National Institute for Health and Care Excellence

FINAL

Antenatal care

[V] Management of unexplained vaginal bleeding in pregnancy

NICE guideline NG201

Evidence reviews underpinning recommendations 1.4.16 to 1.4.21

August 2021

Final

These evidence reviews were developed by the National Guideline Alliance, which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Management of unexplained vaginal bleeding in pregnancy

Review question

What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Introduction

Some women may experience unexplained vaginal bleeding during pregnancy. For some women an initial bleed can lead to more severe bleeding which could lead to adverse outcomes. It is therefore important that women are treated appropriately when presenting with unexplained vaginal bleeding. The aim of this review is to find out which interventions are the most effective in managing unexplained vaginal bleeding during pregnancy.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Pregnant women with unexplained vaginal bleeding in second or third trimester

Intervention	• Departmental or formal ultrasound scan
	• Hospitalisation
	• Non-prophylactic anti-D immunoglobulin treatment
	• Steroids
	  ○ Betamethasone
	  ○ Dexamethasone
	  ○ Betamethasone + dexamethasone

Comparison	• Listed intervention versus no intervention • Listed intervention versus placebo (for anti-D immunoglobulin treatment or steroid comparisons)
Outcomes	**Critical** • Bleeding/haemorrhage after treatment (either ≥1000 ml loss or requiring a blood transfusion) • Birth within a week of receiving intervention • Fetal death from 16 weeks of gestational age (including termination of pregnancy) • Infant death up to 1-year chronological age **Important** • Admission to intensive care unit for treatment of unexplained vaginal bleeding • Duration of hospitalisation for treatment of unexplained vaginal bleeding • Women's experience and/or satisfaction of care (include feeling of reassurance related to treatment) during or at end of treatment for unexplained vaginal bleeding • Small for gestational age

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

One retrospective cohort study was included in this review (Ogueh 1998). This study was conducted in a UK hospital and compared pregnant women who were hospitalised for the management of unexplained vaginal bleeding to those who were not (who were discharged on the day of presentation). The included study is summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Ogueh 1998 Retrospective cohort study UK	Pregnant women with mild antepartum haemorrhage of unknown origin N=78	Hospitalisation Women were hospitalised as appropriate on day of hospital presentation.	No hospitalisation Women were discharged from hospital.	**Critical** • Fetal death from 16 weeks of gestational age

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of clinical outcomes included in the evidence review

See the evidence profiles appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

There was no economic evidence identified for this review question and therefore there is no excluded studies list in appendix K.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Hospitalisation versus no hospitalisation

Critical outcomes

Bleeding/haemorrhage after treatment

No evidence was identified to inform this outcome.

Birth within a week of receiving intervention

No evidence was identified to inform this outcome.

Fetal death from 16 weeks of gestational age

- Very low quality evidence from 1 retrospective cohort (N=78) showed that there is no statistically significant difference between women with unexplained vaginal bleeding who were hospitalised or who were discharged from hospital on fetal deaths: RD 0 (95% CI -0.06 to 0.06) p=1.00

Infant death up to 1-year chronological age

No evidence was identified to inform this outcome.

Important outcomes

Admission to intensive care unit for treatment of unexplained vaginal bleeding

No evidence was identified to inform this outcome.

Duration of hospitalisation for treatment of unexplained vaginal bleeding

No evidence was identified to inform this outcome.

Women's experience and/or satisfaction of care

No evidence was identified to inform this outcome.

Small for gestational age

No evidence was identified to inform this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Bleeding or haemorrhage after intervention was considered as a critical outcome for the woman because this indicates the ineffectiveness of management of unexplained vaginal bleeding. Delivery within a week of receiving intervention was also regarded as a critical outcome for the woman as uncontrolled vaginal bleeding during pregnancy can require urgent delivery of the baby. Fetal and infant death were considered critical outcomes for this review as a failure to treat vaginal bleeding can be fatal for the baby. For the woman, admission to intensive care unit or duration of hospitalisation for treatment of unexplained vaginal bleeding was considered to be important as this reflects severity of antenatal bleeding. Women's experience and satisfaction of care was also an important outcome. Small for gestational age was also considered an important outcome as vaginal bleeding may affect utero-placental blood flow and restrict fetal growth.

The quality of the evidence

There was 1 retrospective cohort study identified for the review on the effectiveness of hospitalisation amongst pregnant women with unexplained vaginal bleeding. The quality of the evidence was very low. This was mainly due to a serious risk of bias as there was no adjustment for confounding factors and a significant amount of missing data (~20%); imprecision around the estimate of effect and issues around indirectness, as the study did not specify whether the women were in the second or third trimester, as specified in the protocol.

No evidence was identified for the following outcomes: bleeding/haemorrhage after treatment, birth within a week of receiving intervention, infant death of up to 1-year, admission to intensive care unit for the treatment of unexplained vaginal bleeding, duration of hospitalisation for the treatment of unexplained vaginal bleeding, women's experience or satisfaction of care, or small for gestational age.

There was no evidence identified for the interventions: departmental or formal ultrasound scan, non-prophylactic anti-D immunoglobulin or steroids.

Benefits and harms

Non-prophylactic anti-D

Vaginal bleeding may indicate that there is bleeding occurring from fetus to mother, which can lead to a significant sensitisation event. No evidence was identified on the effectiveness of non-prophylactic anti-D immunoglobulin, meaning use of anti-D immunoglobulin as treatment when there is vaginal bleeding. It is current practice to offer anti-D immunoglobulin for rhesus D negative women who present with vaginal bleeding. In the absence of evidence, the committee agreed by informal consensus not to change current practice and recommended that women who are rhesus D negative and at risk of isoimmunisation who present with vaginal bleeding after 13 weeks of pregnancy should be offered anti-D immunoglobulin. The NICE technology appraisal on routine antenatal anti-D prophylaxis for women who are rhesus D negative (TA 156) covers the prophylactic use of anti-D immunoglobulin for all pregnant women who are rhesus D negative.

Referral and hospitalisation

The committee agreed via informal consensus that women who present in primary care with unexplained vaginal bleeding after 13 weeks should be referred to secondary care for review.

In relation to whether or not women with unexplained vaginal bleeding should be admitted to inpatient care, only 1 retrospective cohort study was identified which was relevant for this review but only reported on one relevant outcome. The study reported that there were no fetal deaths in either the women who were hospitalised or women who were discharged on the day of presentation. Given the limited and low quality evidence from a relatively old study with a small sample size, the committee based the recommendations on their knowledge and experience.

The committee agreed that hospitalisation for pregnant women at risk may be warranted as it enables maternal and fetal monitoring, administration of corticosteroids, and ensures proximity to the neonatal unit if needed. The committee made a recommendation to consider whether or not to hospitalise women with unexplained vaginal bleeding taking into account their risk of placental abruption, preterm delivery, the extent of the bleeding and their ability to attend secondary care in the case of emergency. These would be logistical/practical considerations that consider how quickly she's able to rush to the hospital in case she is not admitted and she starts bleeding more or otherwise there's an emergency, for example her proximity to the hospital, if she has a phone, car, a partner to bring her, childcare issues.

Given the lack of evidence on the benefits and harms of managing unexplained vaginal bleeding via hospitalisation, the committee agreed that a research recommendation on this topic was merited, particularly in the population of women where the clinical benefit of hospitalisation may be uncertain (in other words those with relatively mild bleeding). See appendix L for more details.

Ultrasound scan

The risk of bleeding is dependent on the site of the placenta with low lying placenta (placenta praevia) having an increased risk of bleeding. In order to start appropriate management, the location of the placental bleeding site needs to be known. Therefore, the committee recommended that an ultrasound scan should be conducted when the location of the placenta is not known.

Considering increased chance of preterm birth

Maternal blood loss can affect the growth of the fetus. The committee recommended by informal consensus, that corticosteroid administration, which promotes fetal maturity, should be considered as appropriate for all pregnant women who are hospitalised for unexplained vaginal bleeding and who are deemed to be at risk of preterm birth within 48 hours, in line with the recommendations in section 1.9 of the NICE guideline on preterm birth and delivery (NG25).

The committee also agreed that discussion about the potential increased risk of preterm birth may be useful with women with unexplained vaginal bleeding.

Cost effectiveness and resource use

No economic evidence was identified which was relevant to this review question.

These recommendations reflect current practice and will not lead to any change in resource use.

References

Ogueh 1998

Ogueh, O., Johnson, M. R., What is the value of hospitalisation in antepartum haemorrhage of uncertain origin?, Journal of Obstetrics & Gynaecology, 18, 120-2, 1998

Appendices

Appendix A – Review protocols

Review protocol for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Review question	What interventions are effective in managing unexplained vaginal bleeding during pregnancy? Note: the safety of pharmacological interventions to treat unexplained vaginal bleeding during pregnancy will not be covered in this review. For information on the safety of any pharmacological interventions, please consult the BNF/MHRA.
Type of review question	Intervention
Objective of the review	The aim of this review is to evaluate the outcomes of different interventions among women with unexplained vaginal bleeding during the second and third trimester and to establish whether there are any harms to the women or baby associated with them.
Eligibility criteria – population	Pregnant women with unexplained vaginal bleeding in second or third trimester. Note: • Studies may refer to 'minor antepartum haemorrhage', which is defined as bleeding from the genital tract after the 20th week of pregnancy and before the onset of labour. • 'Second trimester' defined as: 13 weeks + 0 days to 26 weeks + 6 days. • 'Third trimester' defined as: 27 weeks + 0 days onwards.

Eligibility criteria – intervention(s)	• Departmental or formal ultrasound scan (Note: bedside ultrasound scans will not be included).
	• Hospitalisation
	• Non-prophylactic anti-D immunoglobulin treatment
	• Steroids
	  ○ Betamethasone
	  ○ Dexamethasone
	  ○ Betamethasone + dexamethasone
	Note: Data for all listed steroids will be pooled and analysed together.

Eligibility criteria – comparator(s)	• Listed intervention vs no intervention • Listed intervention vs placebo (for anti-D immunoglobulin treatment or steroid comparisons)
Outcomes and prioritisation	**Critical** • Bleeding/haemorrhage after treatment (either ≥1000 ml loss or requiring a blood transfusion) • Birth within a week of receiving intervention

Field (based on PRISMA-P)	Content
	• Fetal death from 16 weeks of gestational age (including termination of pregnancy) • Infant death up to 1-year chronological age **Important** • Admission to intensive care unit for treatment of unexplained vaginal bleeding • Duration of hospitalisation for treatment of unexplained vaginal bleeding • Women's experience and/or satisfaction of care (include feeling of reassurance related to treatment) during or at end of treatment for unexplained vaginal bleeding • Small for gestational age (SGA) Note: SGA is defined as having a birth weight below the 10th centile. Some studies will report this as low birth weight adjusted for gestational age rather than as SGA.
Eligibility criteria – study design	INCLUDE: • Systematic reviews • Randomised or quasi-randomised controlled trials If no evidence of these types is found for a listed class of intervention, the following types of non-randomised studies in order of priority will be considered: • Non-randomised controlled trials • Prospective cohort studies • Retrospective cohort studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other - exclusion criteria	**Exclusion** POPULATION: • Multiple pregnancy • Pregnancy with congenital anomalies • Current diagnosis of placenta praevia STUDY DESIGN: • Case-control studies • Cross-over studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies LANGUAGE: • Non-English YEAR OF PUBLICATION: • This is a new review so there is no date restriction PUBLICATION STATUS: • Conference abstract **Inclusion**

Field (based on PRISMA-P)	Content
	COUNTRY: • No restriction
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroup analysis will be conducted according to trimester in which bleeding occurs and according to World Bank status (High-income countries; Low and middle-income countries) will be conducted (see https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups for classification of countries). Note that the use of the World Bank definitions of low-, middle- and high-income countries in this guideline is consistent with its use in the Postnatal care up to 8 weeks after birth (update) NICE guideline CG37. In the presence of heterogeneity, the following subgroup analyses will be conducted: • Recurrence of bleeding (Recurrence; No recurrence) • Type of steroid These subgroup factors will be used as confounding factors to assess risk of bias of any included cohort studies using the relevant checklist. Other confounding factors that will be considered in the risk of bias evaluation when including cohort studies are: • Age • Parity status • Substance misuse during pregnancy Statistical heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value≥50% indicating serious heterogeneity, and ≥80% indicating very serious heterogeneity).
Selection process – duplicate screening/selection/analysis	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 above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Data management (software)	NGA STAR software will be used to generate bibliographies/citations, and conduct study sifting and data extraction. Pairwise meta-analyses, if possible, will be conducted using Cochrane Review Manager (RevMan5). For details please see the Supplement 1: methods. 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (date, study design): • Date limit: none • Apply standard animal/non-English language exclusion; • Limit to RCTs and systematic reviews in first instance but download all results.
Identify if an update	This antenatal care update will replace the 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62), which will be withdrawn in due course. The 2008 NICE guideline on antenatal care for uncomplicated pregnancies (CG62) did not specifically cover unexplained vaginal bleeding and therefore there are no relevant recommendations to be updated.
Author contacts	Developer: National Guideline Alliance.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B of this report.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables) of this report.

Field (based on PRISMA-P)	Content
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables) of this report.
Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs or quasi-RCTs • ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for analysis – combining studies and exploring (in)consistency	For details please see the Supplement 1: methods.
Meta-bias assessment – publication bias, selective reporting bias	For details please see the Supplement 1: methods and section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – Current management	For details please see the introduction to the evidence review of this report.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Kate Harding in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the Supplement 1: methods.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	This protocol is not registered with PROSPERO.

BNF: British National Formulary; CCTR: Cochrane Controlled Trials Register; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MHRA: Medicines and Healthcare products Regulatory Agency; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; OECD:

Organisation for Economic Co-operation and Development; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk Of Bias In Systematic reviews tool; ROBINS-I: Risk Of Bias In Non-randomized studies – of Interventions tool; SGA: small for gestational age.

Appendix B – Literature search strategies

Literature search strategies for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Database(s): Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2020 September 04, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to September 04, 2020
Date of last search: 7th September 2020
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Pregnancy/ use ppez
2	Pregnant Women/ use ppez
3	pregnancy/ use emczd
4	pregnant woman/ use emczd
5	pregnan$.tw,kw.
6	1 or 2 or 3 or 4 or 5
7	Uterine Hemorrhage/ use ppez
8	uterus bleeding/ use emczd
9	antepartum hemorrhage/ use emczd
10	vagina bleeding/ use emczd
11	(antepart$ adj3 h?emorrhag$).tw.
12	((vagina$ or unexplain$ or trimester or pregnan$ or antenatal$ or ante-natal$ or prenatal$ or pre-natal$) adj3 bleed$).tw.
13	7 or 8 or 9 or 10 or 11 or 12
14	exp Hospitalization/ use ppez
15	exp hospitalization/ use emczd
16	hospitali?ation$.tw.
17	(hospital$ adj (stay$ or admission$)).tw.
18	((inpatient or outpatient or expectant) adj management).tw.
19	Rh-Hr Blood-Group System/ use ppez
20	Rh Isoimmunization/ use ppez
21	"Rho(D) Immune Globulin"/ use ppez
22	(blood group rhesus system/ or blood group, Rh/) use emczd
23	(Rh Isoimmunization/ or rhesus isoimmunization/ or rhesus immunization/) use emczd
24	(rhesus D antibody/ or rhesus antibody/ or rhesus antigen/) use emczd
25	((Rhesus$ or Rh$) adj3 (antibod$ or anti-bod$ or prophylax$ or immunoprophylax$ or isoimmuni?ation or immuni?ation or sensiti?ation)).tw.
26	(anti-D adj3 (antibod$ or anti-bod$ or prophylax$ or immunoprophylax$ or isoimmuni?ation or immuni?ation or sensiti?ation or serum$)).tw.
27	((Rh$ or anti-D) adj immune$ globulin$).tw.
28	((Rh$ or anti-D) adj immunoglobulin$).tw.
29	RhIG$.tw.
30	(Rhesus$ adj (negativ$ or factor$ or status$)).tw.
31	(Rh adj (factor$ or status$)).tw.
32	(Rh$ adj negativ$).tw.
33	exp Dexamethasone/ use ppez
34	exp dexamethasone derivative/ use emczd
35	exp Betamethasone/ use ppez
36	exp betamethasone derivative/ use emczd
37	(dexamethason$ or betamethason$).tw.
38	((f?etal$ or antenatal or prenatal) adj (steroid$ or corticosteroid$ or cortico-steroid$)).tw.
39	exp Ultrasonography/ use ppez
40	exp echography/ use emczd
41	(ultrasound$ or ultrasonograph$ or sonogra$ or endosonogra$ or doppler$).mp.
42	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	6 and 13 and 42
44	limit 43 to english language
45	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.

#	Searches
46	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
47	meta-analysis/
48	meta-analysis as topic/
49	systematic review/
50	meta-analysis/
51	(meta analy* or metanaly* or metaanaly*).ti,ab.
52	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
53	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
54	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
55	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
56	(search* adj4 literature).ab.
57	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
58	cochrane.jw.
59	((pool* or combined) adj2 (data or trials or studies or results)).ab.
60	letter/
61	editorial/
62	news/
63	exp historical article/
64	Anecdotes as Topic/
65	comment/
66	case report/
67	(letter or comment*).ti.
68	60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69	randomized controlled trial/ or random*.ti,ab.
70	68 not 69
71	animals/ not humans/
72	exp Animals, Laboratory/
73	exp Animal Experimentation/
74	exp Models, Animal/
75	exp Rodentia/
76	(rat or rats or mouse or mice).ti.
77	70 or 71 or 72 or 73 or 74 or 75 or 76
78	letter.pt. or letter/
79	note.pt.
80	editorial.pt.
81	case report/ or case study/
82	(letter or comment*).ti.
83	78 or 79 or 80 or 81 or 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/
91	exp Rodent/
92	(rat or rats or mouse or mice).ti.
93	85 or 86 or 87 or 88 or 89 or 90 or 91 or 92
94	77 use ppez
95	93 use emczd
96	94 or 95
97	45 use ppez
98	46 use emczd
99	97 or 98
100	(or/47-48,51,53-58) use ppez
101	(or/49-52,54-59) use emczd
102	100 or 101
103	(antepart$ adj3 h?emorrhag$).m_titl.
104	limit 103 to english language
105	44 or 104
106	96 and 105
107	105 not 106
108	99 or 102
109	107 and 108 [RCT/SR data]
110	107 not 109 [Non-RCT/SR data]

Database(s): Cochrane Library
Last searched on **Cochrane Database of Systematic Reviews**, Issue 9 of 12, September 2020, **Cochrane Central Register of Controlled Trials**, Issue 9 of 12, September 2020
Date of last search: 7th September 2020

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Pregnant Women] this term only
#3	(pregnan*):ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Uterine Hemorrhage] this term only
#6	((antepart* NEAR/3 (haemorrhag* or hemorrhag*))):ti,ab,kw
#7	(((vagina* or unexplain* or trimester or pregnan* or antenatal* or ante-natal* or prenatal* or pre-natal*) NEAR/3 bleed*)):ti,ab,kw
#8	#5 or #6 or #7
#9	#4 AND #8
#10	MeSH descriptor: [Hospitalization] explode all trees
#11	(((hospitali?ation*))):ti,ab,kw
#12	((hospital* NEXT (stay* or admission*))):ti,ab,kw
#13	(((inpatient or outpatient or expectant) NEXT management)):ti,ab,kw
#14	MeSH descriptor: [Rh-Hr Blood-Group System] this term only
#15	MeSH descriptor: [Rh Isoimmunization] this term only
#16	MeSH descriptor: [Rho(D) Immune Globulin] this term only
#17	((((Rhesus* or Rh*) NEAR/3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmunisation or immunisation or sensitisation or isoimmunization or immunization or sensitization)))):ti,ab,kw
#18	(((((anti-D) NEAR/3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmunisation or immunisation or sensitisation or isoimmunization or immunization or sensitization or serum*))))):ti,ab,kw
#19	((((Rh* or anti-D) NEXT immune* globulin*))):ti,ab,kw
#20	((((Rh* or anti-D) NEXT immunoglobulin*))):ti,ab,kw
#21	((RhIG*)):ti,ab,kw
#22	(((Rhesus* NEXT (negativ* or factor* or status*)))):ti,ab,kw
#23	(((Rh NEXT (factor* or status*)))):ti,ab,kw
#24	(((Rh* NEXT negativ*))):ti,ab,kw
#25	MeSH descriptor: [Dexamethasone] explode all trees
#26	MeSH descriptor: [Betamethasone] explode all trees
#27	((dexamethason* or betamethason*)):ti,ab,kw
#28	(((fetal$ or foetal$ or antenatal or prenatal) NEXT (steroid* or corticosteroid* or cortico-steroid*))):ti,ab,kw
#29	MeSH descriptor: [Ultrasonography] explode all trees
#30	((ultrasound* or ultrasonograph* or sonogra* or endosonogra* or doppler*)):ti,ab,kw
#31	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	#9 AND #31
#33	(((antepart* NEAR/3 (haemorrhag* or hemorrhag*)))):ti
#34	#32 OR #33

Database(s): CRD: Database of Abstracts of Reviews of Effects (DARE), HTA Database
Date of last search: 7th September 2020

#	Searches
1	MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES IN DARE,HTA
2	MeSH DESCRIPTOR Pregnant Women EXPLODE ALL TREES IN DARE,HTA
3	(pregnan*) IN DARE, HTA
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Uterine Hemorrhage EXPLODE ALL TREES IN DARE,HTA
6	(((antepart* NEAR (haemorrhag* or hemorrhag*)))) IN DARE, HTA
7	((((vagina* or unexplain* or trimester or pregnan* or antenatal* or ante-natal* or prenatal* or pre-natal*) NEAR bleed*))) IN DARE, HTA
8	#5 OR #6 OR #7
9	#4 AND #8
10	MeSH DESCRIPTOR Hospitalization EXPLODE ALL TREES IN DARE,HTA
11	((hospitalisation* or hospitalization*)) IN DARE, HTA
12	(hospital* stay*) IN DARE, HTA
13	(hospital* admission*) IN DARE, HTA
14	((((inpatient or outpatient or expectant) NEAR management))) IN DARE, HTA
15	MeSH DESCRIPTOR Rh-Hr Blood-Group System EXPLODE ALL TREES IN DARE,HTA
16	MeSH DESCRIPTOR Rh Isoimmunization EXPLODE ALL TREES IN DARE,HTA
17	MeSH DESCRIPTOR Rho(D) Immune Globulin EXPLODE ALL TREES IN DARE,HTA
18	(((((Rhesus* or Rh*) NEAR (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmunisation or immunisation or sensitisation or isoimmunization or immunization or sensitization))))) IN DARE, HTA

#	Searches
19	((((((anti-D) NEAR (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmunisation or immunisation or sensitisation or isoimmunization or immunization or sensitization or serum*)))))) IN DARE, HTA
20	(((((Rh* or anti-D) NEAR immune* globulin*)))) IN DARE, HTA
21	(((((Rh* or anti-D) NEAR immunoglobulin*)))) IN DARE, HTA
22	(((RhIG*))) IN DARE, HTA
23	((((Rhesus* NEAR (negativ* or factor* or status*)))))) IN DARE, HTA
24	((((Rh NEAR (factor* or status*)))))) IN DARE, HTA
25	((((Rh* NEAR negativ*)))) IN DARE, HTA
26	MeSH DESCRIPTOR Dexamethasone EXPLODE ALL TREES IN DARE,HTA
27	MeSH DESCRIPTOR Betamethasone EXPLODE ALL TREES IN DARE,HTA
28	(((dexamethason* or betamethason*))) IN DARE, HTA
29	((((fetal* or foetal* or antenatal or prenatal) NEAR (steroid* or corticosteroid* or cortico-steroid*)))) IN DARE, HTA
30	MeSH DESCRIPTOR Ultrasonography EXPLODE ALL TREES IN DARE,HTA
31	(((ultrasound* or ultrasonograph* or sonogra* or endosonogra* or doppler*))) IN DARE, HTA
32	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33	#9 AND #32
34	((antepart* NEAR (haemorrhag* or hemorrhag*))):TI IN DARE, HTA
35	#33 OR #34

Database(s): Cinahl Plus

Date of last search: 7th September 2020

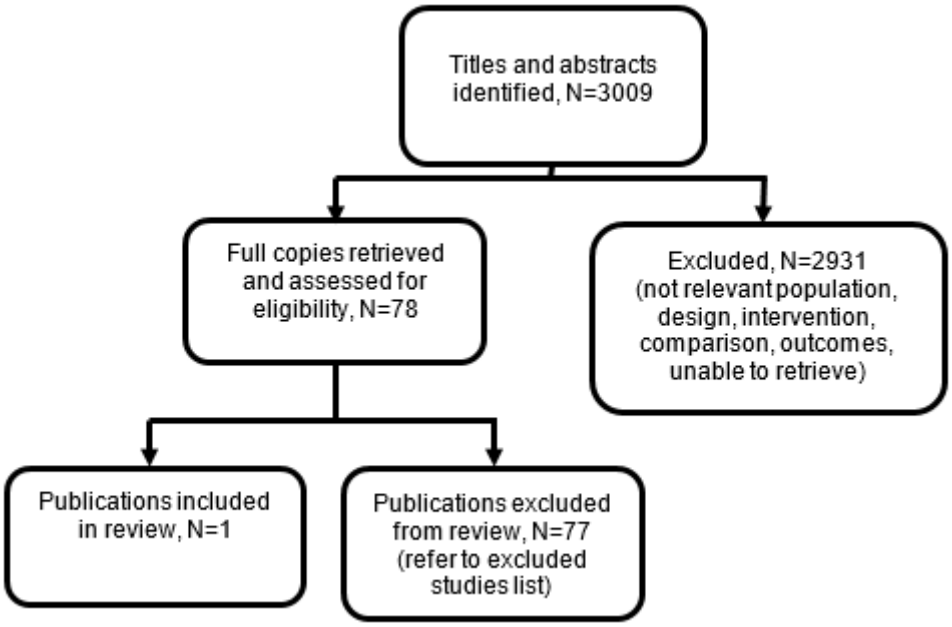
#	Searches
S39	S36 OR S38 Limiters - English Language
S38	S37 NOT S34
S37	TI (antepart* N3 h?emorrhag*)
S36	S33 NOT S34
S35	S33 NOT S34
S34	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S33	S4 AND S9 AND S31
S32	S4 AND S9 AND S31
S31	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
S30	TI (ultrasound* or ultrasonograph* or sonogra* or endosonogra* or doppler*) OR AB (ultrasound* or ultrasonograph* or sonogra* or endosonogra* or doppler*)
S29	(MH "Ultrasonography+")
S28	TI ((f?etal* or antenatal or prenatal) N1 (steroid* or corticosteroid* or cortico-steroid*)) OR AB ((f?etal* or antenatal or prenatal) N1 (steroid* or corticosteroid* or cortico-steroid*))
S27	TI (dexamethason* or betamethason*) OR AB (dexamethason* or betamethason*)
S26	(MH "Betamethasone")
S25	(MH "Dexamethasone")
S24	TI (Rh* N1 negativ*) OR AB (Rh* N1 negativ*)
S23	TI (Rh N1 (factor* or status*)) OR AB (Rh N1 (factor* or status*))
S22	TI (Rhesus* N1 (negativ* or factor* or status*)) OR AB (Rhesus* N1 (negativ* or factor* or status*))
S21	TI RhIG* OR AB RhIG*
S20	TI ((Rh* or anti-D) N1 immunoglobulin*) OR AB ((Rh* or anti-D) N1 immunoglobulin*)
S19	TI ((Rh* or anti-D) N1 immune* globulin*) OR AB ((Rh* or anti-D) N1 immune* globulin*)
S18	TI (anti-D N3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmuni?ation or immuni?ation or sensiti?ation or serum*)) OR AB (anti-D N3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmuni?ation or immuni?ation or sensiti?ation or serum*))
S17	TI ((Rhesus* or Rh*) N3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmuni?ation or immuni?ation or sensiti?ation)) OR AB ((Rhesus* or Rh*) N3 (antibod* or anti-bod* or prophylax* or immunoprophylax* or isoimmuni?ation or immuni?ation or sensiti?ation))
S16	(MH "Rho(D) Immune Globulin")
S15	(MH "RH Isoimmunization")
S14	(MH "Rh-Hr Blood-Group System")
S13	TI ((inpatient or outpatient or expectant) N1 management) OR AB ((inpatient or outpatient or expectant) N1 management)
S12	TI (hospital* N1 (stay* or admission*)) OR AB (hospital* N1 (stay* or admission*))
S11	TI hospitali?ation* OR AB hospitali?ation*
S10	(MH "Hospitalization+")
S9	S5 OR S6 OR S7 OR S8
S8	TI ((vagina* or unexplain* or trimester or pregnan* or antenatal* or ante-natal* or prenatal* or pre-natal*) N3 bleed*) OR AB ((vagina* or unexplain* or trimester or pregnan* or antenatal* or ante-natal* or prenatal* or pre-natal*) N3 bleed*)

#	Searches
S7	TI (antepart* N3 h?emorrhag*) OR AB (antepart* N3 h?emorrhag*)
S6	(MH "Metrorrhagia")
S5	(MH "Uterine Hemorrhage")
S4	S1 OR S2 OR S3
S3	TI pregnan* or AB pregnan*
S2	(MH "Expectant Mothers")
S1	(MH "Pregnancy")

Appendix C – Clinical evidence study selection

Clinical study selection for: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ogueh, O., Johnson, M. R., What is the value of hospitalisation in antepartum haemorrhage of uncertain origin?, Journal of Obstetrics & Gynaecology18, 120-2, 1998 **Ref Id** 939280 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** To evaluate the role of hospitalisation among women with antepartum haemorrhage of unknown origin	**Sample size** N=78 **Characteristics** Not reported **Inclusion criteria** • Women with antepartum haemorrhage identified from the databases during the defined study period • Antepartum haemorrhage of unknown origin was defined as antepartum haemorrhage in the absence of placenta praevia (diagnosed by ultrasound scan), placental abruption (diagnosed clinically, by ultrasound scan or at delivery) and local causes of haemorrhage in the lower genital tract (such as cervical polyp)	**Interventions** Intervention: Hospitalisation for unexplained vaginal bleeding, n=53 Control: No hospitalisation (Discharge on the day of presentation as appropriate), n=25	**Details** Cases identified from single hospital computer database.	**Results** *Fetal death* Intervention 0/53; Control 0/25	**Limitations** <u>Quality assessment using ROBINS-I</u> 1. Pre-intervention • Bias due to confounding i) Is there potential for confounding of the effect of intervention in this study? No information ii) Was the analysis based on splitting participants' follow up time according to intervention received? No information iii) Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? No information iv) Did the authors use an appropriate analysis method that controlled for all the important confounding domains? No v) Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? No information vi) Did the authors control for any post-intervention variables that could have been affected by the intervention? No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates February 1993 to December 1995 **Source of funding** Not reported	**Exclusion criteria** Not reported				vii) Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding? No information viii) Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study? No information Risk – High • Bias in selection of participants into the study i) Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? Yes ii)Were the post-intervention variables that influenced selection likely to be associated with intervention? Yes iii) Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? Yes iv) Do start of follow-up and start of intervention coincide for most participants? No information v) Were adjustment techniques used that are likely to correct for the presence of selection biases? No Risk - High 2. At intervention • Bias in classification of interventions i) Were intervention groups clearly defined? No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					ii) Was the information used to define intervention groups recorded at the start of the intervention? No information iii) Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? No Risk - Critical/No information 3. Post-intervention • Bias due to deviation from intended interventions i) Were there deviations from the intended intervention beyond what would be expected in usual practice? No information ii) Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome? Yes iii) Were important co-interventions balanced across intervention groups? No information iv) Was the intervention implemented successfully for most participants? No v) Did study participants adhere to the assigned intervention regimen? Probably yes vi) Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? No Risk – Critical • Bias due to missing data i) Were outcome data available for all or nearly all participants? Probably no ii) Were participants excluded due to missing data on intervention status?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Yes iii) Were participants excluded due to missing data on other variables needed for the analysis? No information vi) Are the proportion of participants and reasons for missing data similar across interventions? Not applicable v) Is there evidence that results were robust to the presence of missing data? No Risk – Critical • Bias in measurement of outcomes i) Could the outcome measure have been influenced by knowledge of the intervention received? Probably no ii) Were outcomes assessors aware of the intervention received by study participants? Probably yes iii) Were the methods of outcome assessment comparable across intervention groups? No information iv) Were any systematic errors in measurement of the outcome related to intervention received? No information Risk – High • Bias in selection of the reported result Is the reported effect estimate likely to be selected on the basis of results from i) multiple outcome measurement within the outcome domain? No information ii) multiple analyses of the intervention-outcome relationship? No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					iii) different subgroups? No information Risk - No information **Other information** There were a total of 175 women with antepartum haemorrhage in cohort (126 with antepartum haemorrhage of unknown origin, 26 with placenta praevia, 22 with placental abruption, 1 with cervical polyp). However, data for hospitalisation and no hospitalisation cohorts were only available for 78 women.

ROBINS-I: Risk Of Bias In Non-randomized studies – of Interventions tool

Appendix E – Forest plots

Forest plots for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Appendix F – GRADE tables

GRADE tables for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Table 5: Clinical evidence profile for hospitalisation versus no hospitalisation for pregnant women with unexplained vaginal bleeding:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hospitalisation	No hospitalisation	Relative (95% CI)	Absolute		
Fetal mortality												
1 (Ogueh 1998)	Retrospective cohort	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/53 (0%)	0/25 (0%)	RD 0 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL

CI: confidence interval; RD: risk difference
[1]Evidence downgraded by 2 levels as no information on confounders and no adjusted analysis.
[2] Evidence downgraded by 1 level and there is no information provided as to whether women were in the 2nd or 3rd trimester, as specified in the protocol.
[3] Evidence downgraded by 2 levels due to very serious imprecision surrounding small sample size.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Clinical studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Ahmadi, F., Akhbari, F., Indication of first trimester sonongraphy, International Journal of Fertility and Sterility, 1), 139, 2013	Review
Ahmadi, F., Javam, M., First trimester complications & emergencies: Differential diagnosis by transvaginal ultrasound, Journal of Obstetrics and Gynaecology Research, 1), 97, 2015	Conference abstract publication only
Ajayio, R. A., Soothill, P. W., Campbells,, Nicolaides, K. H., Antenatal testing to predict outcome in pregnancies with unexplained antepartum haemorrhage, British Journal of Obstetrics and Gynaecology, 99, 122-125, 1992	Comparison outside of interest: all women with unexplained vaginal bleeding received Doppler ultrasound scan and the results were compared across different resistance index of uterine artery flow.
Al-Ma'ani, W., Solomayer, E. F., Hammadeh, M., Expectant versus surgical management of first-trimester miscarriage: A randomised controlled study, Archives of gynecology and obstetrics, 289, 1011-1015, 2014	Intervention outside of interest: surgical evacuation versus expectant management of retained products of conception
Aoki, S., Inagaki, M., Kurasawa, K., Okuda, M., Takahashi, T., Hirahara, F., Retrospective study of pregnant women placed under expectant management for persistent hemorrhage, Archives of Gynecology & ObstetricsArch Gynecol Obstet, 289, 307-11, 2014	Comparison outside of interest: pregnancy outcomes between persistent subchorionic haematoma versus chorionic abruption
Aziz,S., Cho,R.C., Baker,D.B., Chhor,C., Filly,R.A., "Empty" sac in pregnant women with bleeding: are measurements answering the right question?, Journal of Clinical Ultrasound, 37, 249-252, 2009	Descriptive study
Beals, T., Naraghi, L., Schafer, J., Balk, D., Lee, C., Hoffmann, B., Bedside pelvic ultrasound decreases length of stay in the emergency department, Academic Emergency Medicine, 25 (Supplement 1), S31, 2018	Conference abstract
Ben-Haroush,A., Yogev,Y., Mashiach,R., Meizner,I., Pregnancy outcome of threatened abortion with subchorionic hematoma: possible benefit of bed-rest?, Israel Medical Association Journal: Imaj, 5, 422-424, 2003	Intervention outside of interest: bed-rest versus usual activity (working)
Braun, T., Sloboda, D. M., Tutschek, B., Harder, T., Challis, J. R., Dudenhausen, J. W., Plagemann, A., Henrich, W., Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration, International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 130, 64-9, 2015	Population outside of interest: pregnant women with preterm labour
Braun, T., Weichert, A., Gil, H. C., Sloboda, D. M., Tutschek, B., Harder, T., Dudenhausen, J. W., Plagemann, A., Henrich, W., Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration in twin pregnancies,	Population outside of interest: twin pregnancy at risk of preterm birth

International Journal of Gynaecology & ObstetricsInt J Gynaecol Obstet, 134, 329-35, 2016	
Cetin,A., Cetin,M., Diagnostic and therapeutic decision-making with transvaginal sonography for first trimester spontaneous abortion, clinically thought to be incomplete or complete, Contraception, 57, 393-397, 1998	Comparison outside of interest: groups were formed by contents left in the uterine cavity after abortion
Coleman, G., Venables, H., Is ultrasound screening for vasa praevia clinically justified and a financially viable screening test? A literature review, Ultrasound, 26, 6-15, 2018	Unavailable
Davidson, C., Monga, M., Ellison, D., Vidaeff, A., Continuation of pregnancy after antenatal corticosteroid administration: Opportunity for rescue?, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 55, 14-18, 2010	All women with antenatal bleeding received antenatal corticosteroid and the study examined the risk of having preterm birth (<34 weeks) among these women
De Silva, D., Lisonkova, S., Von Dadelszen, P., Synnes, A., Magee, L., Can we predict preterm delivery in a high-risk obstetric population? Results from a clinical prediction model based on admission characteristics, Journal of Perinatal Medicine. Conference: 12th World Congress of Perinatal Medicine, 43, 2015	Conference abstract publication only
Dickey,R.P., Olar,T.T., Curole,D.N., Taylor,S.N., Matulich,E.M., Relationship of first-trimester subchorionic bleeding detected by color Doppler ultrasound to subchorionic fluid, clinical bleeding, and pregnancy outcome, Obstetrics and Gynecology, 80, 415-420, 1992	Comparison outside of interest: outcomes were not compared between with and without ultrasound
Dong, A., McLeod, S. L., Thompson, D., Roebotham, R. W., Emergency department point-of-care ultrasound in symptomatic early trimester patients: A description of practice management patterns, Canadian Journal of Emergency Medicine, 17 (Supplement 2), S38, 2015	Conference abstract
Drassinower, D., Ananth, C., Gyamfi-Bannerman, C., Obican, S., Levin, H., Vink, J., Does vaginal bleeding increase the risk of developing a short cervix?, American Journal of Obstetrics and Gynecology, 1), S235, 2015	Conference abstract publication only
Drumm, J. E., Clinch, J., Ultrasound in management of clinically diagnosed threatened abortion, British Medical Journal, 2, 424, 1975	Descriptive study: all women received ultrasound
Durham,B., Lane,B., Burbridge,L., Balasubramaniam,S., Mateer,J., Pelvic ultrasound performed by emergency physicians for the detection of ectopic pregnancy in complicated first-trimester pregnancies, Annals of Emergency Medicine, 29, 338-347, 1997	Diagnostic study
Eaton, J. L., Zhang, X., Kazer, R. R., First-trimester bleeding and twin pregnancy outcomes following in vitro fertilization (IVF), Reproductive Sciences, 1), 235A, 2014	Descriptive study: all women received ultrasound scan
Elshami, M., Alaloul, E., Elshami, A., Bottcher, B., The management of antepartum haemorrhage at Al-Helal Al-Emirati Hospital in Gaza Strip: A clinical audit, BJOG: An International Journal of Obstetrics and Gynaecology, 124 (Supplement 1), 131, 2017	Conference abstract publication only
Farine, D., Fox, H. E., Jakobson, S., Timor-Tritsch, I. E., Vaginal ultrasound for diagnosis of placenta previa, American Journal of Obstetrics and Gynecology, 159, 566-569, 1988	Comparison outside of interest: the study compared between transabdominal and transvaginal ultrasound scan among women with vaginal bleeding

Fishman, S., Maheshwari, B., Chasen, S., Factors associated with emergent delivery in women with placenta previa and strong suspicion for placenta accreta, American Journal of Obstetrics and Gynecology, 1), S65, 2009	Conference abstract publication only
French, S., Henry, T., Williams, E. W., Evaluation of waiting times and sonographic findings in patients with first trimester vaginal bleeding at the University Hospital of the West Indies. Can Emergency Department sonography make a difference?, West Indian Medical Journal, 6), 65, 2012	Descriptive study: all women received ultrasound scan
Gelber, S., Jong, K., Chasen, S., Risk factors for subchorionic hematoma and poor pregnancy outcome, American Journal of Obstetrics and Gynecology, 1), S70-S71, 2009	Conference abstract publication only
Geyer, B. C., Stone, M. B., Adduci, A. J., Sodickson, A. D., Raja, A. S., Overuse of laboratory testing in symptomatic first trimester pregnant patients in the emergency department, Annals of Emergency Medicine, 62, S85-S86, 2013	Conference abstract publication only
Geyman,J.P., Expectant, medical, or surgical treatment of spontaneous abortion in first trimester of pregnancy? A pooled quantitative literature evaluation, Journal of the American Board of Family Practice, 12, 55-64, 1999	Interventions outside of interest: surgical or medical (progesterone) or expectant management of retained products of placenta
Gouhar, G. K., Sadek, S. M., Siam, S., Ahmad, R. A., Role of transperineal sonography in diagnosis of placenta previa/accreta: a prospective study, Egyptian journal of radiology and nuclear medicine, 43, 637â□□645, 2012	Population outside of interest: women diagnosed with placental previa by different ultrasound techniques
Hannafin, B., Lovecchio, F., Blackburn, P., Do Rh-negative women with first trimester spontaneous abortions need Rh immune globulin?, American Journal of Emergency Medicine, 24, 487-489, 2006	Intervention outside of interest: prophylactic Rh-negative treatment
Heaman, M., Gupton, A., Perceptions of bed rest by women with high-risk pregnancies: a comparison between home and hospital, Birth: Issues in Perinatal Care, 25, 252-258, 1998	Population outside of interest: high-risk women were those who need bed rest
Hoe, E., Varner, C., Ivankovic, M., Excluding ectopic pregnancy in patients presenting to a community emergency department with first trimester bleeding, Canadian Journal of Emergency Medicine, 20 (Supplement 1), S81-S82, 2018	Conference abstract publication only
Holland, M. G., Blackwell, S. C., Time to delivery and antenatal corticosteroid therapy in women presenting with threatened preterm birth < 24 weeks gestation, Reproductive Sciences, 1), 307A, 2011	Conference abstract publication only
Hussain, S., Aqeel, S., Moiz, B., Reproductive health in females with inherited bleeding disorder, Haemophilia, 22 (Supplement 4), 137, 2016	Conference abstract publication only
Kabiri, D., Safrai, M., Wattad, H., Lipschuetz, M., Ezra, Y., Amsalem, H., Does a single episode of third trimester bleeding really matter?, American Journal of Obstetrics and Gynecology, 216 (1 Supplement 1), S417, 2017	Conference abstract publication only
Kao, A., Trent, S. A., Kendall, J., Randomized trial of the effect of ED bedside ultrasound on time to diagnosis and length of stay among pregnant women with an estimated gestational age less than 20 weeks, Academic Emergency Medicine, 1), S131-S132, 2015	Conference abstract
Kapoor, S., Thomas, J. T., Petersen, S. G., Gardener, G. J., Is the third trimester repeat ultrasound scan for placental localisation needed if the placenta is low lying but clear of the os at the mid-trimester morphology scan?, Australian & New	Comparison outside of interest: different distances of placeta from the os by ultrasound

Zealand Journal of Obstetrics & GynaecologyAust N Z J Obstet Gynaecol, 54, 428-32, 2014	
Kong, G. W. S., Lok, I. H., Yiu, A. K. W., Hui, A. S. Y., Lai, B. P. Y., Chung, T. K. H., Clinical and psychological impact after surgical, medical or expectant management of first-trimester miscarriage - A randomised controlled trial, Australian and New Zealand Journal of Obstetrics and Gynaecology, 53, 170-177, 2013	Intervention outside of interest: surgical, medical (misoprostol) versus expectant management of retained products after miscarriage in first trimester
Kovac,V., Reljic,M., Vlaisavljevic,V., Prospective control study on coagulation abnormalities in womenwith vaginal bleeding in the first trimester of pregnancy, Human Reproduction, 26, i157-, 2011	Conference abstract publication only
Lee,W., Lee,V.L., Kirk,J.S., Sloan,C.T., Smith,R.S., Comstock,C.H., Vasa previa: prenatal diagnosis, natural evolution, and clinical outcome, Obstetrics and Gynecology, 95, 572-576, 2000	Population outside of interest: asymptomatic pregnant women referred for ultrasound
Lehnert, B. E., Dighe, M. K., Second and third trimester bleeding, Ultrasound Quarterly, 29, 303-5, 2013	Review
Lewis,T., Winblad,O., Rosenthal,S., Ultrasound evaluation of early pregnancy bleeding: What every emergency radiologist should know, Emergency Radiology, 18, 475-, 2011	Conference abstract publication only
Linden, J. A., Grimmnitz, B., Hagopian, L., Breaud, A. H., Langlois, B. K., Nelson, K. P., Hart, L. L., Feldman, J. A., Brown, J., Reid, M., Desormeau, E., Mitchell, P. M., Is the Pelvic Examination Still Crucial in Patients Presenting to the Emergency Department With Vaginal Bleeding or Abdominal Pain When an Intrauterine Pregnancy Is Identified on Ultrasonography? A Randomized Controlled Trial, Annals of Emergency Medicine, 70, 825-834, 2017	Intervention outside of interest: pelvic examination versus no pelvic examination
Lourens, R. J., Steyn, D. W., Antepartum haemorrhage of unknown origin after 24 weeks of pregnancy - How to approach it, Obstetrics and Gynaecology Forum, 21, 38-39, 2011	Unavailable
Luke, B., Gopal, D., Cabral, H., Diop, H., Stern, J. E., Adverse pregnancy, birth, and infant outcomes in twins: Effects of method of conception and zygosity, American Journal of Obstetrics and Gynecology, 216 (1 Supplement 1), S497, 2017	Conference abstract publication only
Mantoni, M., Ultrasound studies of patients with bleeding in early pregnancy, Danish medical bulletin, 34, 250-260, 1987	Diagnostic study
Manuck, T., Romero, S., Esplin, S., Parry, S., Zhang, H., Huang, H., Biggio, J., Bukowski, R., Saade, G., Andrews, W., Baldwin, D., Sadovsky, Y., Reddy, U., Ilekis, J., Varner, M., Suboptimal antenatal corticosteroid (ACS) administration among women with spontaneous preterm birth (PTB), Reproductive Sciences, 1), 273A, 2016	Conference abstract publication only
Masri, M. A., Omar, B., Yong, C. M., Ganesalingam, M., Major placenta praevia with previous scars - A 2-year review, BJOG: An International Journal of Obstetrics and Gynaecology, 1), 59, 2012	Conference abstract publication only
Matthias, G., Autoimmunity and perinatal outcomes in women with threatened miscarriages-a prospective case control study, Journal of Reproductive Immunology, 86 (1), 55, 2010	Conference abstract publication only
McCormack,R.A., Doherty,D.A., Magann,E.F., Hutchinson,M., Newnham,J.P., Antepartum bleeding of unknown origin in the second half of pregnancy and pregnancy outcomes, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 1451-1457, 2008	The study compared antepartum bleeding of unknown origin (ABUO) versus No ABUO

McRae,A., Edmonds,M., Murray,H., Diagnostic accuracy and clinical utility of emergency department targeted ultrasonography in the evaluation of first-trimester pelvic pain and bleeding: A systematic review, Canadian Journal of Emergency Medicine, 11, 355-364, 2009	Diagnostic review
Mendelson,E.B., Bohm-Velez,M., Saker,M., Transvaginal sonography in the abnormal first trimester, Seminars in Ultrasound, CT and MR, 11, 34-43, 1990	Review
Naqvi, M., Ali, M., Namath, A. G., Fox, N. S., Subchorionic hematomas and adverse pregnancy outcomes among twin pregnancies, American Journal of Obstetrics and Gynecology, 218 (1 Supplement 1), S278-S279, 2018	Conference abstract publication only
Nct,, A Randomized Prospective Analysis of Time to Diagnosis and Length of Stay of Emergency Department Pelvic Ultrasonography, Https://clinicaltrials.gov/show/nct02268877, 2014	Clinical trial record
Nielsen,S., Hahlin,M., Expectant management of first-trimester spontaneous abortion, Lancet, 345, 84-86, 1995	Intervention outside of interest: expectant management versus dilation and curettage of women with first-trimester abortion
Panebianco, N., Mangili, A., Mohammad, A., Fields, J. M., Anderson, K., Dean, A. J., The additional utility of emergency bedside transvaginal ultrasound after nondiagnostic transabdominal ultrasound in the evaluation of first trimester pregnancy, Academic Emergency Medicine, 1), S11, 2010	Conference abstract publication only
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Park, S. H., Kim, J. D., Jeong, M., Heo, Y. S., Kim, J. H., Jeong, Y. J., Antepartum Expectant Management of Placenta Previa, Inpatient Versus Outpatient, Korean journal of obstetrics and gynecology, 46, 1140-1144, 2003	Non-English article
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Plavsic, B., Kupesic Plavsic, S., Guerra Caroll, M., Paul, L., Bleeding in pregnancy: Significance of imaging, American Journal of Roentgenology, 196 (5 SUPPL.), A176, 2011	Conference abstract publication only
Plavsic, S. K., What you should know about preconception ultrasound?, Journal of Perinatal Medicine, 45 (Supplement 2), 150, 2017	Conference abstract publication only
Pri-Paz, S., Devine, P. C., Fuchs, K. M., Bonanno, C., Gaddipati, S., Wright, J. D., Outcome of pregnancies complicated by placenta accreta at different Gestational Ages (GA), Reproductive Sciences, 1), 183A, 2011	Conference abstract publication only
Ramaeker, D., Simhan, H., Independent and interactive contribution of sonographic cervical length and vaginal bleeding to risk of preterm birth, American Journal of Obstetrics and Gynecology, 204 (1 SUPPL.), S28-S29, 2011	Conference abstract publication only
Sahay,S., McLeod,S.L., Skoretz,T., EMERGENCY department use of Rh immune prophylaxis in early pregnancy, Canadian Journal of Emergency Medicine, 12, 257-258, 2010	Conference abstract publication only

Sajan, R., Pulikkathodi, M., Vahab, A., Kunjitty, V. M., Imrana, H. S., Expectant versus surgical management of early pregnancy miscarriages - A prospective study, Journal of Clinical and Diagnostic Research, 9, QC06-QC09, 2015	Intervention outside of interest: expectant management versus dilatation and evacuation
Saraswat, L., Maheshwari, A., Bhattacharya, S., Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: A systematic review, BJOG: An International Journal of Obstetrics and Gynaecology, 117, 245-257, 2010	Intervention outside of interest: comparing women with or without bleeding in first trimester
Sekiguchi, A., Nakai, A., Kawabata, I., Hayashi, M., Takeshita, T., Type and location of placenta previa affect preterm delivery risk related to antepartum hemorrhage, International Journal of Medical Sciences, 10, 1683-1688, 2013	Population outside of interest: women with placenta previa
Skoll, A., Boutin, A., Bujold, E., Burrows, J., Crane, J., Geary, M., Jain, V., Lacaze-Masmonteil, T., Liauw, J., Mundle, W., Murphy, K., Wong, S., Joseph, K. S., No. 364-Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes, Journal of Obstetrics and Gynaecology Canada, 40, 1219-1239, 2018	Population outside of interest: pregnant women at risk of preterm birth
Stainton,M.C., Lohan,M., Fethney,J., Woodhart,L., Islam,S., Women's responses to two models of antepartum high-risk care: day stay and hospital stay, Women and Birth: Journal of the Australian College of Midwives, 19, 89-95, 2006	Population outside of interest: high-risk women included pregnant women with bleeding but not limited to this. No subgroup analysis performed for this group.
Swank, Morgan L., Vasa previa: diagnosis and management, American Journal of Obstetrics and Gynecology, 215, 223.e1-223.e6, 2016	Comparison outside of interest: comparison groups formed by different types of vasa previa
Teitge, B., Fisher, S., Sambasivam, N., Practice variation in the early pregnancy bleeding patient amongst Canadian emergency physicians, Canadian Journal of Emergency Medicine, 17 (Supplement 2), S42, 2015	Conference abstract
Thompson, J. M., Bhanich Supapol, W., Sandu, V., Trivedi, V., Upadhye, S., The utility of pelvic exams in emergency department patients with first trimester vaginal bleeding: A feasibility study and medical record review, Canadian Journal of Emergency Medicine, 17 (Supplement 2), S53, 2015	Conference abstract
Tutera, G., Newman, R. L., Placental localization and diagnosis of antenatal hemorrhage by ultrasonography, Obstetrics and Gynecology, 42, 684-688, 1973	Non-comparative study
Varma, T. R., The value of ultrasonic B scanning in diagnosis when bleeding is present in early pregnancy, American journal of obstetrics and gynecology (Print), 114, 607-612, 1972	Descriptive study
Varner, C., Balaban, D., Carver, S. M., McLeod, S. L., Borgundvaag, B., Assessing future fetal viability following ED point of care ultrasound for vaginal bleeding in early pregnancy, Canadian Journal of Emergency Medicine, 17 (Supplement 2), S37, 2015	Conference abstract publication only
Weinberg,L., Use of anti-D immunoglobulin in the treatment of threatened miscarriage in the accident and emergency department, Emergency Medicine Journal, 18, 444-447, 2001	Descriptive study: all women received anti-D immunoglobulin for treatment of threatened miscarriage
Wing,D.A., Paul,R.H., Millar,L.K., Management of the symptomatic placenta previa: A randomized, controlled trial of inpatient versus outpatient expectant management, American Journal of Obstetrics and Gynecology, 175, 806-811, 1996	Population outside of interest: women with placenta previa

Yip, S. K., Sahota, D., Cheung, L. P., Lam, P., Haines, C. J., Kwok-Hung Chung, T., Accuracy of clinical diagnostic methods of threatened abortion, Gynecologic and Obstetric Investigation, 56, 38-42, 2003	Descriptive study: all women with antepartum bleeding were performed ultrasound scan

Economic studies

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

Appendix L – Research recommendations

Research recommendations for review question: What interventions are effective in managing unexplained vaginal bleeding during pregnancy?

Research question

What is the clinical and cost effectiveness of hospitalisation compared with outpatient management for pregnant women with unexplained vaginal bleeding?

Why this is important

The committee made a research recommendation to find out the clinical and cost effectiveness of hospitalisation compared with outpatient management for women with unexplained vaginal bleeding. They agreed the evidence included in this review was insufficient to answer the review question.

Table 7: Research recommendation rationale

Research question	What is the clinical and cost effectiveness of hospitalisation compared with outpatient management for pregnant women with unexplained vaginal bleeding?
Why is this needed	
Importance to 'patients' or the population	Between 6 and 10 in every 100 pregnant women will experience unexplained vaginal bleeding. For some women and their unborn babies, an initial (apparently unexplained) bleed can precede a life-threatening bleed due to placental abruption. Providing women with clear advice and safe care when managing unexplained vaginal bleeding in pregnancy is important to ensure that they feel reassured and experience good outcomes.
Relevance to NICE guidance	Bleeding in pregnancy is a common occurrence and warrants clarity on the best pathway to use for women depending on the stage of pregnancy. There are significant costs associated with admitting women with unexplained vaginal bleeding to hospital. It is not clear whether this approach is justified hence the need for evidence-based guidance.
Relevance to the NHS	Women with unexplained vaginal bleeding cost the NHS a lot of money due to admission to hospital and frequency of ultrasound scanning. Clear evidence would support or refute the need for this financial cost incurred by admitting women to hospital.
National priorities	Low
Current evidence base	Clinical opinion.
Equality considerations	None known,
Feasibility	No concerns.
Other comments	

Table 8: Research recommendation modified PICO table

Criterion	Explanation
Population	Women with light or moderate (for example <20mls or spotting only) unexplained vaginal bleeding during pregnancy
Intervention	Hospitalisation
Comparator	Outpatient management
Outcomes	Bleeding of >1000ml

Criterion	Explanation
	Birth within a week of intervention Fetal death from 16 weeks of gestational age Infant death up to 1-year chronological age Admission to intensive care unit for treatment of bleeding Duration of hospitalisation for treatment of bleeding Women's experience and satisfaction with care Babies being born small for gestational age
Study design	RCT or non-randomised cohort study with adequate adjustment for confounding
Timeframe	At least 12 months of follow-up
Additional information	Heavy vaginal bleeding would be expected to require hospitalisation, the key question is whether less severe bleeding could be managed in an outpatient setting

RCT: randomised controlled trial