMATOSUS, SYSTEMIC/
8	systemic lupus erythematosus.ti,ab.
9	ANTIPHOSPHOLIPID SYNDROME/
10	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
11	Evans syndrome.ti,ab.
12	(Platelet adj3 (Disorder? or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
13	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab.
14	exp HEMORRHAGIC DISORDERS/
15	(Hemorrhagic Disorder? or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab.
16	exp BLOOD COAGULATION DISORDERS, INHERITED/
17	((Blood Coagulation Disorder? adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
18	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
19	or/1-18
20	LABOR STAGE, THIRD/
21	((third or 3rd) adj5 stage? adj10 labo?r$).ti,ab.
22	(involution$ adj3 stage?).ti,ab.

#	Searches
23	or/20-22
24	((placenta? or membrane?) adj3 (expul$ or expel$)).ti,ab.
25	afterbirth?.ti,ab.
26	PLACENTA, RETAINED/
27	(placenta? adj3 retain$).ti,ab.
28	PLACENTA ACCRETA/
29	(placenta? adj3 (accreta$ or increta$ or precreta$ or adherent)).ti,ab.
30	or/24-29
31	POSTPARTUM HEMORRHAGE/
32	((Postpartum? or Post-partum?) adj3 h?emorrhag$).ti,ab.
33	or/31-32
34	(activ$ adj3 manag$).ti,ab.
35	exp HEMOSTATICS/
36	(H?emostatic? or Aprotinin or Arginine Vasopressin or Batroxobin or Calcium Dobesilate or Oxidized Cellulose or Chitosan or Deamino Arginine Vasopressin or Ethamsylate or Fibrin Foam or Fibrin Tissue Adhesive? or Gelatin Sponge? or Lypressin or Ornipressin or Thrombin or Thromboplastin or Tolonium Chloride or Vasopressin?).mp.
37	DDAVP.mp.
38	exp ANTIFIBRINOLYTIC AGENTS/
39	(antifibrinolytic? or anti-fibrinolytic? or Aminocaproic Acid or Tranexamic Acid or Vitamin K? or alpha-2-Antiplasmin).mp.
40	BLOOD TRANSFUSION/
41	BLOOD COMPONENT TRANSFUSION/
42	PLATELET TRANSFUSION/
43	PLASMA EXCHANGE/
44	(platelet? adj3 transfusion?).ti,ab.
45	fresh$ frozen plasma?.ti,ab.
46	FFP.ti,ab.
47	(plasma? adj3 transfusion?).ti,ab.
48	BLOOD COAGULATION FACTORS/
49	(factor? adj3 (therap$ or treat$)).ti,ab.
50	(factor? adj3 concentrat$).ti,ab.
51	RECOMBINANT PROTEINS/tu [Therapeutic Use]
52	(recombinant adj3 factor?).ti,ab.
53	(obstetric$ adj3 intervention?).ti,ab.
54	SUTURE TECHNIQUES/
55	(brace adj3 (suture? or procedure?)).ti,ab.
56	(B-Lynch adj3 (suture? or procedure?)).ti,ab.
57	UTERINE BALLOON TAMPONADE/
58	((Intrauterine or uterine or uterus) adj3 balloon?).ti,ab.
59	occlusion.ti,ab.

#	Searches
60	RADIOLOGY, INTERVENTIONAL/
61	((Intervention$ or vascular$ or surgical$) adj3 radiolog$).ti,ab.
62	LIGATION/ and (ILIAC ARTERY/ or ILIAC VEIN/)
63	((ligation? or ligature?) adj5 iliac).ti,ab.
64	exp HYSTERECTOMY/
65	hysterectom$.ti,ab.
66	or/34-65
67	19 and 23
68	19 and (30 or 33) and 66
69	or/67-68
70	limit 69 to english language
71	LETTER/
72	EDITORIAL/
73	NEWS/
74	exp HISTORICAL ARTICLE/
75	ANECDOTES AS TOPIC/
76	COMMENT/
77	CASE REPORT/
78	(letter or comment*).ti.
79	or/71-78
80	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
81	79 not 80
82	ANIMALS/ not HUMANS/
83	exp ANIMALS, LABORATORY/
84	exp ANIMAL EXPERIMENTATION/
85	exp MODELS, ANIMAL/
86	exp RODENTIA/
87	(rat or rats or mouse or mice).ti.
88	or/81-87
89	70 not 88

Database: Cochrane Central Register of Controlled Trials

#	Searches
1	exp BLOOD PLATELET DISORDERS/
2	(Blood Platelet Disorder? or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab,kw.
3	HELLP SYNDROME/
4	HELLP.ti,ab.

#	Searches
5	HEMOLYTIC-UREMIC SYNDROME/
6	hemolytic uremic syndrome.ti,ab,kw.
7	LUPUS ERYTHEMATOSUS, SYSTEMIC/
8	systemic lupus erythematosus.ti,ab,kw.
9	ANTIPHOSPHOLIPID SYNDROME/
10	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
11	Evans syndrome.ti,ab,kw.
12	(Platelet adj3 (Disorder? or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
13	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab,kw.
14	exp HEMORRHAGIC DISORDERS/
15	(Hemorrhagic Disorder? or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab,kw.
16	exp BLOOD COAGULATION DISORDERS, INHERITED/
17	((Blood Coagulation Disorder? adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
18	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
19	or/1-18
20	LABOR STAGE, THIRD/
21	((third or 3rd) adj5 stage? adj10 labo?r$).ti,ab.
22	(involution$ adj3 stage?).ti,ab.
23	or/20-22
24	((placenta? or membrane?) adj3 (expul$ or expel$)).ti,ab.
25	afterbirth?.ti,ab.
26	PLACENTA, RETAINED/
27	(placenta? adj3 retain$).ti,ab.
28	PLACENTA ACCRETA/
29	(placenta? adj3 (accreta$ or increta$ or precreta$ or adherent)).ti,ab.
30	or/24-29
31	POSTPARTUM HEMORRHAGE/
32	((Postpartum? or Post-partum?) adj3 h?emorrhag$).ti,ab.
33	or/31-32
34	(activ$ adj3 manag$).ti,ab.
35	exp HEMOSTATICS/

#	Searches
36	(H?emostatic? or Aprotinin or Arginine Vasopressin or Batroxobin or Calcium Dobesilate or Oxidized Cellulose or Chitosan or Deamino Arginine Vasopressin or Ethamsylate or Fibrin Foam or Fibrin Tissue Adhesive? or Gelatin Sponge? or Lypressin or Ornipressin or Thrombin or Thromboplastin or Tolonium Chloride or Vasopressin?).mp.
37	DDAVP.mp.
38	exp ANTIFIBRINOLYTIC AGENTS/
39	(antifibrinolytic? or anti-fibrinolytic? or Aminocaproic Acid or Tranexamic Acid or Vitamin K? or alpha-2-Antiplasmin).mp.
40	BLOOD TRANSFUSION/
41	BLOOD COMPONENT TRANSFUSION/
42	PLATELET TRANSFUSION/
43	PLASMA EXCHANGE/
44	(platelet? adj3 transfusion?).ti,ab.
45	fresh$ frozen plasma?.ti,ab,kw.
46	FFP.ti,ab.
47	(plasma? adj3 transfusion?).ti,ab.
48	BLOOD COAGULATION FACTORS/
49	(factor? adj3 (therap$ or treat$)).ti,ab.
50	(factor? adj3 concentrat$).ti,ab.
51	RECOMBINANT PROTEINS/tu [Therapeutic Use]
52	(recombinant adj3 factor?).ti,ab.
53	(obstetric$ adj3 intervention?).ti,ab.
54	SUTURE TECHNIQUES/
55	(brace adj3 (suture? or procedure?)).ti,ab.
56	(B-Lynch adj3 (suture? or procedure?)).ti,ab.
57	UTERINE BALLOON TAMPONADE/
58	((Intrauterine or uterine or uterus) adj3 balloon?).ti,ab.
59	occlusion.ti,ab.
60	RADIOLOGY, INTERVENTIONAL/
61	((Intervention$ or vascular$ or surgical$) adj3 radiolog$).ti,ab.
62	LIGATION/ and (ILIAC ARTERY/ or ILIAC VEIN/)
63	((ligation? or ligature?) adj5 iliac).ti,ab.
64	exp HYSTERECTOMY/
65	hysterectom$.ti,ab,kw.
66	or/34-65
67	19 and 23
68	19 and (30 or 33) and 66
69	or/67-68

Database: Cochrane Database of Systematic Reviews

#	Searches
1	BLOOD PLATELET DISORDERS.kw.
2	(Blood Platelet Disorder? or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab.
3	HELLP SYNDROME.kw.
4	HELLP.ti,ab.
5	HEMOLYTIC-UREMIC SYNDROME.kw.
6	hemolytic uremic syndrome.ti,ab.
7	LUPUS ERYTHEMATOSUS, SYSTEMIC.kw.
8	systemic lupus erythematosus.ti,ab.
9	ANTIPHOSPHOLIPID SYNDROME.kw.
10	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
11	Evans syndrome.ti,ab.
12	(Platelet adj3 (Disorder? or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
13	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab.
14	HEMORRHAGIC DISORDERS.kw.
15	(Hemorrhagic Disorder? or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab.
16	BLOOD COAGULATION DISORDERS, INHERITED.kw.
17	((Blood Coagulation Disorder? adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
18	PREGNANCY COMPLICATIONS, HEMATOLOGIC.kw.
19	or/1-18
20	LABOR STAGE, THIRD.kw.
21	((third or 3rd) adj5 stage? adj10 labo?r$).ti,ab.
22	(involution$ adj3 stage?).ti,ab.
23	or/20-22
24	((placenta? or membrane?) adj3 (expul$ or expel$)).ti,ab.
25	afterbirth?.ti,ab.
26	PLACENTA, RETAINED.kw.
27	(placenta? adj3 retain$).ti,ab.

#	Searches
28	PLACENTA ACCRETA.kw.
29	(placenta? adj3 (accreta$ or increta$ or precreta$ or adherent)).ti,ab.
30	or/24-29
31	POSTPARTUM HEMORRHAGE.kw.
32	((Postpartum? or Post-partum?) adj3 h?emorrhag$).ti,ab.
33	or/31-32
34	(activ$ adj3 manag$).ti,ab.
35	HEMOSTATICS.kw.
36	(H?emostatic? or Aprotinin or Arginine Vasopressin or Batroxobin or Calcium Dobesilate or Oxidized Cellulose or Chitosan or Deamino Arginine Vasopressin or Ethamsylate or Fibrin Foam or Fibrin Tissue Adhesive? or Gelatin Sponge? or Lypressin or Ornipressin or Thrombin or Thromboplastin or Tolonium Chloride or Vasopressin?).mp.
37	DDAVP.mp.
38	ANTIFIBRINOLYTIC AGENTS.kw.
39	(antifibrinolytic? or anti-fibrinolytic? or Aminocaproic Acid or Tranexamic Acid or Vitamin K? or alpha-2-Antiplasmin).mp.
40	BLOOD TRANSFUSION.kw.
41	BLOOD COMPONENT TRANSFUSION.kw.
42	PLATELET TRANSFUSION.kw.
43	PLASMA EXCHANGE.kw.
44	(platelet? adj3 transfusion?).ti,ab.
45	fresh$ frozen plasma?.ti,ab.
46	FFP.ti,ab.
47	(plasma? adj3 transfusion?).ti,ab.
48	BLOOD COAGULATION FACTORS.kw.
49	(factor? adj3 (therap$ or treat$)).ti,ab.
50	(factor? adj3 concentrat$).ti,ab.
51	RECOMBINANT PROTEINS.kw.
52	(recombinant adj3 factor?).ti,ab.
53	(obstetric$ adj3 intervention?).ti,ab.
54	SUTURE TECHNIQUES.kw.
55	(brace adj3 (suture? or procedure?)).ti,ab.
56	(B-Lynch adj3 (suture? or procedure?)).ti,ab.
57	UTERINE BALLOON TAMPONADE.kw.
58	((Intrauterine or uterine or uterus) adj3 balloon?).ti,ab.
59	occlusion.ti,ab.
60	RADIOLOGY, INTERVENTIONAL.kw.
61	((Intervention$ or vascular$ or surgical$) adj3 radiolog$).ti,ab.
62	(LIGATION and (ILIAC ARTERY or ILIAC VEIN)).kw.
63	((ligation? or ligature?) adj5 iliac).ti,ab.
64	HYSTERECTOMY.kw.

#	Searches
65	hysterectom$.ti,ab.
66	or/34-65
67	19 and 23
68	19 and (30 or 33) and 66
69	or/67-68

Database: Database of Abstracts of Reviews of Effects

#	Searches
1	BLOOD PLATELET DISORDERS.kw.
2	(Blood Platelet Disorder? or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).tw,tx.
3	HELLP SYNDROME.kw.
4	HELLP.tw,tx.
5	HEMOLYTIC-UREMIC SYNDROME.kw.
6	hemolytic uremic syndrome.tw,tx.
7	LUPUS ERYTHEMATOSUS, SYSTEMIC.kw.
8	systemic lupus erythematosus.tw,tx.
9	ANTIPHOSPHOLIPID SYNDROME.kw.
10	((antiphospholipid or anti-phospholipid) adj3 syndrome?).tw,tx.
11	Evans syndrome.tw,tx.
12	(Platelet adj3 (Disorder? or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).tw,tx.
13	(Bone marrow suppression or myelotoxic$ or myelosuppression).tw,tx.
14	HEMORRHAGIC DISORDERS.kw.
15	(Hemorrhagic Disorder? or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).tw,tx.
16	BLOOD COAGULATION DISORDERS, INHERITED.kw.
17	((Blood Coagulation Disorder? adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).tw,tx.
18	PREGNANCY COMPLICATIONS, HEMATOLOGIC.kw.
19	or/1-18
20	LABOR STAGE, THIRD.kw.

#	Searches
21	((third or 3rd) adj5 stage? adj10 labo?r$).tw,tx.
22	(involution$ adj3 stage?).tw,tx.
23	or/20-22
24	((placenta? or membrane?) adj3 (expul$ or expel$)).tw,tx.
25	afterbirth?.tw,tx.
26	PLACENTA, RETAINED.kw.
27	(placenta? adj3 retain$).tw,tx.
28	PLACENTA ACCRETA.kw.
29	(placenta? adj3 (accreta$ or increta$ or precreta$ or adherent)).tw,tx.
30	or/24-29
31	POSTPARTUM HEMORRHAGE.kw.
32	((Postpartum? or Post-partum?) adj3 h?emorrhag$).tw,tx.
33	or/31-32
34	(activ$ adj3 manag$).tw,tx.
35	HEMOSTATICS.kw.
36	(H?emostatic? or Aprotinin or Arginine Vasopressin or Batroxobin or Calcium Dobesilate or Oxidized Cellulose or Chitosan or Deamino Arginine Vasopressin or Ethamsylate or Fibrin Foam or Fibrin Tissue Adhesive? or Gelatin Sponge? or Lypressin or Ornipressin or Thrombin or Thromboplastin or Tolonium Chloride or Vasopressin?).mp.
37	DDAVP.mp.
38	ANTIFIBRINOLYTIC AGENTS.kw.
39	(antifibrinolytic? or anti-fibrinolytic? or Aminocaproic Acid or Tranexamic Acid or Vitamin K? or alpha-2-Antiplasmin).mp.
40	BLOOD TRANSFUSION.kw.
41	BLOOD COMPONENT TRANSFUSION.kw.
42	PLATELET TRANSFUSION.kw.
43	PLASMA EXCHANGE.kw.
44	(platelet? adj3 transfusion?).tw,tx.
45	fresh$ frozen plasma?.tw,tx.
46	FFP.tw,tx.
47	(plasma? adj3 transfusion?).tw,tx.
48	BLOOD COAGULATION FACTORS.kw.
49	(factor? adj3 (therap$ or treat$)).tw,tx.
50	(factor? adj3 concentrat$).tw,tx.
51	RECOMBINANT PROTEINS.kw.
52	(recombinant adj3 factor?).tw,tx.
53	(obstetric$ adj3 intervention?).tw,tx.
54	SUTURE TECHNIQUES.kw.
55	(brace adj3 (suture? or procedure?)).tw,tx.
56	(B-Lynch adj3 (suture? or procedure?)).tw,tx.
57	UTERINE BALLOON TAMPONADE.kw.

#	Searches
58	((Intrauterine or uterine or uterus) adj3 balloon?).tw,tx.
59	occlusion.tw,tx.
60	RADIOLOGY, INTERVENTIONAL.kw.
61	((Intervention$ or vascular$ or surgical$) adj3 radiolog$).tw,tx.
62	(LIGATION and (ILIAC ARTERY or ILIAC VEIN)).kw.
63	((ligation? or ligature?) adj5 iliac).tw,tx.
64	HYSTERECTOMY.kw.
65	hysterectom$.tw,tx.
66	or/34-65
67	19 and 23
68	19 and (30 or 33) and 66
69	or/67-68

Database: Health Technology Assessment

#	Searches
1	exp BLOOD PLATELET DISORDERS/
2	(Blood Platelet Disorder? or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).tw.
3	HELLP SYNDROME/
4	HELLP.tw.
5	HEMOLYTIC-UREMIC SYNDROME/
6	hemolytic uremic syndrome.tw.
7	LUPUS ERYTHEMATOSUS, SYSTEMIC/
8	systemic lupus erythematosus.tw.
9	ANTIPHOSPHOLIPID SYNDROME/
10	((antiphospholipid or anti-phospholipid) adj3 syndrome?).tw.
11	Evans syndrome.tw.
12	(Platelet adj3 (Disorder? or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).tw.
13	(Bone marrow suppression or myelotoxic$ or myelosuppression).tw.
14	exp HEMORRHAGIC DISORDERS/
15	(Hemorrhagic Disorder? or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? or Waterhouse-

#	Searches
	Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).tw.
16	exp BLOOD COAGULATION DISORDERS, INHERITED/
17	((Blood Coagulation Disorder? adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).tw.
18	PREGNANCY COMPLICATIONS, HEMATOLOGIC/
19	or/1-18
20	LABOR STAGE, THIRD/
21	((third or 3rd) adj5 stage? adj10 labo?r$).tw.
22	(involution$ adj3 stage?).tw.
23	or/20-22
24	((placenta? or membrane?) adj3 (expul$ or expel$)).tw.
25	afterbirth?.tw.
26	PLACENTA, RETAINED/
27	(placenta? adj3 retain$).tw.
28	PLACENTA ACCRETA/
29	(placenta? adj3 (accreta$ or increta$ or precreta$ or adherent)).tw.
30	or/24-29
31	POSTPARTUM HEMORRHAGE/
32	((Postpartum? or Post-partum?) adj3 h?emorrhag$).tw.
33	or/31-32
34	(activ$ adj3 manag$).tw.
35	exp HEMOSTATICS/
36	(H?emostatic? or Aprotinin or Arginine Vasopressin or Batroxobin or Calcium Dobesilate or Oxidized Cellulose or Chitosan or Deamino Arginine Vasopressin or Ethamsylate or Fibrin Foam or Fibrin Tissue Adhesive? or Gelatin Sponge? or Lypressin or Ornipressin or Thrombin or Thromboplastin or Tolonium Chloride or Vasopressin?).mp.
37	DDAVP.mp.
38	exp ANTIFIBRINOLYTIC AGENTS/
39	(antifibrinolytic? or anti-fibrinolytic? or Aminocaproic Acid or Tranexamic Acid or Vitamin K? or alpha-2-Antiplasmin).mp.
40	BLOOD TRANSFUSION/
41	BLOOD COMPONENT TRANSFUSION/
42	PLATELET TRANSFUSION/
43	PLASMA EXCHANGE/
44	(platelet? adj3 transfusion?).tw.
45	fresh$ frozen plasma?.tw.
46	FFP.tw.
47	(plasma? adj3 transfusion?).tw.
48	BLOOD COAGULATION FACTORS/
49	(factor? adj3 (therap$ or treat$)).tw.
50	(factor? adj3 concentrat$).tw.

#	Searches
51	RECOMBINANT PROTEINS/tu [Therapeutic Use]
52	(recombinant adj3 factor?).tw.
53	(obstetric$ adj3 intervention?).tw.
54	SUTURE TECHNIQUES/
55	(brace adj3 (suture? or procedure?)).tw.
56	(B-Lynch adj3 (suture? or procedure?)).tw.
57	UTERINE BALLOON TAMPONADE/
58	((Intrauterine or uterine or uterus) adj3 balloon?).tw.
59	occlusion.tw.
60	RADIOLOGY, INTERVENTIONAL/
61	((Intervention$ or vascular$ or surgical$) adj3 radiolog$).tw.
62	LIGATION/ and (ILIAC ARTERY/ or ILIAC VEIN/)
63	((ligation? or ligature?) adj5 iliac).tw.
64	exp HYSTERECTOMY/
65	hysterectom$.tw.
66	or/34-65
67	19 and 23
68	19 and (30 or 33) and 66
69	or/67-68

Database: Embase

#	Searches
1	exp *THROMBOCYTE DISORDER/
2	(Blood Platelet Disorder? or Bernard-Soulier Syndrome or Gray Platelet Syndrome or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or Thrombasthenia or Thrombocytopeni$ or Jacobsen Distal 11q Deletion Syndrome or Kasabach-Merritt Syndrome or Thrombotic Microangiopath$ or Hemolytic-Uremic Syndrome or (Purpura adj3 Thrombocytopeni$) or Glanzmann$ thrombastenia).ti,ab.
3	*HELLP SYNDROME/
4	HELLP.ti,ab.
5	*HEMOLYTIC UREMIC SYNDROME/
6	hemolytic uremic syndrome.ti,ab.
7	*SYSTEMIC LUPUS ERYTHEMATOSUS/
8	systemic lupus erythematosus.ti,ab.
9	*ANTIPHOSPHOLIPID SYNDROME/
10	((antiphospholipid or anti-phospholipid) adj3 syndrome?).ti,ab.
11	Evans syndrome.ti,ab.
12	(Platelet adj3 (Disorder? or dysfunction$) adj10 (infect$ or human immunodeficiency virus$ or HIV or parvovirus or (Drug adj3 (relat$ or due or induced)) or Liver disease?)).ti,ab.
13	(Bone marrow suppression or myelotoxic$ or myelosuppression).ti,ab.
14	*BLEEDING DISORDER/
15	*BLOOD CLOTTING DISORDER/

#	Searches
16	*ACTIVATED PROTEIN C RESISTANCE/
17	exp *BLOOD CLOTTING FACTOR DEFICIENCY/
18	*DISSEMINATED INTRAVASCULAR CLOTTING/
19	(Hemorrhagic Disorder? or Afibrinogenemia or Bernard-Soulier Syndrome or Disseminated Intravascular Coagulation or Factor V Deficien$ or Factor VII Deficien$ or Factor X Deficien$ or Factor XI Deficien$ or Factor XII Deficien$ or Factor XIII Deficien$ or H?emophilia? or Hemostatic Disorder? or Cryoglobulinemia or Ehlers-Danlos Syndrome or (Hemangioma? adj3 Cavernous) or Multiple Myeloma or Pseudoxanthoma Elasticum or (Purpura adj3 Hyperglobulinemic) or (Purpura adj3 Schoenlein-Henoch) or Scurvy or Shwartzman Phenomenon or (Telangiectasia adj3 Heredit$) or Waldenstrom Macroglobulinemia or Hypoprothrombinemia? or (Prothrombin adj3 Deficien$) or Platelet Storage Pool Deficien$ or Hermanski-Pudlak Syndrome or (Purpura adj3 Thrombocytopeni$) or Thrombasthenia or Thrombocythemia or Vitamin K Deficien$ or von Willebrand Disease? or Waterhouse-Friderichsen Syndrome or Wiskott-Aldrich Syndrome or (Fibrinogen adj3 Deficien$) or Dysfibrinogenemia or Hypofibrinogenemia).ti,ab.
20	((Blood Coagulation Disorder? adj3 Inherit$) or Activated Protein C Resistan$ or Antithrombin III Deficien$ or Protein C Deficien$).ti,ab.
21	or/1-20
22	LABOR STAGE 3/
23	((third or 3rd) adj5 stage? adj10 labo?r$).ti,ab.
24	(involution$ adj3 stage?).ti,ab.
25	or/22-24
26	((placenta? or membrane?) adj3 (expul$ or expel$)).ti,ab.
27	afterbirth?.ti,ab.
28	*RETAINED PLACENTA/
29	(placenta? adj3 retain$).ti,ab.
30	*PLACENTA ACCRETA/
31	(placenta? adj3 (accreta$ or increta$ or precreta$ or adherent)).ti,ab.
32	or/26-31
33	*POSTPARTUM HEMORRHAGE/
34	((Postpartum? or Post-partum?) adj3 h?emorrhag$).ti,ab.
35	or/33-34
36	(activ$ adj3 manag$).ti,ab.
37	exp *HEMOSTATIC AGENT/
38	(H?emostatic? or Aprotinin or Arginine Vasopressin or Batroxobin or Calcium Dobesilate or Oxidized Cellulose or Chitosan or Deamino Arginine Vasopressin or Ethamsylate or Fibrin Foam or Fibrin Tissue Adhesive? or Gelatin Sponge? or Lypressin or Ornipressin or Thrombin or Thromboplastin or Tolonium Chloride or Vasopressin?).mp.
39	DDAVP.mp.
40	exp *ANTIFIBRINOLYTIC AGENT/
41	(antifibrinolytic? or anti-fibrinolytic? or Aminocaproic Acid or Tranexamic Acid or Vitamin K? or alpha-2-Antiplasmin).mp.
42	*BLOOD TRANSFUSION/
43	exp *BLOOD COMPONENT THERAPY/

#	Searches
44	*PLASMA EXCHANGE/
45	*FRESH FROZEN PLASMA/
46	(platelet? adj3 transfusion?).ti,ab.
47	fresh$ frozen plasma?.ti,ab.
48	FFP.ti,ab.
49	(plasma? adj3 transfusion?).ti,ab.
50	exp *BLOOD CLOTTING FACTOR/
51	(factor? adj3 (therap$ or treat$)).ti,ab.
52	(factor? adj3 concentrat$).ti,ab.
53	exp *RECOMBINANT PROTEIN/
54	(recombinant adj3 factor?).ti,ab.
55	(obstetric$ adj3 intervention?).ti,ab.
56	*SUTURE TECHNIQUE/
57	(brace adj3 (suture? or procedure?)).ti,ab.
58	(B-Lynch adj3 (suture? or procedure?)).ti,ab.
59	*INTRAUTERINE BALLOON/
60	((Intrauterine or uterine or uterus) adj3 balloon?).ti,ab.
61	*BLOOD VESSEL OCCLUSION/
62	occlusion.ti,ab.
63	*INTERVENTIONAL RADIOLOGY/
64	((Intervention$ or vascular$ or surgical$) adj3 radiolog$).ti,ab.
65	LIGATION/ and (ILIAC ARTERY/ or ILIAC VEIN/)
66	((ligation? or ligature?) adj5 iliac).ti,ab.
67	exp *HYSTERECTOMY/
68	hysterectom$.ti,ab.
69	or/36-68
70	21 and 25
71	21 and (32 or 35) and 69
72	or/70-71
73	limit 72 to english language
74	letter.pt. or LETTER/
75	note.pt.
76	editorial.pt.
77	CASE REPORT/ or CASE STUDY/
78	(letter or comment*).ti.
79	or/74-78
80	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
81	79 not 80
82	ANIMAL/ not HUMAN/
83	NONHUMAN/

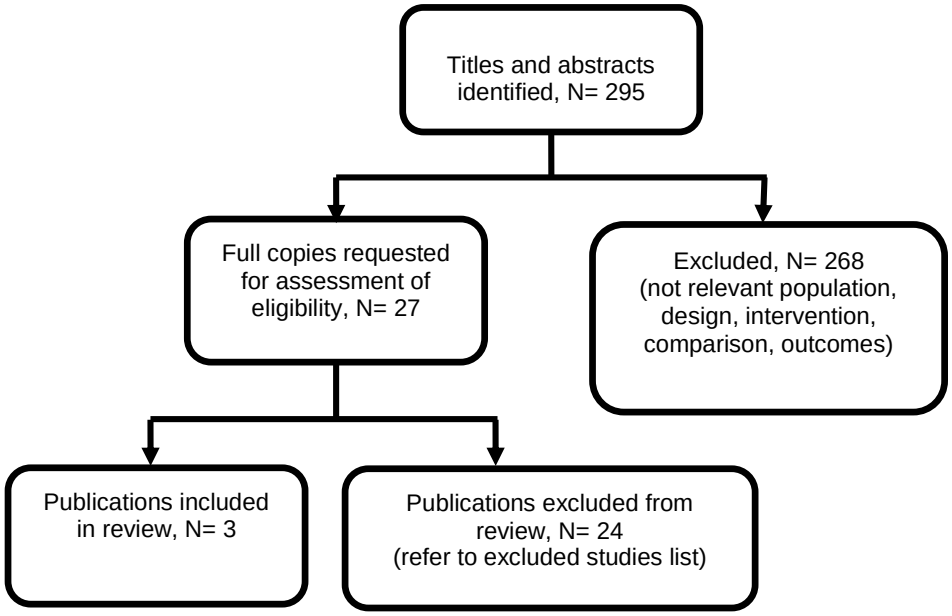
#	Searches
84	exp ANIMAL EXPERIMENT/
85	exp EXPERIMENTAL ANIMAL/
86	ANIMAL MODEL/
87	exp RODENT/
88	(rat or rats or mouse or mice).ti.
89	or/81-88
90	73 not 89

1

Appendix C – Clinical evidence study selection

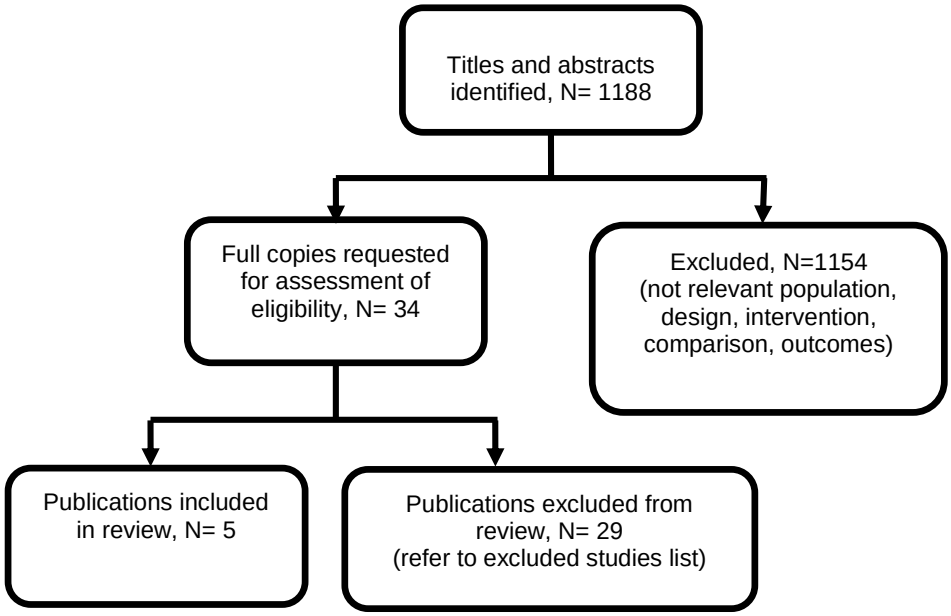
Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Figure 1: Flow diagram of clinical article selection for intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia



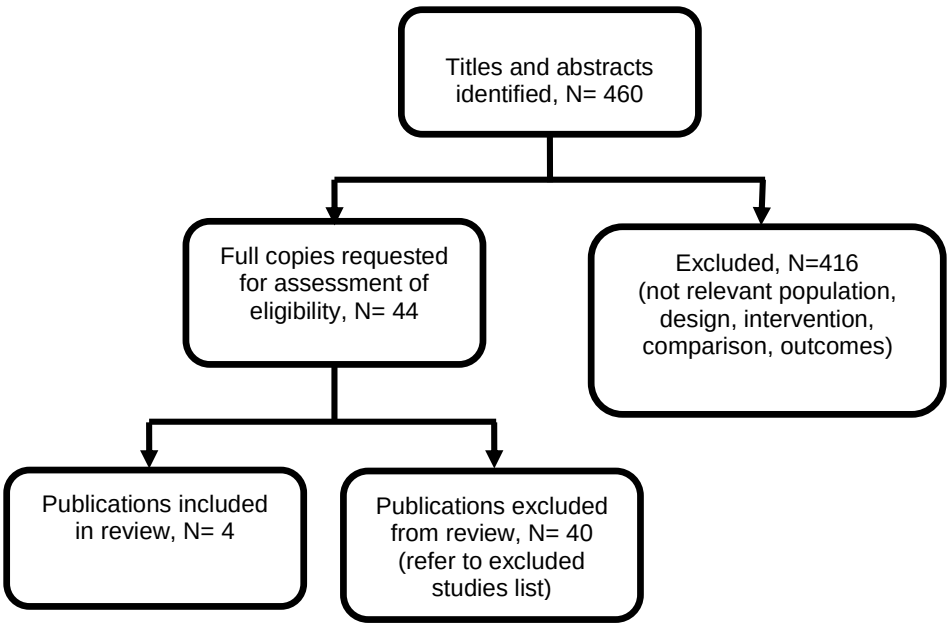
Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Figure 2: Flow diagram of clinical article selection for Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function



Intrapartum care for women with haemostatic disorders – third stage of labour

Figure 3: Flow diagram of clinical article selection for Intrapartum care for women with haemostatic disorders – third stage of labour



Appendix D – Excluded studies

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Clinical studies

Study	Reason for exclusion
Attias, J., Abecassis, P. P., Utility of thromboelastogram (TEG) for decision making to perform neuroaxial block in thrombocytopenic parturients, Clinical Chemistry and Laboratory Medicine, 55, S699, 2017	Conference abstract
Beilin,Y., Zahn,J., Comerford,M., Safe epidural analgesia in thirty parturients with platelet counts between 69,000 and 98,000 mm(-3), Anesthesia and Analgesia, 85, 385-388, 1997	Data included from Lee 2017 systematic review
Bernstein, J., Hua, B., Kahana, M., Shaparin, N., Yu, S., Davila-Velazquez, J., Neuraxial Anesthesia in Parturients with Low Platelet Counts, Anesthesia and Analgesia, 123, 165-167, 2016	Data included from Lee 2017 systematic review
Bernstein, Jeffrey, Hua, Betty, Kahana, Madelyn, Shaparin, Naum, Yu, Simon, Davila-Velazquez, Juan, Neuraxial Anesthesia in Parturients with Low Platelet Counts, Anesthesia and analgesia, 123, 165-7, 2016	No relevant data - no outcomes presented according to different platelet count thresholds
Care, A., Pavord, S., Knight, M., Alfirevic, Z., Current management and perinatal outcomes in women with idiopathic severe thrombocytopenia in pregnancy: National cohort study, British Journal of Haematology, 173, 18, 2016	No denominator reported
Chi,C., Lee,C.A., England,A., Hingorani,J., Paintsil,J., Kadir,R.A., Obstetric analgesia and anaesthesia in women with inherited bleeding disorders, Thrombosis and Haemostasis, 101, 1104-1111, 2009	No relevant outcome data - data is not reported according to bleeding disorder
Demers, C., Derzko, C., David, M., Douglas, J., No. 163-Gynaecological and Obstetric Management of Women With Inherited Bleeding Disorders, Journal of Obstetrics and Gynaecology Canada, 40, e91-e103, 2018	Canadian guideline with no relevant articles to include
Dikman, D., Elstein, D., Levi, G. S., Granovsky-Grisaru, S., Samueloff, A., Gozal, Y., Ioscovich, A., Effect of thrombocytopenia on mode of analgesia/anesthesia and maternal and neonatal outcomes, Journal of Maternal-Fetal & Neonatal Medicine, 27, 597-602, 2014	Case control study - not appropriate study design for a prognostic review
Douglas, M. J., Platelets, the parturient and regional anesthesia, International Journal of Obstetric Anesthesia, 10, 113-120, 2001	Narrative literature review
Duggan, S., Dockrell, L., McCaul, C., A retrospective, single-centre study of central neuraxial blockade in haemophilia carrier parturients, Irish Journal of Medical Science, 186, S155, 2017	Conference abstract
Goodier, C. G., Lu, J. T., Hebbar, L., Segal, B. S., Goetzl, L., Neuraxial Anesthesia in Parturients with Thrombocytopenia: A Multisite Retrospective Cohort Study, Anesthesia & Analgesia, 121, 988-91, 2015	Data included from Lee 2017 systematic review

Study	Reason for exclusion
Huang, J., McKenna, N., Babins, N., Utility of thromboelastography during neuraxial blockade in the parturient with thrombocytopenia, AANA Journal, 82, 127-30, 2014	No relevant outcome data
Marrache,D., Mercier,F.J., Boyer-Neumann,C., Roger-Christoph,S., Benhamou,D., Epidural analgesia for parturients with type 1 von Willebrand disease, International Journal of Obstetric Anesthesia, 16, 231-235, 2007	Data included from Choi 2009 systematic review
Orlikowski, C. E., Rocke, D. A., The coagulopathic parturient: Anesthetic management, Anesthesiology Clinics of North America, 16, 349-373, 1998	Narrative literature review
Palit,S., Palit,G., Vercauteren,M., Jacquemyn,Y., Regional anaesthesia for primary caesarean section in patients with preterm HELLP syndrome: a review of 102 cases, Clinical and Experimental Obstetrics and Gynecology, 36, 230-234, 2009	Data included from Lee 2017 systematic review
Rasmus,K.T., Rottman,R.L., Kotelko,D.M., Wright,W.C., Stone,J.J., Rosenblatt,R.M., Unrecognized thrombocytopenia and regional anesthesia in parturients: a retrospective review, Obstetrics and Gynecology, 73, 943-946, 1989	Data included from Lee 2017 systematic review
Reuveni, A., Orbach-Zinger, S., Eidelman, L. A., Ginosar, Y., Ioscovich, A., Peripartum anesthetic management of patients with Factor XI deficiency, Journal of Perinatal Medicine, 42, 295-300, 2014	No relevant outcomes reported
Reynen, Emily, James, Paula, Von Willebrand Disease and Pregnancy: A Review of Evidence and Expert Opinion, Seminars in thrombosis and hemostasis, 42, 717-723, 2016	Narrative literature review
Sibai,B.M., Taslimi,M.M., el-Nazer,A., Amon,E., Mabie,B.C., Ryan,G.M., Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia, American Journal of Obstetrics and Gynecology, 155, 501-509, 1986	Data included from Lee 2017 systematic review
Tanaka,M., Balki,M., McLeod,A., Carvalho,J.C., Regional anesthesia and non-preeclamptic thrombocytopenia: time to re-think the safe platelet count, Revista Brasileira de Anestesiologia, 59, 142-153, 2009	Data included from Lee 2017 systematic review
Verghese, L., Tingi, E., Thachil, J., Hay, C., Byrd, L., Management of parturients with Factor XI deficiency-10 year case series and review of literature, European Journal of Obstetrics Gynecology and Reproductive Biology, 215, 85-92, 2017	A case series with no relevant data
Vigil-De Gracia, P., Silva, S., Montufar, C., Carrol, I., De Los Rios, S., Anesthesia in pregnant women with HELLP syndrome, International Journal of Gynaecology & Obstetrics, 74, 23-7, 2001	Data included from Lee 2017 systematic review
Webert, K. E., Mittal, R., Sigouin, C., Heddle, N. M., Kelton, J. G., A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura, Blood, 102, 4306-11, 2003	Data included from Lee 2017 systematic review
Yousuf, S., Cohen, A. J., Eris, E., Astsaturov, A., A single institutional study on pregnancy outcomes in patients with von willebrand disease, Blood. Conference: 59th Annual	Conference abstract

Study	Reason for exclusion
Meeting of the American Society of Hematology, ASH, 130, 2017	

Economic studies

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Clinical studies

Study	Reason for exclusion
Anteby, E., Shalev, O., Clinical relevance of gestational thrombocytopenia of <100,000/mul, American Journal of Hematology, 47, 118-122, 1994	Fewer than 25 pregnancies reported
Bergmann, F., Rath, W., The Differential Diagnosis of Thrombocytopenia in Pregnancy, Deutsches Arzteblatt International, 112, 795-802, 2015	Intervention not relevant - study examines differential diagnosis of thrombocytopenia
Bernstein, J., Hua, B., Kahana, M., Shaparin, N., Yu, S., Davila-Velazquez, J., Neuraxial Anesthesia in Parturients with Low Platelet Counts, Anesthesia and Analgesia, 123, 165-167, 2016	No relevant comparative data reported
Burrows, R. F., Kelton, J. G., Pregnancy in patients with idiopathic thrombocytopenic purpura: assessing the risks for the infant at delivery, Obstetrical & Gynecological Survey, 48, 781-8, 1993	Narrative literature review - neonatal thrombocytopenia
Burrows, R. F., Kelton, J. G., Low fetal risks in pregnancies associated with idiopathic thrombocytopenic purpura, American Journal of Obstetrics and Gynecology, 163, 1147-1150, 1990	No relevant outcome data reported
Care, A., Pavord, S., Knight, M., Alfirevic, Z., Current management and perinatal outcomes in women with idiopathic severe thrombocytopenia in pregnancy: National cohort study, British Journal of Haematology, 173, 18, 2016	Conference abstract
Dan,U., Barkai,G., David,B., Goldenberg,M., Kukkia,E., Mashiach,S., Management of labor in patients with idiopathic thrombocytopenic purpura, Gynecologic and Obstetric Investigation, 27, 193-196, 1989	Fewer than 25 pregnancies reported
Devendra,K., Koh,L.P., Pregnancy in women with idiopathic thrombocytopaenic purpura, Annals of the Academy of Medicine, Singapore, 31, 276-280, 2002	Fewer than 25 pregnancies reported
Dikman, D., Elstein, D., Levi, G. S., Granovsky-Grisaru, S., Samueloff, A., Gozal, Y., Ioscovich, A., Effect of thrombocytopenia on mode of analgesia/anesthesia and maternal and neonatal outcomes, Journal of Maternal-Fetal & Neonatal Medicine, 27, 597-602, 2014	Case control study - not appropriate study design for a prognostic review
Freedman, J., Musclow, E., Garvey, B., Abbott, D., Unexplained periparturient thrombocytopenia, American Journal of Hematology, 21, 397-407, 1986	No relevant comparative data reported

Study	Reason for exclusion
Garmel,S.H., Craigo,S.D., Morin,L.M., Crowley,J.M., D'Alton,M.E., The role of percutaneous umbilical blood sampling in the management of immune thrombocytopenic purpura, Prenatal Diagnosis, 15, 439-445, 1995	No relevant outcome data reported
George, J. N., For low platelets, how low is dangerous?, Cleveland Clinic Journal of Medicine, 71, 277-8, 2004	Narrative literature review
Kim, B. J., Kim, H. S., Kim, J. H., Lee, K. Y., Moderate to Severe Thrombocytopenia During Pregnancy: A Single Institutional Experience, Indian Journal of Hematology and Blood Transfusion, 1-5, 2017	Fewer than 25 pregnancies reported
Leader, A., Pereg, D., Lishner, M., Are platelet volume indices of clinical use? A multidisciplinary review, Annals of Medicine, 44, 805-16, 2012	Narrative literature review - no relevant data for intrapartum care of women
Lee, L. O., Bateman, B. T., Kheterpal, S., Klumpner, T. T., Housey, M., Aziz, M. F., Hand, K. W., MacEachern, M., Goodier, C. G., Bernstein, J., Bauer, M. E., Risk of epidural hematoma after neuraxial techniques in thrombocytopenic parturients a report from the multicenter perioperative outcomes group, Anesthesiology, 126, 1053-1064, 2017	Population do not meet inclusion criteria
Levy, N., Goren, O., Cattan, A., Weiniger, C. F., Matot, I., Neuraxial block for delivery among women with low platelet counts: A retrospective analysis, International Journal of Obstetric Anesthesia, 2018	No relevant outcome data reported
Melekoglu, N. A., Bay, A., Aktekin, E. H., Yilmaz, M., Sivasli, E., Neonatal Outcomes of Pregnancy with Immune Thrombocytopenia, Indian Journal of Hematology and Blood Transfusion, 33, 211-215, 2017	No relevant outcome data reported
Nagey, D. A., Alger, L. S., Edelman, B. B., Heyman, M. R., Pupkin, M. J., Crenshaw Jr, C., Reacting appropriately to thrombocytopenia in pregnancy, Southern Medical Journal, 79, 1385-1388, 1986	Unclear when platelet counts were performed during pregnancy
Nisaratanaporn, S., Sukcharoen, N., Outcome of idiopathic thrombocytopenic purpura in pregnancy in King Chulalongkorn Memorial Hospital, Journal of the Medical Association of Thailand, 89 Suppl 4, S70-5, 2006	A full text copy of the article could not be obtained
Sainio, S., Kekomaki, R., Riikonen, S., Teramo, K., Maternal thrombocytopenia at term: a population-based study, Acta Obstetricia et Gynecologica Scandinavica, 79, 744-9, 2000	No relevant outcome data reported
Sainio,S., Joutsi,L., Jarvenpaa,A.L., Kekomaki,R., Koistinen,E., Riikonen,S., Teramo,K., Idiopathic thrombocytopenic purpura in pregnancy, Acta Obstetricia et Gynecologica Scandinavica, 77, 272-277, 1998	No relevant outcome data - results not reported by platelet count threshold
Shamoon, R. P., Muhammed, N. S., Jaff, M. S., Prevalence and etiological classification of thrombocytopenia among a group of pregnant women in Erbil City, Iraq, Turkish Journal of Hematology, 26, 123-128, 2009	County of study not included in the protocol - Iraq is considered a developing country
Song, T. B., Kim, E. K., Obstetric prognosis of the gestational thrombocytopenia, Haematologia, 31, 25-31, 2001	No relevant outcome data reported
Subbaiah, M., Kumar, S., Roy, K. K., Sharma, J. B., Singh, N., Pregnancy outcome in patients with idiopathic	Country not included in the protocol - India is considered a developing country

Study	Reason for exclusion
thrombocytopenic purpura, Archives of Gynecology & Obstetrics, 289, 269-73, 2014	
Vincelot, A., Nathan, N., Collet, D., Mehaddi, Y., Grandchamp, P., Julia, A., Platelet function during pregnancy: An evaluation using the PFA-100 analyser, British Journal of Anaesthesia, 87, 890-893, 2001	No relevant outcome data reported
Vishwekar, P. S., Yadav, R. K., Gohel, C. B., Thrombocytopenia during pregnancy and its outcome - a prospective study, Journal of Krishna Institute of Medical Sciences University, 6, 82-89, 2017	Country not included in the protocol - India is considered a developing country
Webert, K. E., Mittal, R., Sigouin, C., Heddle, N. M., Kelton, J. G., A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura, Blood, 102, 4306-11, 2003	No relevant outcome data reported
Yamada, H., Kato, E. H., Kishida, T., Negishi, H., Makinoda, S., Fujimoto, S., Risk factors for neonatal thrombocytopenia in pregnancy complicated by idiopathic thrombocytopenic purpura, Annals of Hematology, 76, 211-214, 1998	No relevant outcome data reported
Yuce,T., Acar,D., Kalafat,E., Alkilic,A., Cetindag,E., Soylemez,F., Thrombocytopenia in pregnancy: do the time of diagnosis and delivery route affect pregnancy outcome in parturients with idiopathic thrombocytopenic purpura?, International Journal of Hematology, 100, 540-544, 2014	No comparative data reported

Economic studies

2 See Supplement 2 (Health economics) for details of economic evidence reviews and health
3 economic modelling.

Intrapartum care for women with haemostatic disorders – third stage of labour

Clinical studies

Study	Reason for exclusion
Ahmed, S., Byrne, B., How efficient is fibrinogen concentrate in the management of major obstetric haemorrhage in comparison to cryoprecipitate?, International Journal of Gynecology and Obstetrics, 119, S818, 2012	Conference abstract
Ahmed, S., Johnson, S., Varadkar, S., Fleming, J., Fanning, R., Flynn, C., Byrne, B., Management of acquired hypofibrinogenaemia secondary to major obstetric haemorrhage: Fibrinogen concentrate versus cryoprecipitate, Irish Journal of Medical Science, 180, S141-S142, 2011	Conference abstract
Ahmed, S., Johnson, S., Varadkar, S., Fleming, J., McMorrow, S., Fanning, R., Flynn, C., Byrne, B., Does fibrinogen concentrate reduce blood products use in major obstetric haemorrhage?, Archives of Disease in Childhood: Fetal and Neonatal Edition, 96, Fa77-Fa78, 2011	Conference abstract
Al Shakhshir, O., Hensch, S., Rajesh, S., Hill, Q., Ciantar, E., Primary immune thrombocytopenia (ITP) in pregnancy-	Conference abstract

Study	Reason for exclusion
an audit on its management in a large tertiary unit, Thrombosis Research, 135, S76, 2015	
Alexander,J.M., Sarode,R., McIntire,D.D., Burner,J.D., Leveno,K.J., Whole blood in the management of hypovolemia due to obstetric hemorrhage, Obstetrics and Gynecology, 113, 1320-1326, 2009	Population do not meet inclusion criteria - women do not have bleeding disorders
Al-Nuaim, L. A., Mustafa, M. S., Abdel Gader, A. G., Disseminated intravascular coagulation and massive obstetric hemorrhage. Management dilemma, Saudi Medical Journal, 23, 658-62, 2002	Non-comparative study - all women with DIC received blood products
Balchin, I., Razzaque, M., Beski, S., Bowles, L., Pregnancy outcomes in women with, or carriers of, inherited bleeding disorders in a London obstetric unit with haemophilia comprehensive care centre, Haemophilia, 18, 203, 2012	Conference abstract
Baudo, F., De Cataldo, F., Bari, S. M., Catanzaro, S. R., Firenze, L. S., Niguarda, M., Mostarda, G., Policlinico, M., Santagostino, E., Pavia, G. G., Pescara, D. A., Roma, M. G., Torino, S. P., Vicenza, C. G., Acquired factor VIII inhibitors in pregnancy: Data from the Italian Haemophilia Register relevant to clinical practice, BJOG: An International Journal of Obstetrics and Gynaecology, 110, 311-314, 2003	Inappropriate comparison of treatment and control
Baumann Kreuziger,L.M., Morton,C.T., Reding,M.T., Is prophylaxis required for delivery in women with factor VII deficiency?, Haemophilia, 19, 827-832, 2013	Systematic review of case reports
Bjoring,A., Baxi,L., Use of DDAVP as prophylaxis against postpartum hemorrhage in women with von Willebrand's disease: a case series demonstrating safety and efficacy, Journal of Women's Health, 13, 845-847, 2004	Non-comparative study
Bonnet,M.P., Basso,O., Prohemostatic interventions in obstetric hemorrhage, Seminars in Thrombosis and Hemostasis, 38, 259-264, 2012	Narrative literature review
Borel-Derlon, A., Goudemand, J., Boyer-Neumann, C., Claeyssens, S., Bertrand, M. A., Henriet, C., Chatelanaz, C., Bridey, F., Gynecological & obstetrical events from a french post-marketing survey of a von Willebrand factor concentrate with a low factor VIII content, Journal of Thrombosis and Haemostasis, 9, 667-668, 2011	Conference abstract
Care, A., Parvord, S., Knight, M., Alfirevic, Z., Severe primary immune thrombocytopenia in Pregnancy UK Obstetric Surveillance System (UKOSS) Study, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 5, 2016	Duplicate study of UKOSS (Care 2018)
Care, A., Pavord, S., Knight, M., Alfirevic, Z., Current management and perinatal outcomes in women with idiopathic severe thrombocytopenia in pregnancy: National cohort study, British Journal of Haematology, 173, 18, 2016	Abstract only - full text included in this review (Care 2018)
Carney, S. K., Kemp, S., Hay, C., Nash, M., Hay, E., Hobson, M., Byrd, L., Carriers of haemophilia a and B-a 5 year retrospective audit of management in pregnancy in the setting of a tertiary referral clinic, Archives of Disease in Childhood: Fetal and Neonatal Edition, 97, A47, 2012	Conference abstract
Cavaignac-Vitalis, M., Vidal, F., Simon-Toulza, C., Boulot, P., Guerby, P., Chantalat, E., Parant, O., Conservative	No relevant interventions

Study	Reason for exclusion
versus active management in HELLP syndrome: results from a cohort study, Journal of Maternal-Fetal and Neonatal Medicine, 1-7, 2017	
Centre for Reviews and Dissemination, A systematic review: the use of desmopressin for treatment and prophylaxis of bleeding disorders in pregnancy (Provisional abstract), Database of Abstracts of Reviews of Effects, 2015	Systematic review of non-comparative studies, articles not relevant for inclusion
Centre for Reviews and Dissemination, Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum (Structured abstract), Database of Abstracts of Reviews of Effects, 2015	Population do not meet inclusion criteria - women do not have haemostatic disorders
de Wee, E. M., Knol, H. M., Mauser-Bunschoten, E. P., van der Bom, J. G., Eikenboom, J. C. J., Fijnvandraat, K., de Goede-Bolder, A., Gorkom, B. L. V., Ypma, P. F., Zweegman, S., Meijer, K., Leebeek, F. W. G., Gynaecological and obstetric bleeding in moderate and severe von willebrand disease, Thrombosis and Haemostasis, 106, 885-892, 2011	No relevant outcome data presented
Demers, C., Derzko, C., David, M., Douglas, J., No. 163-Gynaecological and Obstetric Management of Women With Inherited Bleeding Disorders, Journal of Obstetrics and Gynaecology Canada, 40, e91-e103, 2018	Canadian recommendations - no evidence in relation to management of third stage of labour
Hensch, S., Al Shakhshir, O., Rajesh, S., Ciantar, E., The management of patients with primary immune thrombocytopenia during pregnancy in Leeds, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A124-A125, 2014	Conference abstract
Hobisch-Hagen,P., Mortl,M., Schobersberger,W., Hemostatic disorders in pregnancy and the peripartum period, Acta Anaesthesiologica Scandinavica, Supplementum. 111, 216-217, 1997	Opinion article
Hundegger,R., Husslein,P., Berghammer,P., Egarter,C., Kyrle,A., Postpartum bleeding and von Willebrand's disease, Archives of Gynecology and Obstetrics, 266, 160-162, 2002	Intervention not relevant
James, A. H., Konkle, B. A., Kouides, P., Ragni, M. V., Thames, B., Gupta, S., Sood, S., Fletcher, S. K., Philipp, C. S., Postpartum von Willebrand factor levels in women with and without von Willebrand disease and implications for prophylaxis, Haemophilia, 21, 81-87, 2015	No relevant outcomes
James, A., Konkle, B., Kouides, P., Ragni, M., Thames, B., Philipp, C., Current postpartum treatment strategies for von Willebrand disease may not adequately replace von Willebrand factor, Haemophilia, 18, 204-205, 2012	Conference abstract
Jayakody Arachchillage, D., Chattree, S., Vowels, J., Varty, P., Talks, K., Pregnancy Outcome of Women with Congenital Bleeding Disorders Managed by Multidisciplinary Team in an U.K. Hemophilia Comprehensive Care Centre Over Three-Year Period, Haemophilia, 18, 205, 2012	Conference abstract
Jayakody Arachchillage, D., Vowels, J., Varty, P., Talks, K., Pregnancy outcome in hemophilia A carriers over a 5-year period in a U.K. hemophilia comprehensive care centre (CCC), Haemophilia, 18, 13, 2012	Conference abstract

Study	Reason for exclusion
Jones, E., Al-Biatty, R., Ciantar, E., The obstetric management of haemophilia carriers and patients with von willebrand's disease in leeds, Archives of Disease in Childhood: Fetal and Neonatal Edition. Conference: 16th Annual Conference of the British Maternal and Fetal Medicine Society. Dublin Ireland. Conference Start, 98, 2013	Conference abstract
Jones, R. M., De Lloyd, L., Kealaher, E. J., Lilley, G. J., Precious, E., Burckett St Laurent, D., Hamlyn, V., Collis, R. E., Collins, P. W., Bruynseels, D., Hall, J., Sanders, J., Platelet count and transfusion requirements during moderate or severe postpartum haemorrhage, Anaesthesia, 71, 648-656, 2016	Population do not meet inclusion criteria - women do not have haemostatic disorders
Kalina, M., Babenko, C., Fulda, G., Factor VIIa improves coagulopathy and reduces predicted mortality in massive postpartum hemorrhage, Critical Care Medicine, 37 (12 SUPPL.), A400, 2009	Conference abstract
Kalina,M., Tinkoff,G., Fulda,G., Massive postpartum hemorrhage: recombinant factor VIIa use is safe but not effective, Delaware Medical Journal, 83, 109-113, 2011	Full copy of reference unavailable
Kinugasa, M., Tamai, H., Miyake, M., Shimizu, T., Uterine balloon tamponade in combination with topical administration of tranexamic Acid for management of postpartum hemorrhage, Case Reports in Obstetrics and Gynecology, 2015, 195036, 2015	Population do not meet inclusion criteria - women do not have haematological disorders
Kong, Z., Qin, P., Li, H., Yang, R., Liu, X., Luo, J., Cui, Z., Li, Z., Ji, G., Bai, Y., Wu, Y., Peng, J., Ma, J., Hou, M., A multicenter open-labeled pilot study on recombinant human thrombopoietin in the management of immune thrombocytopenia in pregnancy, Blood. Conference: 58th Annual Meeting of the American Society of Hematology, ASH, 128, 2016	Full copy of reference unavailable
Kulkarni,A.A., Lee,C.A., Kadir,R.A., Pregnancy in women with congenital factor VII deficiency, Haemophilia, 12, 413-416, 2006	Case series study
Messina,M., Pollio,B., Gollo,E., Maio,M., Menaldo,E., Pagliarino,M., Safety and efficacy of fibrinogen concentrate in severe post-partum haemorrhage, Blood Transfusion, 10, s180-s181, 2012	Full copy of reference unavailable
Myers, B., Pavord, S., Kean, L., Hill, M., Dolan, G., Pregnancy outcome in Factor XI deficiency: Incidence of miscarriage, antenatal and postnatal haemorrhage in 33 women with Factor XI deficiency, BJOG: An International Journal of Obstetrics and Gynaecology, 114, 643-646, 2007	No outcome data on haemostatic intervention
Susen, S., Tournoys, A., Duhamel, A., Elkalioubie, A., Dupont, A., Debize, G., De Prost, D., Huissoud, C., Jude, B., Ducloy-Bouthors, A. S., Tranexamic acid inhibits fibrinolysis-induced coagulopathy associated with post-partum hemorrhage, Journal of Thrombosis and Haemostasis, 11, 221, 2013	Population do not meet inclusion criteria -women with known haemostatic disorders before pregnancy and women with a history of thrombosis were excluded
Trigg,D.E., Stergiotou,I., Peitsidis,P., Kadir,R.A., A Systematic Review: The use of desmopressin for treatment	Systematic review of non-comparative studies

Study	Reason for exclusion
and prophylaxis of bleeding disorders in pregnancy, Haemophilia, 18, 25-33, 2012	
Verghese, L., Tingi, E., Thachil, J., Hay, C., Byrd, L., Management of parturients with Factor XI deficiency-10 year case series and review of literature, European Journal of Obstetrics Gynecology and Reproductive Biology, 215, 85-92, 2017	Case series, no relevant data reported
Wilson, E., Dennis, A., Pavlov, T., Khalafallah, A., Do bleeding disorders interfere with pregnancy outcomes?: Assessment of factors influencing outcomes of pregnant women with von Willebrand disease at regional centre in Australia, Australian and New Zealand Journal of Obstetrics and Gynaecology, 57, 67, 2017	Conference abstract

Economic studies

2 See Supplement 2 (Health economics) for details of economic evidence reviews and health
3 economic modelling.

Appendix E – Clinical evidence tables

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Choi, S., Brull, R., Neuraxial techniques in obstetric and non-obstetric patients with common bleeding diatheses, Anesthesia & Analgesia, 109, 648-60, 2009 **Ref Id** 635226 **Country/ies where the study was carried out** United States **Study type** Systematic review **Aim of the study** To assist anaesthetists considering neuraxial techniques in patients with haemophilia, vWD, or ITP by conducting a review of the available literature **Study dates** January 1, 1975 and October 1, 2008	**Sample size** The review included 30 studies of which 5 were relevant for this review. **Characteristics** **Women with von Willebrand's disease** 4 studies were relevant to this review: <u>Varughese 2007</u> Type/N: I N = 14, IIA N = 1 No. of blocks:17 Pretreatment coagulation parameters: Median % normal: FVIII = 65, vWF = 46; vWRCo = 50 Treatment None Posttreatment coagulation parameters N/A Gauge/type N/A Difficult insertion N/A <u>Marrache 2007</u> Type I N =9 No. of blocks:9 Pretreatment coagulation parameters: Mean (IU mL1):	**Interventions** Women received neuraxial technique	**Details** Searches Performed: date not provided PubMed, MEDLINE, and EMBASE databases (controlled search terms) Date restrictions January 1, 1975 and October 1, 2008 Reference lists of all relevant publications were examined to identify any additional relevant references. Web of Science used to manage citations of the included studies. Study inclusion Two authors reviewed each article Data extraction The quality of evidence for each identified article was independently graded by each of the author. Where possible, the pre-and posttreatment coagulation	**Results** **Women with von Willebrand's disease** No haemorrhagic complications associated with neuraxial technique (with or without subsequent neurologic compromise) were identified in any study **Women with haemophilia** No haemorrhagic complications associated with neuraxial technique (with or without subsequent neurologic compromise) were identified	**Limitations** ROBIS Checklist (for systematic review) DOMAIN 1: STUDY ELIGIBILITY CRITERIA 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? Yes 1.2 Were the eligibility criteria appropriate for the review question? Yes 1.3 Were eligibility criteria unambiguous? Probably yes 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? No information 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding None stated	FVIII =1.42 0.42; vWF =1.42 0.62; vWRCo =1.42 0.79 Treatment None Posttreatment coagulation parameters N/A Gauge/type N/A Difficult insertion None <u>Suddeth 2003</u> Type N/A N = 34 No. of blocks:34 Pretreatment coagulation parameters: N/A Treatment: DDAVP to 5 patients (dose N/A) Posttreatment coagulation parameters N/A Gauge/type N/A Difficult insertion N/A <u>Kadir 1998</u> vWD subtypes not indicated N = 8 No. of blocks:8 Pretreatment coagulation parameters: Median (IU mL_1): FVIII_0.5; vWF _0.5; vWRCo _0.5 Treatment N/A Posttreatment coagulation parameters N/A Gauge/type N/A Difficult insertion N/A		variables, platelet counts, treatment administered, needle gauge/type used for the block, difficulties noted with placement, and the source authors' recommendations regarding management of the bleeding diatheses were included in the summary tables.		Concerns regarding specification of study eligibility criteria LOW DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? 2.2 Were methods additional to database searching used to identify relevant reports? Yes 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Yes 2.4 Were restrictions based on date, publication format, or language appropriate? No information 2.5 Were efforts made to minimise error in selection of studies? Yes Concerns regarding methods used to identify and/or select studies LOW DOMAIN 3: DATA COLLECTION AND STUDY

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Women with haemophilia One study was relevant to this review: Kadir 1997 Type/N Haemophilia subtype not indicated A/B N = 6 No. of blocks = 6 Pretreatment coagulation parameters: type or dosage of factor replacement not specified FVIII/IX levels 50% in 5 out of 6 LEAs Treatment N/A Posttreatment coagulation parameters N/A Gauge/type N/A Difficult insertion N/A **Inclusion criteria** Only studies in which neuraxial techniques were performed on patients with the aforementioned bleeding diatheses were included. **Exclusion criteria** Acquired forms of hemophilia were excluded.				APPRAISAL 3.1 Were efforts made to minimise error in data collection? Yes 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? No 3.3 Were all relevant study results collected for use in the synthesis? No information 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? No 3.5 Were efforts made to minimise error in risk of bias assessment? No Concerns regarding methods used to collect data and appraise studies HIGH Rationale for concern: High risk of bias from individual studies as no formal risk of bias assessment was made for each study. DOMAIN 4: SYNTHESIS AND FINDINGS 4.1 Did the synthesis include all studies that it should? Probably yes 4.2 Were all pre-defined

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					analyses reported or departures explained? Probably yes 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? No 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? No 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? No 4.6 Were biases in primary studies minimal or addressed in the synthesis? No Concerns regarding the synthesis and findings HIGH Rationale for concern: Studies were case series that provided descriptive data only, are susceptible to selection bias and low internal validity. Information about treatment prior to labour was limited in the systematic review, thus it is unclear as to whether the populations from different

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					studies are sufficiently similar to be synthesised Other information None **Other information**
Full citation Lee, L. O., Bateman, B. T., Kheterpal, S., Klumpner, T. T., Housey, M., Aziz, M. F., Hand, K. W., MacEachern, M., Goodier, C. G., Bernstein, J., Bauer, M. E., Lirk, P., Wilczak, J., Soto, R., Tom, S., Cuff, G., Biggs, D. A., Coffman, T., Saager, L., Levy, W. J., Godbold, M., Pace, N. L., Wethington, K. L., Paganelli, W. C., Durieux, M. E., Domino, K. B., Nair, B., Ehrenfeld, J. M., Wanderer, J. P., Schonberger, R. B., Berris, J., Lins, S., Coles, P., Cummings, K. C., Maheshwari, K., Berman, M. F., Wedeven, C., LaGorio, J., Fleishut, P. M., Ellis,	**Sample size** Primary study N= 573 parturients with a platelet count <100,000 Systematic review N=15 studies (including primary study) **Characteristics** Characteristics Age in years, mean ± SD: 30 ± 6 ASA physical status classification, n (%): Class 2: 391 (68%) Class 3: 130 (23%) Class 4: 10 (2%) Emergent: 75 (13%) Missing: 42 (7%) Aetiology of thrombocytopenia, n (%): HELLP syndrome: 31 (5%) Preeclampsia: 67 (12%)	**Interventions** Platelet count prior to neuraxial technique performed for delivery. No details regarding the platelet count methods were presented	**Details** <u>Primary study:</u> MPOG database queried with search terms and free text terms to identify the target population and details of their characteristics and treatment. Billing codes were used to identify women who underwent surgical evacuation of an epidural hematoma within 6 weeks of receiving a neuraxial technique. Where these were not available, operative episodes within 6 weeks of receiving a neuraxial technique were manually reviewed to identify decompressive laminectomies with manual review of medical records to confirm. Women were stratified into 3 predefined categories based on their platelet count	**Results** <u>Primary study:</u> Frequency of Epidural Hematoma Requiring Surgical Decompression 0–49 x 10^9/l: 0/15, 95% CI for risk of event 0-20% 50-69 x 10^9/l: 0/36, 95% CI for risk of event 0-8% 70-100 x 10^9/l: 0/522, 95% CI for risk of event 0-0.6% <u>Systematic review:</u> A total of 1,524 neuraxial techniques performed in thrombocytopenic parturients with platelet count at or less than 100 x 10^9/l After combining data from previous case series with the data from MPOG:	**Limitations** Joanna Briggs Institute Critical Appraisal Checklist for Case Series 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Yes 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes (all eligible women were retrospectively sought from a database and included in the analysis) 5. Did the case series have complete inclusion of participants? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
T. A., 2nd, Molina, S., Carl, C., Kadry, B., van Klei, W. A., Pasma, W., Jameson, L. C., Helsten, D. L., Avidan, M. S., Multicenter Perioperative Outcomes Group, Investigators, Risk of Epidural Hematoma after Neuraxial Techniques in Thrombocytopenic Parturients: A Report from the Multicenter Perioperative Outcomes Group, Anesthesiology, 126, 1053-1063, 2017 **Ref Id** 635274 **Country/ies where the study was carried out** United States of America **Study type** Retrospective case series and systematic review **Aim of the study** To estimate the risk of epidural hematoma in thrombocytopenic parturients who received a neuraxial technique identified using the Multicenter Perioperative	Idiopathic thrombocytopenic purpura: 25 (4%) Gestational thrombocytopenia: 34 (6%) Missing: 416 (73%) Anaesthetic technique, n (%): Epidural: 327 (57%) Spinal: 200 (35%) Combined spinal–epidural: 46 (8%) Neuraxial techniques converted to general anaesthesia: 9 (2%) **Inclusion criteria** Women identified using the MPOG database who were obstetric patients aged 18 to 55 years; had a platelet count <100 x 109L within 72h before receipt of a neuraxial technique (epidural, spinal and combined spinal-epidural analgesia/anaesthesia) For the systematic review: studies reporting neuraxial techniques in thrombocytopenic parturients; description of whether epidural		(0 to 49,000 mm–3, 50,000 to 69,000 mm–3, and 70,000 to 99,000 mm–3) The 95% CIs for the incidence of epidural hematoma of each platelet range were reported using the rule of 3, a statistical method to estimate the upper bound of the 95% CI for zero numerator problems, which states that, for trials in which no events have occurred, the upper bound of the 95% CI can be estimated by 3/n. <u>For the systematic review:</u> Searches: -Performed June 9, 2016 -PubMed and EMBASE (controlled search terms and freetext) -English-language, human studies restrictions No date restrictions -Conference abstracts and articles, letters, and editorials were included -Key articles were used to derive search terms and test the effectiveness of the searches.	0-49 x 10^9/l: 0/27, 95% CI for risk of event 0-11% 50-69 x 10^9/l: 0/89, 95% CI for risk of event 0-3% 70-100 x 10^9/l: 0/1286, 95% CI for risk of event 0-0.2%	6. Was there clear reporting of the demographics of the participants in the study? Yes 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Yes 10. Was statistical analysis appropriate? Yes ROBIS Checklist for systematic review DOMAIN 1: STUDY ELIGIBILITY CRITERIA 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? Yes 1.2 Were the eligibility criteria appropriate for the review question? Yes 1.3 Were eligibility criteria unambiguous? Probably yes 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Outcomes Group (MPOG) database. To perform a systematic review of studies reporting 10 or more thrombocytopenic parturients who received neuraxial techniques, combining results from the primary study to increase the power of the study to define the risk of epidural hematoma. **Study dates** January 2004 to September 2015 **Source of funding** Award No. K08HD075831 Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health, Bethesda, Maryland	hematomas occurred; platelet count stratification **Exclusion criteria** Underlying coagulopathy diagnosis (von Willebrand disease, platelet dysfunction, factor XIII deficiency, factor VII deficiency, Evan's syndrome, haemophilia carrier, history of abnormal bleeding, pharmacologically induced, May–Hegglin anomaly, or platelet storage pool deficiency); using an antiplatelet medication. For the systematic review: Studies (or information within studies) were excluded where there had been platelet transfusion prior to neuraxial technique and where parturients with normal platelet counts became thrombocytopenic after receiving a neuraxial technique.		-Web of Science used to manage citations of the included studies. Study inclusion -Two authors reviewed each article Data extraction -Authors were emailed for additional information if clarification of data was required -Data were extracted by one author and validated by another.		information 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? No information Concerns regarding specification of study eligibility criteria LOW DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? 2.2 Were methods additional to database searching used to identify relevant reports? Yes 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Yes 2.4 Were restrictions based on date, publication format, or language appropriate? No information 2.5 Were efforts made to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					minimise error in selection of studies? Yes Concerns regarding methods used to identify and/or select studies LOW DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL 3.1 Were efforts made to minimise error in data collection? Yes 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? No 3.3 Were all relevant study results collected for use in the synthesis? No information 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? No 3.5 Were efforts made to minimise error in risk of bias assessment? No Concerns regarding methods used to collect data and appraise studies HIGH Rationale for concern: High risk of bias from individual

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					studies as no formal risk of bias assessment was made for each study. DOMAIN 4: SYNTHESIS AND FINDINGS 4.1 Did the synthesis include all studies that it should? Probably yes 4.2 Were all pre-defined analyses reported or departures explained? Probably yes 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? No 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? N the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? No 4.6 Were biases in primary studies minimal or addressed in the synthesis? No Concerns regarding the synthesis and findings HIGH Rationale for concern: Studies were case series that

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					provided descriptive data only, are susceptible to selection bias and low internal validity. Information about treatment prior to labour was not made available in the systematic review, thus it is unclear as to whether the populations from different studies are sufficiently similar to be synthesised **Other information** Agaram et al., 2006, Beilin et al., 1997, Beilin et al., 2006, Bernstein et al., 2016, Campbell et al., 1999, Frenk et al., 2005, Goodier et al., 2015, Huang et al., 2014, Palit et al., 2009, Shalev and Anteby, 1996, Sibai et al., 1986, Tanaka et al., 2009, Vigil-De Gracia et al., 2001 and Webert et al., 2003 Studies where platelet count categories did not discretely fall within the platelet count ranges used in the analysis of MPOG were not included in the risk analysis for these ranges but were included in the overall reported number

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					of neuraxial procedures performed in thrombocytopenic parturients.
Full citation Levy, N., Goren, O., Cattan, A., Weiniger, C. F., Matot, I., Neuraxial block for delivery among women with low platelet counts: A retrospective analysis, International Journal of Obstetric Anesthesia, 2018 **Ref Id** 834280 **Country/ies where the study was carried out** Israel **Study type** Retrospective case series (+ combined analysis using data from previous studies) **Aim of the study** To assess the anaesthetic management, complications and outcomes of women with low platelet counts, and to expand the existing data regarding the safety	**Sample size** Primary study N=471 women with platelet counts <100,000/µL of which n=308 received neuraxial blockade **Characteristics** Characteristics according to platelet count subgroups Age in years, mean±SD: 0-49 x 10^9/l: 32.2±6.3 50-69 x 10^9/l: 31.9±5.0 70-99 x 10^9/l: 32.8±5.2 Gestational age in weeks, mean±SD: 0-49 x 10^9/l: 36.7±4.0 50-69 x 10^9/l: 38.0±4.0 70-99 x 10^9/l: 39.0±2.2 Gravidity, median (IQR): 0-49 x 10^9/l: 1.5 (1-2.25) 50-69 x 10^9/l: 2 (1-3) 70-99 x 10^9/l: 2 (1-3) Parity, median (IQR): 0-49 x 10^9/l: 0 (0-1) 50-69 x 10^9/l: 1 (0-1) 70-99 x 10^9/l: 1 (0-1)	**Interventions** Platelet count measured prior to birth and neuraxial technique.	**Details** Electronic patient database was retrospectively screened for women who gave birth and had a platelet count <100,000/µL before birth. A microscopic 'manual' count or a second automated platelet count performed before birth was also sought in order to exclude cases representing a laboratory error. Maternal and obstetric characteristics were also obtained from the database, including data on analgesia/anaesthesia and mode of birth. Occurrence of spinal epidural haematoma or other nueurologic complication was also searched in the database for these women.	**Results** Combined data from the original case series and data from Lee 2017 (which includes their original case series and data from a systematic review) Spinal epidural haematoma, number of events and 95% CI of risk 0-49 x 10^9/l: 0/32 95% CI of risk 0%-9% 50-69 x 10^9/l: 0/112 CI of risk 0%-2.6% 70-99 x 10^9/l: 0/1,566 CI of risk 0%-0.19%	**Limitations** Joanna Briggs Institute Critical Appraisal Checklist for Case Series 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Yes 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes (all eligible women were retrospectively sought from a database and included in the analysis) 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of neuraxial blockade in this population. **Study dates** January 1st 2011 to December 31st 2014 **Source of funding** No funding received.	Underlying diagnosis, n (%): idiopathic thrombocytopenic purpura 0-49 x 10^9/l: 2 (11) 50-69 x 10^9/l: 1 (2) 70-99 x 10^9/l: 5 (1) preeclampsia/HELLP 0-49 x 10^9/l: 4 (22) 50-69 x 10^9/l: 5 (9) 70-99 x 10^9/l: 20 (5) Gestational/unspecified 0-49 x 10^9/l: 12 (67) 50-69 x 10^9/l: 53 (90) 70-99 x 10^9/l: 369 (94) **Inclusion criteria** All women with a platelet count <100 000/µL giving birth between January 1st 2011 and December 31st 2014 in the study hospitals. **Exclusion criteria** None reported.				7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Yes 10. Was statistical analysis appropriate? Yes For appraisal of the combined data please see Lee 2017. **Other information**

ASA: American Society of Anethesiologists; CI: confidence interval; DDAVP: desmopressin (tradename); FVIII: factor VIII; HELLP: haemolysis with elevated liver enzymes and low platelets; IQR: interquartile range; ITP: immune thrombocytopenic purpura; IU: international unit; MPOG: Multicenter Perioperative Outcomes Group; N/A: not applicable; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation; vWD: von Willebrand Disease; vWF: von Willebrand factor; vWRCo: von Willebrand Ristocetin Co-factor activity

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
Full citation Boehlen, F., Hohlfeld, P., Extermann, P., Perneger, T. V., De Moerloose, P., Platelet count at term pregnancy: A reappraisal of the threshold, Obstetrics and Gynecology, 95, 29-33, 2000 **Ref Id** 596371 **Country/ies where the study was carried out** Switzerland **Study type** Case-control observational study **Aim of the study** To determine a safe threshold value of platelet count for the definition of maternal thrombocytopenia at the end of pregnancy for avoiding unnecessary investigations **Study dates** Publication date: 2000	**Sample size** N=6770 women recruited; n=786 analysed N=6103 neonates **Characteristics** Age at delivery, mean (range): 29.8 (15-47) Type of thrombocytopenia: gestational n=738 immune n=4 other n=44 Platelet count: 116-149 x 10^9/l n=621 women <116 x 10^9/l n=165 women **Inclusion criteria** The study sample was consecutively included in the study period Selection criteria (including inclusion and exclusions) are not reported **Exclusion criteria** None	**Interventions** Platelet count (analysed with a cell counter Sysmex K-1000-Toa Medical Electronics, Kobe, Japan)	**Details** Data collection (retrospective/prospective): prospective Clinical setting (multi/ single-centre): multicentre - two university hospitals of Lausanne and Geneva. Timing of the test and/or modification of care: on admission to the labor ward or during a prenatal visit during the last month of pregnancy.	**Results** Maternal mortality according to platelet count[1] 116-149 x 10^9/l 0 <116 x 10^9/l not reported Maternal morbidities[1] 116-149 x 10^9/l 0 <116 x 10^9/l 0 Perinatal mortality 116-149 x 10^9/l 0 <116 x 10^9/l not reported Major neonatal morbidity 116-149 x 10^9/l 0	**Limitations** Limitations assessed using the Joanna Briggs Institute critical appraisal checklist for case series 1. Were there clear criteria for inclusion in the case series? No (inclusion/exclusion criteria not clearly reported) 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Yes 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
Data collection/patients enrollment: not reported **Source of funding** This collaborative work was partly funded by a grant from the Henri Dubois-Ferrie`re Dinu Lipatti Foundation.				<116 x 10^9/l not reported	consecutive inclusion of participants? Yes 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? Yes 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? No 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? No 10. Was statistical analysis appropriate? Yes

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					Other information The Authors concluded that in "healthy pregnant women, a platelet count over 115 X 10^9/l late in pregnancy does not require further investigation during pregnancy and may be considered a safe threshold"
Full citation Gasparovic, V. E., Ahmetasevic, S. G., Beljan, P., Skrablin, S., Effect of severe gestational thrombocytopenia to perinatal outcome, Signa Vitae, 9, 49-53, 2014 **Ref Id** 596500 **Country/ies where the study was carried out** Croatia **Study type** Case series	**Sample size** N=80 women By platelet count: 50-100 x 10^9/l n=63 <50 x 10^9/l n=17 **Characteristics** Age at delivery, mean (range): 50-100 x 10^9/ group: 30 (19-44) <50 x 10^9/l group: 29 (21-41) Type of thrombocytopenia (immune/gestational): gestational	**Interventions** Review including the following variables: • platelet counts (counter tool not reported) • age of mother • gestational age • method of conception (natural or assisted reproductive technology) • previous abortions	**Details** Data collection (retrospective/prospective): unclear Clinical setting (multi/ single-centre): singlecentre - Neonatal Intensive Care Unit; University Hospital Centre: Zagreb. Timing of the test and/or modification of care: after 24 weeks of gestation	**Results** Maternal morbidities 50-100 x 10^9/l group: 0 <50 x 10^9/l group: 0 Perinatal mortality 50-100 x 10^9/l group: 0 <50 x 10^9/l group: 0	**Limitations** Limitations assessed using the Joanna Briggs Institute critical appraisal checklist for case series 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
Aim of the study To investigate if the severity of maternal gestational thrombocytopenia affect perinatal outcome and to define if the severity of maternal gestational thrombocytopenia implicates the appearance of neonatal thrombocytopenia. **Study dates** Publication date: 2014 Data collection/patients enrollment: 2007-2012 **Source of funding** Not reported	Platelet count. median (range): 50-100 x 10^9/l group: 82 (51-98) <50 x 10^9/l group: 37 (7-49) **Inclusion criteria** All singleton deliveries with a gestation more than 24 weeks were included **Exclusion criteria** Patients were excluded if they had: 1) chronic hypertension, diabetes mellitus, liver diseases (acute hepatitis, acute fatty liver, and/ or liver cirrhosis), renal diseases 2) autoimmune disorders such as systemic lupus erythematosus 3) ITP	• thrombocytopenia and fetal death in previous pregnancies Thrombocytopenia was defined as moderate (50 to 99 x 10^9/l), or severe (<50 x 10^9/l).		Major neonatal morbidity 50-100 x 10^9/l group: 0 <50 x 10^9/l group: 0	participants included in the case series? No (platelet counter tool not reported) 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? Yes 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					outcomes or follow up results of cases clearly reported? No 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? No 10. Was statistical analysis appropriate? Yes **Other information**
Full citation Payne, S. D., Resnik, R., Moore, T. R., Hedriana, H. L., Kelly, T. F., Maternal characteristics and risk of severe neonatal thrombocytopenia and intracranial hemorrhage in pregnancies complicated by autoimmune thrombocytopenia, American Journal of Obstetrics & Gynecology, 177, 149-55, 1997 **Ref Id**	**Sample size** Primary study included N=55 pregnancies in women with thrombocytopenia. The study also reviewed other studies published earlier and reported results that combined all these studies with total n=601 newborns. **Characteristics** Primary study:	**Interventions** Primary study Chart review including the following variables: • platelet counts (analyzed with ethylenediaminetetraacetic acid-antcoagulated specimen with a Coulter (Coulter Co., Hialeah, Fla.) counter) • maternal presence of antiplatelet antibodies	**Details** Primary study Data collection: retrospective Clinical setting: multicentre - three medical centers in San Diego: University of California Medical Center, Kaiser Permanente Medical Center, and the Mercy Hospital and Medical Center.	**Results** Neonatal intracranial haemorrhage 6/601	**Limitations** Limitations assessed using the Joanna Briggs Institute critical appraisal checklist for case series 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
506814 **Country/ies where the study was carried out** USA **Study type** Case series, plus review of studies **Aim of the study** To investigate if maternal autoimmune thrombocytopenia is related with mode of delivery. **Study dates** Data collection/patients enrollment: 1984-1994 **Source of funding** Not reported	Age at delivery, mean (range): 27 (15-44) Type of thrombocytopenia (immune/gestational): immune Mode of birth Normal spontaneous vaginal delivery: 31 (56%) Cesarean section 24 (44%) Platelet count at delivery, mean (range): 107 x 10^9/l (7-498 x 10^9/l) Review of studies: 17 studies reported on neonatal intracranial haemorrhage (listed here in chronological order): Territo 1973 n=5 Laros and Sweet 1975 n=17 Jones 1977 n=20 O'Reilly and Taber 1978 n=9 Noriega-Guerra 1979 n=21 Scott 1980 n=12 Karpatkin 1981 n=19 Kelton 1982 n=39 Walbeh 1984 n=15 Moise 1988 n=22 Scioscia 1988 n=20 Ballem 1989 n=24	• history of autoimmune thrombocytopenia antedating pregnancy • mode of delivery • use of fetal scalp platelet determinations Thrombocytopenia was defined as mild (100 to 150 ×10^9/l), moderate (50 to 99 × 10^9/l), or severe (<50 × 10^9/l).	Timing of the test and/or modification of care: Data abstracted included maternal platelet counts at the first prenatal visit, at the nadir during pregnancy, and at delivery. No details of the review of other studies are provided.		way for all participants included in the case series? Yes 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? Yes 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
	Samuels 1990 n=162 Burrows and Kelton 1990 n=60 Moutet 1990 n=32 Cook 1991 n=32 Garmel 1995 n=41 **Inclusion criteria** Primary study 1) patients with autoimmune thrombocytopenia. Maternal thrombocytopenia was defined as a platelet count <150,000 x 10^9/l. 2) ICD-9 diagnosis for pregnancy and thrombocytopenia, as well as immune thrombocytopenia, history of immune thrombocytopenia, and splenectomy 3) people without : (1) unexplained thrombocytopenia during pregnancy with megakaryocytosis demonstrated on bone marrow biopsy, (2) history of undocumented thrombocytopenia with a				up results of cases clearly reported? No 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? No 10. Was statistical analysis appropriate? Yes ROBIS Checklist for systematic review DOMAIN 1: STUDY ELIGIBILITY CRITERIA 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? No information 1.2 Were the eligibility criteria appropriate for the review question? No information

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
	platelet count <50 × 109/L in the index pregnancy before the third trimester, and (3) thrombocytopenia with demonstrable antiplatelet antibodies **Exclusion criteria** Primary study 1) "incidental" thrombocytopenia of pregnancy 2) patients with a diagnosis of preeclampsia, other hematologic disorders or medical illnesses that might be associated with thrombocytopenia, or collagen vascular disorders.				1.3 Were eligibility criteria unambiguous? No information 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? No information 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? No information Concerns regarding specification of study eligibility criteria UNCLEAR

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? No information 2.2 Were methods additional to database searching used to identify relevant reports? No information 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? No information 2.4 Were restrictions based

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					on date, publication format, or language appropriate? No information 2.5 Were efforts made to minimise error in selection of studies? No information Concerns regarding methods used to identify and/or select studies UNCLEAR DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL 3.1 Were efforts made to minimise error in data collection? No information 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					results? No information 3.3 Were all relevant study results collected for use in the synthesis? No information 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? No information 3.5 Were efforts made to minimise error in risk of bias assessment? No information Concerns regarding methods used to collect data and appraise studies UNCLEAR DOMAIN 4: SYNTHESIS AND FINDINGS 4.1 Did the synthesis include all studies that it

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					should? No information 4.2 Were all pre-defined analyses reported or departures explained? No 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? No information 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? N the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? No information

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					4.6 Were biases in primary studies minimal or addressed in the synthesis? No Concerns regarding the synthesis and findings HIGH Rationale for concern: No information about the review was provided. Studies were case series that provided descriptive data only, are susceptible to selection bias and low internal validity. It is unclear as to whether the populations from different studies are sufficiently similar to be synthesised. **Other information**

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
Full citation Tanaka, M., Balki, M., McLeod, A., Carvalho, J. C. A., Regional anesthesia and non-preeclamptic thrombocytopenia: Time to re-think the safe platelet count. [Portuguese, English], Revista Brasileira de Anestesiologia, 59, 142-153, 2009 **Ref Id** 596998 **Country/ies where the study was carried out** Canada **Study type** Case series **Aim of the study** To review the use of regional anesthesia in non-preeclamptic thrombocytopenic parturients, in order to further contribute to data supporting the adoption of a platelet count lower than the current widely accepted 75 to 80 × 10^9.L-	**Sample size** N=75 women **Characteristics** Type of thrombocytopenia: immune n=49 gestational n=20 other n=6 **Inclusion criteria** People with platelet counts below 100 × 10^9/l on the day of anaesthesia **Exclusion criteria** People who were diagnosed with preeclampsia or hypertension	**Interventions** Chart review of the following variables: -the platelet count on the day of anaesthesia -aetiology of the thrombocytopenia -the anaesthetic technique -the mode of delivery -any neurological deficits during hospitalisation	**Details** Data collection: retrospective Clinical setting: single-centre- Mount Sinai, Hospital in Toronto. Timing of the test and/or modification of care: on the day of anestesia	**Results** Maternal morbidities No events (No serious anaesthesia -related complications occurred.)	**Limitations** Limitations assessed using the Joanna Briggs Institute critical appraisal checklist for case series 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all participants included in the case series? No (platelet counter tool was not reported) 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
1 as a safe lower limit for regional anesthesia in this specific subset of obstetric patients. **Study dates** Publication date: 2009 Data collection/patients enrollment: 2001-2006 **Source of funding** Not reported					inclusion of participants? Unclear 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? No (demographics information of included people was not clearly reported) 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? No 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					information? No 10. Was statistical analysis appropriate? Yes **Other information**
Full citation Won,Y.W., Moon,W., Yun,Y.S., Oh,H.S., Choi,J.H., Lee,Y.Y., Kim,I.S., Choi,I.Y., Ahn,M.J., Clinical aspects of pregnancy and delivery in patients with chronic idiopathic thrombocytopenic purpura (ITP), Korean Journal of Internal Medicine, 20, 129-134, 2005 **Ref Id** 67596 **Country/ies where the study was carried out** Republic of South Korea **Study type** Case series **Aim of the study**	**Sample size** N=30 women (n=31 pregnancies) N=29 neonates **Characteristics** Age at delivery, mean (range): 29.2 (24-39) Type of thrombocytopenia: immune Gestational age at delivery in weeks, mean (range): 36.5 (7-43) Mode of delivery: Cesarean section: 15 Vaginal delivery: 14 Dilatation and evacuation: 2 Platelet count: <20 x 10^9/l: 2 20-50 x 10^9/l: 9	**Interventions** Chart review including the following variables: • age • date of ITP diagnosis • underlying medical conditions and medications • platelet count before and during pregnancy and at delivery • signs and symptoms of hemostatic impairment during pregnancy, • treatment received to raise platelet count during pregnancy or at delivery • gestational age at delivery • type of delivery • estimated blood loss at delivery	**Details** Data collection: retrospective Clinical setting: single centre - Hanyang University Medical Center Timing of the test and/or modification of care: platelet count before and during pregnancy(from diagnosis of pregnancy to delivery 1 week ago) and at delivery (from delivery 1 week ago to the time of delivery)	**Results** Maternal mortality <20 x 10^9/l: 1/2 20-50x 10^9/l: 0/9 50-100 x 10^9/l: 0/17 >100 x 10^9/l: 0/3 Maternal morbidities <20 x 10^9/l: 1/2 20-50x 10^9/l: 0/9 50-100 x 10^9/l: 0/17 >100 x 10^9/l: 0/3	**Limitations** Limitations assessed using the Joanna Briggs Institute critical appraisal checklist for case series 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all participants included in the case series? No (platelet counter tool not reported) 3. Were valid methods used for identification of the

To investigate pregnancy and birth outcomes in women with chronic idiopathic thrmbocytopenic purpura (ITP). **Study dates** Publication date: 2005 Data collection/patients enrollment: 1995-2003 **Source of funding** Not reported	50-100 x 10^9/l: 17 >100 x 10^9/l: 3 **Inclusion criteria** 1) people with a diagnosis idiopathic thrombocytopenic purpura (ITP). 2) people with a previous history ITP. 3) the diagnosis of ITP had been established based on standard criteria: thrombocytopenia for >6 months associated with normal white and red blood cells, and exclusion of other known causes of thrombocytopenia **Exclusion criteria** Not reported	• complications at delivery and in the postpartum period.		Perinatal mortality <20 x 10^9/l: 1/2 20-50x 10^9/l: 0/9 50-100 x 10^9/l: 0/17 >100 x 10^9/l: 0/3 Major neonatal morbidity <20 x 10^9/l: 0/2 20-50x 10^9/l: 0/9 50-100 x 10^9/l: 0/17 >100 x 10^9/l: 0/3	condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? Yes 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? No 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? No 10. Was statistical

Study details	Participants	Variables under consideration and Counfonders	Methods	Outcomes and Results	Comments
					analysis appropriate? Yes **Other information**

1 *ICD-9: International Classification of Diseases Ninth Revision; ITP: imnmubne thrombocytopenic purpura; ROBIS: Risk of Bias in Systematic Reviews*

Intrapartum care for women with haemostatic disorders – third stage of labour

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Detti,L., Mecacci,F., Piccioli,A., Ferrarello,S., Carignani,L., Mello,G., Ferguson,J.E., Scarselli,G., Postpartum heparin therapy for patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is associated with significant hemorrhagic	**Sample size** n=32 (16 cases from Italy and 16 controls from USA) **Characteristics** Diagnosis of HELLP syndrome was made when platelets ≤100,000/mm3, AST and ALT ≥70 U/L and presence of objective signs of microangiopathic haemolysis. LDH ≥600U/L and bilirubin ≥1.2mg/dl was considered as signs of haemolysis. 9 of cases and 13 of control group received	**Interventions** Haematocrit, platelets, fibrinogen, antithrombin III activity, D-dimer, PT, PTT, LDH, AST, ALT, Total and direct bilirubin and renal function tests were done 6 hourly. Hypertension were controlled with bolus hydralazine or oral nifedipine.	**Details** Control group were recruited by matching race, gestational age, and severity of syndrome as case group.	**Results** Diagnosis of DIC was made with >/= 3 of the followings: Platelet count ≤100,000/mm3, PT≤70%, PTT≥40s, antithrombin III ≤80%, fibrinogen ≤300mg/dl, either FDP >=40 mg/dL or D-dimer test ≥800. Following HELLP syndrome, the patients were stabilised and underwent CS. All the cases (Italy) were admitted to ICU and were treated with heparin 5000 IU SC 12 hourly. If developed DIC, a dose of 15,000 IU IV was given in continuous infusion every 24 hours until recovery of coagulation parameters and IV antithrombin III (1000 IU/day until antithrombin was above 80%) and FFP. All the controls (USA) were transferred to recovery room soon after surgery and treated supportively. Red blood cells were given if symptomatic (dizziness, tachycardia) or haemoglobin <8 g/dL. Outcome | Italy | USA | p value Eclampsia | 3(18.7%) | 1(6.2%) | NS	**Limitations** Quality Assessment: Newcastle-Ottawa Assessment Scale for Cohort Studies Selection: 1) Representativenes s of the exposed cohort b) somewhat representative of the pregnant women with HELLP syndrome but treatment strategy might or might not represent to those in UK

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>complications, Journal of Perinatology, 25, 236-240, 2005
Ref Id
122332
Country/ies where the study was carried out
Italy and USA
Study type
Retrospective cohort study

Aim of the study
TO examine the role of heparin therapy among women with haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome

Study dates
January 1990 to December 1997

Source of funding
Not reported</td>
<td>IM betamethasone 12 mg every 24 hours for 2 days because <34 weeks gestation.

Age in years: 31±5 (Italy) vs 26±5 (USA); p, 0.04 and no difference in other parameters as baselines.
Average gestational age: 33 weeks

Inclusion criteria
• Consecutive women with HELLP syndrome

Exclusion criteria
• Women with previous medical complications such as cardiovascular and renal diseases and</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>DIC</td><td>9(56.2%)</td><td>1(6.2%)</td><td><0.002</td></tr>
<tr><td>Haemorrhage</td><td>6(37.5%)</td><td>1(6.2%)</td><td><0.03</td></tr>
<tr><td>Hysterectomy</td><td>5(31.5%)</td><td>0</td><td><0.02</td></tr>
<tr><td>Exploratory laparotomy</td><td>7</td><td>0</td><td><0.01</td></tr>
<tr><td>Pulmonary oedema</td><td>0</td><td>1(6.2%)</td><td>NS</td></tr>
<tr><td>Dialysis</td><td>2(12.5%)</td><td>0</td><td>NS</td></tr>
<tr><td>Plamapheresis</td><td>1(6.2%)</td><td>0</td><td>NS</td></tr>
<tr><td>Platelet transfusion</td><td>1(6.2%)</td><td>8(50%)</td><td><0.006</td></tr>
<tr><td>FFP transfusion</td><td>8(50%)</td><td>0</td><td><0.001</td></tr>
<tr><td>RBC transfusion</td><td>12(75%)</td><td>4(25%)</td><td><0.005</td></tr>
<tr><td>Hospital stay (mean)</td><td>11±8</td><td>6±3</td><td><0.001</td></tr>
</table>
</td>
<td>2) Selection of the non exposed cohort
b) drawn from a different country

3) Ascertainment of exposure
a) prospective record

4) Demonstration that outcome of interest was not present at start of study
a) yes

Comparability:
1) Comparability of cohorts on the basis of the design or analysis
Study controls for race, gestational age, and severity of syndrome during design stage but there was statistically different in age at baseline between the group.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td>haemorrhagic diatheses</td><td></td><td></td><td></td><td>Outcome:
1) Assessment of outcome
b) record linkage

2) Was follow-up long enough for outcomes to occur
a) yes

3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for: yes
Overall score: 7/9

Other information</td></tr>
<tr><td>Full citation
Govorov, I., Lofgren, S., Chaireti, R., Holmstrom, M., Bremme, K., Mints, M., Postpartum Hemorrhage in Women with Von Willebrand Disease - A Retrospective Observational Study.[Erratum</td><td>Sample size
Out of 47 eligible women, 34 were included (with n=59 pregnancies and 61 children)

Characteristics
Median age = 32 (19 to 42 years)
known vWD before birth = 28 women with 43 births and vWD following birth = 11 women with 16 births</td><td>Interventions
All patients with known vWD received IV or oral tranexamic acid 8 hourly at the start of labour and continued for a minimum of 10 days (range 2 - 14). In all cases, DDAVP or CFC were</td><td>Details
The participants were included in the study through a local hospital registry containing comprehensive demographic and clinical data. The data was de-identified and handled anonymously.</td><td>Results<table><tr><th></th><th>No treatment (n=16)</th><th>TXA (n=9)</th><th>TXA+ DDAVP (n=12)</th><th>TXA+ CFC (n=22)</th><th>Any treatment (n=43)</th></tr><tr><td>Primary PPH (>500 ml), % (n)</td><td>46.5 (7)</td><td>11.1 (1)</td><td>50 (6)</td><td>59.1 (13)</td><td>37.5 (16)</td></tr><tr><td>Severe primary</td><td>31.3(5)</td><td>11.1(1)</td><td>-</td><td>27.3(6)</td><td>16.3(7)</td></tr></table></td><td>Limitations
Quality Assessment: Newcastle-Ottawa Assessment Scale for Cohort Studies

Selection:
1) Representativeness of the exposed cohort
b) somewhat representative of the average</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>appears in PLoS One. 2017 Feb 9;12 (2):e0172185; PMID: 28182756], PLoS ONE [Electronic Resource], 11, e0164683, 2016
Ref Id
628718
Country/ies where the study was carried out
Sweden
Study type
Retrospective cohort study

Aim of the study
TO examine the role of haemostatic drug treatment among women with vWD complicating PPH

Study dates
1995 to 2012

Source of funding
None</td>
<td>(note - 5 women overlapped)
nullipara = 31 (52.5%)
Gestational age < 36 weeks=3(5.1%)

Inclusion criteria
18-50 years female with vWD diagnosis and obstetric history of at least one delivery

Note - vWD diagnosis was doen by well-recognised criteria: bleeding episodes, family history and low levels of vWF and types were distinguished by RCoF activity and vWF:Ag tests and its ratio.

Exclusion criteria
None reported.</td>
<td>given on top. DDAVP single dose was given in 12 deliveries (11 type 1 and 1 type 2 vWD).

CFC (Haemate-P) was given prior to delivery in 22 pregnancies. Dose of CFC ranged from 1000 to 4000 IU (median 2000 IU) and second dose was administered 12 hours later and then given as daily IV for a median of 9 days (range 1 to 18). The total amount ranged from 2000 to 35000 IU.

vWF were measured</td>
<td>The local registry collects data about patients with bleeding disorders. When a patient is diagnosed with bleeding disorder the patient is included in the registry. Because Sweden has national database for clinical records, clinical history can be tracked back in order to collect necessary clinical information.</td>
<td>
<table>
<tr><td>PPH (>1000 ml), % (n)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Secondary PPH, % (n)</td><td>31.3(5)</td><td>-</td><td>8.3(1)</td><td>4.5(1)</td><td>4.7(2)</td></tr>
<tr><td>Blood transfusion , % (n)</td><td>18.8(3)</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td>
<td>pregnant woman with vWD however the treatment strategy might not represent that in UK

2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort

3) Ascertainment of exposure
a) registry data

4) Demonstration that outcome of interest was not present at start of study
a) yes

Comparability:
1) Comparability of cohorts on the basis of the design or analysis
Study does not control for any important factors</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		using vWF:RCo (0.08 -0.86 kIU/L) and vWF:GpIb (0.08 - 0.86 kIU/L). FVIII activity (0.06 - 2.10 kIU/L) was measured using a well established enzymatic method.			Outcome: 1) Assessment of outcome b) record linkage 2) Was follow-up long enough for outcomes to occur a) yes 3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for: yes Overall score: 7/9 **Other information**
Full citation Hawke, L., Grabell, J., Sim, W., Thibeault, L., Muir, E., Hopman, W., Smith, G., James, P., Obstetric bleeding among women with inherited bleeding disorders: a	**Sample size** n=62 pregnancies of 33 women **Characteristics** Age at delivery: 27±4 years Caesarean section: 23 (37%) Vaginal birth: 39 (63%) immediate PPH =11(18%) from 9 women	**Interventions** Antifibrinolytic tranexamic acid was given to some pregnancies upon discharge (n=36) whereas some did not receive tranexamic acid.	**Details** The clinical charts were reviewed comprehensively for all pregnancies of the patients of the Southeastern Ontario Inherited Bleeding Disorders Clinic from 2002 to 2015.	**Results** Excessive delayed postpartum bleeding Tranexamic acid 7/36 No tranexamic acid 11/26	**Limitations** Quality Assessment: Newcastle-Ottawa Assessment Scale for Cohort Studies Selection: 1) Representativeness of the exposed cohort b) somewhat representative of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
retrospective study, Haemophilia, 22, 906-911, 2016 **Ref Id** 628731 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort **Aim of the study** To examine the use of tranexamic acid in the postpartum treatment of bleeding disorder patients **Study dates** 2002 to 2015 **Source of funding** Bayer, CSL Behring, Octapharma and the Zimmmerman program	delayed PPH= 18(29%) Type of vWD: 1: 39(63%) 2A: 3(5%) 2B: 3(5%) 2M: 1(1.5%) 3: 1(1.5%) Haemophilia A carrier: 11(18%) Factor X deficiency: 2(3%) Platelet function disorder: 2(3%) **Inclusion criteria** Pregnancies in the women with inherited bleeding disorders **Exclusion criteria** None reported.	vWF:Ag and vWF:RCo and FVIII levels were measure during first, second and third trimesters and at delivery. immediaate PPH=estimated blood loss of >500 ml for vaginal deliveries and >1000 ml for CS withing first 24 hours after birth. excessive delayed postpartum bleeding = > 500 ml after 24 hours postpartum and/or lasting up to 6 weeks after delivery			the average pregnant woman with inherited bleeding disorder but treatment strategy might not represent that in UK 2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort 3) Ascertainment of exposure a) registry data 4) Demonstration that outcome of interest was not present at start of study a) yes Comparability: 1) Comparability of cohorts on the basis of the design or analysis Study does not control for any important factors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Outcome: 1) Assessment of outcome b) record linkage 2) Was follow-up long enough for outcomes to occur a) yes 3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for: yes Overall score: 7/9 **Other information**
Full citation Care, A., Pavord, S., Knight, M., Alfirevic, Z., Severe primary autoimmune thrombocytopenia in pregnancy: a national cohort study, BJOG: an international journal of obstetrics and	**Sample size** N=107 pregnant women **Characteristics** Age in years, median (range) No treatment: 33 (19-40) Treatment: 29 (18-42) Primiparous, n (%) No treatment: 8 (36)	**Interventions** n=85 women received treatment before labour: n=38 treated with steroids, n=17 with intravenous immunoglobulin (IVIG), n=28 with steroids plus IVIG	**Details** The UKOSS study obtained information prospectively from all the 202 UK hospitals with consultant-led maternity unit about any severe cases of immune thrombocytopeni	**Results** Maternal mortality No treatment: 0/22 Steroids: 0/38 IVIG: 0/17 Steroids + IVIG: 0/28 Postpartum haemorrhage (blood loss of ≥500 ml after birth) No treatment: 10/22 (45%) Steroids: 17/38 (45%) IVIG: 9/17 (53%) Steroids + IVIG: 18/28 (64%)	**Limitations** Limitations assessed using the Joanna Briggs Institute critical appraisal checklist for case series Inclusion criteria: clearly described Methods for identification and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
gynaecology, 125, 604-612, 2018 **Ref Id** 834391 **Country/ies where the study was carried out** UK **Study type** National prospective case series (UK Obstetric Surveillance System, UKOSS) **Aim of the study** To investigate a UK national cohort of women with idiopathic severely low platelets regarding the management of severe thrombocytopenia and pregnancy outcomes. **Study dates**	Treatment: 36 (42) Diagnosis of ITP before pregnancy, n (%) No treatment: 15 (68) Treatment: 47 (55) Lowest platelet count prior to pregnancy x 10^9/l, median (range) No treatment: 19 (2-74) Treatment: 29.5 (1-119) **Inclusion criteria** Pregnant women with idiopathic severe thrombocytopenia (defined as platelet count <50 x 10^9/l) at any point in pregnancy before birth and where obstetric and hereditory causes had been excluded or if a clinical decision to treat an isolated	n=22 women did not receive any treatment The decision to receive treatment is not explained but likely based on the decision of the treating physician and the woman.	a in women giving birth.	ITU admission No treatment: 0/22 Steroids: 0/38 IVIG: 0/17 Steroids + IVIG: 0/28 Hysterectomy for PPH No treatment: 0/22 Steroids: 0/38 IVIG: 0/17 Steroids + IVIG: 0/28	measurement of the condition: unclear Consecutive inclusion of participants: unclear Complete inclusion of participants: likely yes Demographics of participants: Unclear Clinical information of participants: Parity was not reported; number of women with pregnancy-induced hypertension was reported Outcomes or follow-up results: Unclear Sites demographic information: setting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1st June 2013 to 31st January 2015 **Source of funding** The ITP Support Association, UK	thrombocytopenia was made) **Exclusion criteria** Women with immune thrombocytopenia secondary to systemic lupus erythematosus, hepatitis C, cytomehalovirus, HIV, highly active antiretroviral therapy, or any condition where treatment of thrmobocytopenia is focused on the treatment of the causative disease				and timing clearly stated Statistical analysis: Only descriptive in relation to the outcomes included in this review **Other information**

ALT: alanine transaminase; AST: aspartate transaminase; CFC: clotting factor concentrate; CS: caesarean section; DDAVP: desmopressin (tradename); DIC: disseminated intravascular coagulation; FDP: fibrin degradation product; FFP: fresh frozen plasma; HELLP: haemolysis with elevated liver enzymes and low platelets; ICU: intensive care unit; ITP: immune thrombocytopenic purpura; IU: international unit; IV: intravenous; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; NS: not significant; PPH: postpartum haemorrhage; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cell; RCoF: ristocetin cofactor; SC: subcutaneous; TXA: tranexamic acid; vWD: von Willebrand Disease; vWF: von Willebrand factor

Appendix F – Forest plots

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

No meta-analysis was undertaken for this review and so there are no forest plots.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

No meta-analysis was undertaken for this review and so there are no forest plots.

Intrapartum care for women with haemostatic disorders – third stage of labour

No meta-analysis was undertaken for this review and so there are no forest plots.

Appendix G – GRADE tables

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

Only case series were included in the review so there are no GRADE tables.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

Only case series were included in the review so there are no GRADE tables.

Intrapartum care for women with haemostatic disorders – third stage of labour

Table 18: Clinical evidence profile for heparin versus supportive treatment in women with HELLP syndrome, outcomes for the woman

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparin	Supportive treatment	Relative (95% CI)	Absolute	Quality	Importance
Postpartum haemorrhage												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	6/16 (37.5%)	1/16 (6.3%)	RR 6 (0.81 to 44.35)	312 more per 1000 (from 12 fewer to 1000 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Disseminated intravascular coagulation												

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparin	Supportive treatment	Relative (95% CI)	Absolute		
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	9/16 (56.3%)	1/16 (6.3%)	RR 9 (1.29 to 63.02)	500 more per 1000 (from 18 more to 1000 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Hysterectomy												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	5/16 (31.3%)	0/16 (0%)	RR 11 (0.66 to 183.79)	-[a]	⨁⊖⊖⊖ VERY LOW	CRITICAL
Exploratory laparotomy												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	7/16 (43.8%)	0/16 (0%)	RR 15 (0.93 to 242.43)	-[a]	⨁⊖⊖⊖ VERY LOW	CRITICAL
Dialysis												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	2/16 (12.5%)	0/16 (0%)	RR 5 (0.26 to 96.59)	-[a]	⨁⊖⊖⊖ VERY LOW	CRITICAL
Plasmapharesis												

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparin	Supportive treatment	Relative (95% CI)	Absolute		
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/16 (6.3%)	0/16 (0%)	RR 3 (0.13 to 68.57)	-[a]	⨁⨀⨀⨀ VERY LOW	CRITICAL
Platelet transfusion												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/16 (6.3%)	8/16 (50%)	RR 0.12 (0.02 to 0.89)	440 fewer per 1000 (from 55 fewer to 490 fewer)	⨁⨀⨀⨀ VERY LOW	IMPORTANT
Fresh frozen plasma transfusion												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8/16 (50%)	0/16 (0%)	RR 17 (1.06 to 271.79)	-[a]	⨁⨀⨀⨀ VERY LOW	IMPORTANT
Red blood cell transfusion												
1 (Detti 2005)	Observational studies	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12/16 (75%)	4/16 (25%)	RR 3 (1.23 to 7.34)	500 more per 1000 (from 58 more to	⨁⨀⨀⨀ VERY LOW	IMPORTANT

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparin	Supportive treatment	Relative (95% CI)	Absolute		
										1000 more)		

CI: confidence interval; HELLP: haemolysis with elevated liver enzymes and low platelets; RR: risk ratio
1 Controlling for confounders not adequate, statistically significant difference in age at baseline but this is not controlled for
2 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold
3 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds
a The absolute effect cannot be calculated because of 0 events in the control group

Table 19: Clinical evidence profile for tranexamic acid versus no additional haemostatic therapy in women with von Willebrand disease, outcomes for the woman

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	No haemostatis therapy	Relative (95% CI)	Absolute		
Primary postpartum haemorrhage												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/9 (11.1%)	7/16 (43.8%)	RR 0.25 (0.04 to 1.75)	328 fewer per 1000 (from 420 fewer to	⨁⨀⨀⨀ VERY LOW	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	No haemostatis therapy	Relative (95% CI)	Absolute	Quality	Importance
										328 more)		
Severe primary postpartum haemorrhage (>1000 ml)												
1 (Gov orov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/9 (11.1%)	5/16 (31.3%)	RR 0.36 (0.05 to 2.59)	200 fewer per 1000 (from 297 fewer to 497 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Secondary postpartum haemorrhage (TXA given 8 hourly at the start of labour and continued for a median of 10 days)												
1 (Gov orov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/9 (0%)	5/16 (31.3%)	RR 0.15 (0.01 to 2.51)	266 fewer per 1000 (from 309 fewer to 472 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Secondary postpartum haemorrhage (TXA given on discharge)												

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	No haemostatis therapy	Relative (95% CI)	Absolute		
1 (Hawke 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	7/36 (19.4%)	11/26 (42.3%)	RR 0.46 (0.21 to 1.03)	228 fewer per 1000 (from 334 fewer to 13 more)	⨁◯◯◯ VERY LOW	CRITICAL
Blood transfusion required												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/9 (0%)	3/16 (18.8%)	RR 0.24 (0.01 to 4.23)	142 fewer per 1000 (from 186 fewer to 606 more)	⨁◯◯◯ VERY LOW	CRITICAL

1 *CI: confidence interval; RR risk ratio; TXA: tranexamic acid*
2 *1 The study did not control for any confounders in the analysis*
3 *2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds*
4 *3 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold*

Table 20: Clinical evidence profile for tranexamic acid plus desmopressin versus no additional haemostatic therapy in women with von Willebrand disease, outcomes for the woman

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + desmopressin	No haemostatic therapy	Relative (95% CI)	Absolute	**Quality**	**Importance**
Primary postpartum haemorrhage												
1 (Gorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/12 (50%)	7/16 (43.8%)	RR 1.14 (0.52 to 2.53)	61 more per 1000 (from 210 fewer to 669 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Severe primary postpartum haemorrhage (>1000 ml)												
1 (Gorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/12 (0%)	5/16 (31.3%)	RR 0.12 (0.01 to 1.96)	275 fewer per 1000 (from 309 fewer to 300 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL
Secondary postpartum haemorrhage												
1 (Gorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/12 (8.3%)	5/16 (31.3%)	RR 0.27 (0.04	228 fewer per 1000	⨁⨀⨀⨀	CRITICAL

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + desmopressin	No haemostatic therapy	Relative (95% CI)	Absolute		
									to 1.99)	(from 300 fewer to 309 more)	VERY LOW	
Blood transfusion required												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/12 (0%)	3/16 (18.8%)	RR 0.19 (0.01 to 3.31)	152 fewer per 1000 (from 186 fewer to 433 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL

1 *CI: confidence interval; RR: risk ratio; TXA: tranexamic acid*
2 *1 The study did not control for any confounders in the analysis*
3 *2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses s default MID thresholds*

Table 21: Clinical evidence profile for tranexamic acid plus clotting factor concentrate versus no additional haemostatic therapy in women with von Willebrand disease, outcomes for the woman

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + CFC	No haemostatic therapy	Relative (95% CI)	Absolute	Quality	Importance
Primary postpartum haemorrage												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	13/22 (59.1%)	7/16 (43.8%)	RR 1.35 (0.7 to 2.6)	153 more per 1000 (from 131 fewer to 700 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Severe primary postpartum haemorrage (>1000 ml)												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	6/22 (27.3%)	5/16 (31.3%)	RR 0.87 (0.32 to 2.37)	41 fewer per 1000 (from 213 fewer to 428 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Secondary postpartum haemorrage												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	1/22 (4.5%)	5/16 (31.3%)	RR 0.15 (0.02	266 fewer per 1000	⨁⊖⊖⊖	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA + CFC	No haemostatic therapy	Relative (95% CI)	Absolute	**Quality**	**Importance**
									to 1.13)	(from 306 fewer to 41 more)	VERY LOW	
Blood transfusion required												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/22 (0%)	3/16 (18.8%)	RR 0.11 (0.01 to 1.91)	167 fewer per 1000 (from 186 fewer to 171 more)	⨁⨀⨀⨀ VERY LOW	CRITICAL

CI: confidence interval; CFC: clotting factor concentrate; RR: risk ratio; TXA: tranexamic acid
1 The study did not control for any confounders in the analysis
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds
3 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold

Table 22: Clinical evidence table for any haemostatic therapy versus no haemostatic therapy in women with von Willebrand disease, outcomes for the women

Quality assessment							Number of women		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haemostatic therapy	No haemostatic therapy	Relative (95% CI)	Absolute		
Primary postpartum haemorrage												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16/43 (37.2%)	7/16 (43.8%)	RR 0.85 (0.43 to 1.68)	66 fewer per 1000 (from 249 fewer to 297 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Severe primary postpartum haemorrage (>1000 ml)												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7/43 (16.3%)	5/16 (31.3%)	RR 0.52 (0.19 to 1.41)	150 fewer per 1000 (from 253 fewer to 128 more)	⨁⊖⊖⊖ VERY LOW	CRITICAL
Secondary postpartum haemorrage												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2/43 (4.7%)	5/16 (31.3%)	RR 0.15 (0.03	266 fewer per 1000	⨁⊖⊖⊖	CRITICAL

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haemostatic therapy	No haemostatic therapy	Relative (95% CI)	Absolute	**Quality**	**Importance**
									to 0.69)	(from 97 fewer to 303 fewer)	VERY LOW	
Blood transfusion required												
1 (Govorov 2016)	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	0/43 (0%)	3/16 (18.8%)	RR 0.06 (0 to 1.01)	176 fewer per 1000 (from 188 fewer to 2 more)	⨁⨀⨀⊖ VERY LOW	CRITICAL

1 *CI: confidence interval; RR: risk ratio*
2 *1 The study did not control for any confounders in the analysis*
3 *2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds*
4 *3 The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold*

Appendix H – Economic evidence study selection

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – third stage of labour

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix I – Economic evidence tables

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – third stage of labour

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix J – Health economic evidence profiles

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – third stage of labour

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix K – Health economic analysis

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Intrapartum care for women with haemostatic disorders – third stage of labour

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix L – Research recommendations

Intrapartum care for women with haemostatic disorders – regional anaesthesia and analgesia

In women with thrombocytopenia, does the use of an additional assessment of bleeding risk allow the safe use of neuraxial anaesthesia?

Why this is important

During pregnancy the maternal platelet count falls gradually to a lower limit of around 100 x 10^9/l. Some women have gestational thrombocytopenia or platelet disorders that drive the platelet count down even further. There is a perception that somewhere between a platelet count of between 50 and 80 x 10^9/l it becomes unsafe to offer intrapartum neuraxial anaesthesia or analgesia. In general, anaesthetists make decisions about the safety of neuraxial anaesthesia/analgesia based upon personal experience or local guidance. As a consequence, many women are denied childbirth with neuraxial anaesthesia/analgesia and undergo caesarean section with a potentially unnecessary general anaesthetic.

A platelet count alone is not the only measure of maternal bleeding risk. Coagulation and bleeding risk is influenced by multiple factors, including platelet function. It is unknown how to

best assess the bleeding risk in women with low platelet count, or if there is a platelet count in pregnancy below which neuraxial anaesthesia/analgesia should be avoided.

Evidence is needed to guide anaesthetists, haematologists, obstetricians and pregnant women to make safe choices about intrapartum anaesthesia/analgesia for women with low platelet counts. This study would aim to determine if an additional assessment of bleeding risk (for example thromboelastogram) can help to determine if neuraxial anaesthesia in the intrapartum period is safe for women with thrombocytopenia.

Research recommendation rationale

Research question	What level of platelet count and/or platelet function is safe for neuraxial anaesthesia/analgesia?
Importance to 'patients' or the population	Withholding neuraxial blockade from women with low platelet counts/ function results in them being denied the most effective form of analgesia for labour. Moreover if surgical intervention is required general anaesthesia is the only option, which is associated higher maternal mortality and morbidity. However women with a low platelet count are perceived to be at increased risk of bleeding associated with neuraxial techniques which can result in permanent paralysis and other significant neurologic sequelae.
Relevance to NICE guidance	Currently there is no evidence to base recommendations about what level of platelet count or function neuraxial anaesthesia or analgesia should be avoided. At present, individual decisions have to be taken about the potential use of neuraxial blockade in every case. The consequences of withholding neuraxial techniques and of employing them inappropriately are both very serious.
Relevance to NHS	Minimising harm and maximising positive outcomes including maternal satisfaction and ability to bond with their offspring is important to the NHS
National priorities	An evidence based recommendation on this critical issue supports NHSE aim to reduce maternal morbidity and mortality
Current evidence base	Limited to a few heterogeneous case series. UKOSS includes data collection on the incidence of neuraxial haematoma to understand the extent of the problem.
Equalities	N/A

N/A: not applicable; NHSE: National Health Service England; UKOSS: UK Obstetric Surveillance System

Research recommendation PICO

Criterion	Explanation
Population	Women with a platelet count <80 x 10^9/l requiring intrapartum anaesthesia
Intervention	Use of test of bleeding risk such as thromboelastogram (TEG) to determine whether to use neuraxial anaesthesia or general anaesthesia
Comparator	General anaesthesia
Outcomes	• Need for neurosurgical intervention • Permanent/long-term neurological sequelae • Other complications
Study design	RCT
Timeframe	Intrapartum period and up to 6 months postpartum

RCT: randomised controlled trial; TEG: thromboelastogram

Intrapartum care for women with haemostatic disorders – modification of birth plan according to platelet count or function

No research recommendations were made for this review question.

Intrapartum care for women with haemostatic disorders – third stage of labour

No research recommendations were made for this review question.