



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Uncertainties: which intervention reduces the risk of preterm birth in women with risk factors?

Citation for published version:

Stock, S & Ismail, KMK 2016, 'Uncertainties: which intervention reduces the risk of preterm birth in women with risk factors?', *British Medical Journal (BMJ)*. <https://doi.org/10.1136/bmj.i5206>

Digital Object Identifier (DOI):

[10.1136/bmj.i5206](https://doi.org/10.1136/bmj.i5206)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

British Medical Journal (BMJ)

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.





Uncertainties: Which intervention reduces the risk of preterm birth in women with risk factors?

Journal:	<i>BMJ</i>
Manuscript ID	BMJ.2016.034695.R2
Article Type:	Practice
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
Complete List of Authors:	Stock, Sarah; University of Edinburgh MRC Centre for Reproductive Health, Obstetrics and Gynaecology Ismail, Khaled; University of Birmingham, College of Medical and Dental Sciences
Keywords:	Preterm Birth, Cervical Cerclage, Progesterone, Cervical Pessary, Cervical Length, Multiple Pregnancy, Suture Material

SCHOLARONE™
Manuscripts

1
2
3
4
5
6 **Uncertainties: Which intervention reduces the risk of preterm birth in women**
7 **with risk factors?**
8
9

10
11 Sarah J Stock¹, Khaled M K Ismail^{2*}
12
13

14
15
16 ¹Senior Clinical Lecturer and Subspecialist Maternal and Fetal Medicine

17
18 Tommy's Centre for Maternal and Fetal Health

19
20 MRC Centre for Reproductive Health

21
22 University of Edinburgh Queen's Medical Research Institute

23
24 Little France

25
26 Edinburgh

27
28 EH16 4TJ
29
30

31
32 ²Professor of Obstetrics and Gynaecology

33
34 The Birmingham Centre for Women's and Children's Health

35
36 College of Medical and Dental Sciences

37
38 University of Birmingham

39
40 Edgbaston

41
42 Birmingham

43
44 B15 2TT

45
46 E-mail: k.ismail@bham.ac.uk
47
48

49
50 * Corresponding author

51
52 **Search terms:** Preterm Birth, Cervical Cerclage, Progesterone, Cervical Pessary,

53
54 Cervical Length, Multiple pregnancy, Suture material.
55
56
57
58
59
60

1
2
3
4
5
6 **Word Count:** 1,427 (including online material)
7
8

9
10 **Introduction**

11 The aim of preventing preterm birth is to improve the health of babies by prolonging
12 pregnancy. Preterm birth (PTB), or delivery before 37 weeks gestation, affects 7.3 %
13 of pregnancies in the UK ¹. Around 75% result from spontaneous preterm labour. The
14 remaining 25% are induced for medical reasons are not considered further in this
15 article.
16
17
18
19
20
21

22
23
24 Who is at risk?

25 Specific obstetric clinical risk factors and / or ultrasound scan findings associated
26 with an increased risk of spontaneous PTB are listed in box 1. However these have
27 poor predictive value. Women with multiple pregnancy are also at high risk of
28 preterm birth, and their management is discussed in supplementary online material.
29
30
31
32
33
34

35
36 Box 1: Risk factors for PTB ^{4 5}

37
38 Clinical History*:

- 39
40
41
42
43
44
45
46
47
- *History of mid-trimester loss
 - *History of preterm prelabour rupture of membranes in a previous pregnancy
 - *History of PTB in a previous pregnancy
 - *History of cervical treatment for CIN

48 The presence of any of these clinical risk factors can be considered a trigger for
49 cervical length screening by transvaginal ultrasound scan.
50

51 Imaging:

- 52
53
54
55
- Short cervix (less than 25mm) on transvaginal ultrasound examination
- 56
57
58
59
60

1
2
3
4
5
6 Appraising the evidence

7
8 Three therapeutic interventions are available for women at risk of spontaneous PTB
9
10 (Table 1). However, considerable uncertainty exists over the effectiveness of these
11
12 interventions, in part because clinical trials are hard to perform. Large numbers of
13
14 trial participants are needed because the majority of high-risk women will deliver at
15
16 term, even without treatment. It is both difficult and expensive to include neonatal
17
18 and childhood outcomes in trials, therefore trials mainly focus on rates of preterm
19
20 birth, not longer-term health outcomes of babies. Furthermore, inconsistencies in
21
22 definitions, inclusion criteria and outcomes in studies mean it is difficult to summarise
23
24 trial data in meta-analyses, and difficult to interpret relevance of the findings to
25
26 individual women in the clinic setting.
27

28
29
30 **What is the evidence of uncertainty?**

31
32
33 See Table 2 for summary of evidence.
34
35

36
37 ***Singleton Pregnancies***

38
39 **Cervical Cerclage**

40
41 An individual patient data (IPD) meta-analysis (5 RCTs involving 504 women) and a
42
43 systematic review (12 RCTs involving 3328 women) showed that cervical cerclage
44
45 delayed the gestational age at delivery and reduces PTB in women at risk of early
46
47 delivery^{7,8}. There was no statistically significant difference in perinatal mortality with
48
49 cerclage,^{7,8}. The IPD meta-analysis, which only included women with a short cervix
50
51 (25mm), showed a reduction in composite neonatal morbidity in the cerclage group⁷.
52
53 However, no reduction in morbidity was seen in the larger meta-analysis of summary
54
55
56
57
58
59
60

1
2
3
4
5
6 data, where participants in the included studies had a more diverse range of risk factors
7 for PTB⁸. For women, higher rates of vaginal discharge, vaginal bleeding, pyrexia,
8 and caesarean section were found in those who underwent cerclage⁸.
9
10

11 12 13 14 Vaginal Progesterone

15 An IPD meta-analysis (5 RCTs involving 775 women and 827 infants) and a
16 systematic review (36 RCTs involving 8523 women and 12,515 infants) support
17 vaginal progesterone use to reduce PTB in women with singleton pregnancies at risk
18 of PTB^{9,10}. The results of both systematic reviews are mainly driven by one RCT in
19 which all pregnant women were screened for cervical length with transvaginal
20 ultrasound and progesterone given if the cervix was 10-20mm¹¹. It is difficult to
21 interpret these data where universal screening of cervical length in pregnancy is
22 lacking, such as in the UK¹².
23
24
25
26
27
28
29
30
31

32
33 A large UK based RCT (OPPTIMUM) was published after these systematic reviews
34 and the release of NICE guidelines¹³. OPPTIMUM is the largest RCT of vaginal
35 progesterone and the only one powered to include a childhood primary outcome. It
36 included women at risk of PTB (Box 1) and found that vaginal progesterone did not
37 reduce any of the primary outcomes: PTB, neonatal death or severe morbidity, or the
38 childhood neurodevelopment development (standardised cognitive score (Bayley-III))
39 at 2 years of age¹³. There were no harms associated with progesterone use¹³.
40
41
42
43
44
45
46
47
48

49 Cervical Pessary

50 Two randomised trials of several hundred women have evaluated the Arabin pessary
51 with a short cervix on transvaginal ultrasound^{14,15}. The smaller trial reported a
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 benefit in using the pessary¹⁴, whilst the larger trial found no statistically significant
7
8 difference in PTB rate between women randomised to cervical pessary and those
9
10 randomized to expectant management¹⁵.

11 12 13 14 Comparison of treatments to prevent PTB

15
16 As yet there are no reported trials comparing the effectiveness of cervical cerclage,
17
18 progesterone supplementation and cervical pessary against each other when used in
19
20 isolation or in combined management strategies in women at risk of PTB.

21 22 23 24 *Multiple Pregnancies*

25
26 Overall there is less evidence regarding management in multiple pregnancies. See
27
28 Table 3 (online) for summary of evidence.

29 30 31 **Cervical cerclage**

32
33 A systematic review found no evidence that cervical cerclage reduces PTB in women
34
35 with multiple pregnancy¹⁶. However, only 128 women with multiple pregnancy were
36
37 included, firm conclusions about benefits and harms cannot be made.

38 39 40 41 **Vaginal progesterone**

42
43 Evidence from an IPD meta-analysis of 1,7345 women with multiple pregnancies
44
45 shows no benefit from vaginal progesterone in this group as a whole¹⁷. However,
46
47 progesterone did reduce poor perinatal outcome in a small subgroup of 116 women
48
49 who had both multiple pregnancy and a short cervix. Further evidence is required to
50
51 confirm this observation¹⁷.

Cervical pessary

Two randomised controlled trials included twin pregnancies with no other risk factors for preterm birth and found there was no difference between cervical pessary compared to routine care^{18,19}. A third randomised controlled trial, confined to women with multiple pregnancy and a short cervix has recently been published, and did show a reduction in PTB with a cervical pessary²⁰.

Is ongoing research likely to provide relevant evidence?

Clinical trials addressing uncertainties in clinical management of women at risk of spontaneous PTB were identified through a search of clinical trials databases (Box 2) and are summarized in table 4. Only two of the five identified studies (C-STITCH and STOPPIT-2) have primary outcomes focused on mortality or neonatal health, with other studies using the surrogate outcome of gestation at delivery.

An individual patient data meta-analysis of vaginal progesterone to prevent preterm birth is planned by the US Patient Centred Outcomes Research Initiative (<http://www.pcori.org>), which should help clarify whether progesterone is effective, and if so, which women should be offered it.

It is essential that future studies use standard definitions, protocols and core outcomes so that data regarding important, but uncommon outcomes (like neonatal mortality) can be readily synthesized and guide decision-making.

Box 2: Search Strategy

We searched clinical trials databases (www.controlled-trials.com/isrctn/; <http://clinicaltrials.gov/>) and the UKCRN Portfolio database (<http://public.ukcrn.org.uk/search/>) with search terms relating to PTB, miscarriage, perinatal mortality and neonatal morbidity. We also had personal communication with the Royal College of Obstetricians and Gynaecologists Preterm Birth Clinical Study Group.

What should we do in the light of the uncertainty?

Parents should be aware that a reduction in incidence of early delivery may not necessarily translate into improved health in children.

It is reasonable to follow NICE (UK) guidance on the prevention of preterm birth and offer cervical cerclage when there has been a previous PTB, midtrimester loss, preterm prelabour rupture of membranes or cervical treatment, and the cervix is short⁶. Alternatively, progesterone may be offered⁶, however, the OPPTIMUM trial, (published after the NICE guideline), showed no benefit of vaginal progesterone in this group¹³. We were unable to find any international guidance relating to prevention of preterm birth.

We believe that further evidence is needed before offering the cervical pessary out of a research setting^{14 15}.

In our opinion women with multiple pregnancies should not be offered treatments to prevent PTB (except in the context of clinical trials) as no clear benefit has been

1
2
3
4
5
6 shown¹⁶⁻²⁰.
7
8
9

10 We suggest that clinicians share the uncertainty about PTB and offer women the
11 opportunity to participate in relevant clinical trials.
12
13

14 15 16 **What you need to know**

- 17 • The best intervention for prevention of spontaneous PTB in women with risk
18 factors is still unclear. In women with a singleton pregnancy risk of PTB and a
19 short cervix the evidence for use of cervical cerclage is clearer than that for
20 progesterone or cervical pessary.
21
- 22 • Discuss with parents that prevention of pre term delivery may not necessarily
23 translate into improved health in children.
24
25
26
27
28
29
30
31

32 **BOX 3 Recommendations for future research**

33 ***Future research should:***

- 34 • Use standard definitions, protocols and core outcomes so that data can be
35 meta-analysed.
36
- 37 • Be adequately powered for important outcomes including neonatal morbidity
38 and perinatal mortality, rather than surrogate outcomes such as PTB.
39
- 40 • Include consent to allow follow-up studies so that long term outcomes can be
41 determined.
42
- 43 • Data from trials should be made available for subsequent meta-analysis
44
45
46
47
48
49
50
51
52
53

54 **How patients were involved in the creation of this article**

55
56
57
58
59
60

1
2
3
4
5
6 “Which interventions are most effective to predict or prevent PTB?” was the number
7
8 one uncertainty prioritised by the James Lind Alliance PTB Priority Setting
9
10 Partnership, which brings together patients, carers and clinicians in partnership to
11
12 identify and prioritise research questions and uncertainties relating to a healthcare
13
14 problem.²⁰ No patients were directly involved in creating this article.
15
16
17

18 **References**

- 19
20 1. Gestation-specific Infant Mortality in England and Wales 2014.
21 [22 http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesof](http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesof)
23 [24 death/datasets/gestationspecificinfantmortalityinenglandandwalesreferencetables.](http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesof)
25 Accessed 26th July 2016.
26
27 2. Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for
28 supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev*
29 2013(10):CD001055.
30
31 3. Sandall J, Soltani H, Gates S, et al. Midwife-led continuity models versus other
32 models of care for childbearing women. *Cochrane Database Syst Rev*
33 2016;4:CD004667.
34
35 4. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth.
36 *Obstet Gynecol* 2007;110(2 Pt 1):405-15.
37
38 5. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm
39 birth. *Lancet* 2008;371(9606):75-84.
40
41 6. Preterm Labour and Birth: NICE guideline (NG25), 2015.
42
43 7. Berghella V, Rafael TJ, Szychowski JM, et al. Cerclage for short cervix on
44 ultrasonography in women with singleton gestations and previous preterm birth: a
45 meta-analysis. *Obstet Gynecol* 2011;117(3):663-71.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8 8. Alfirevic Z, Stampalija T, Roberts D, et al. Cervical stitch (cerclage) for preventing
9 preterm birth in singleton pregnancy. The Cochrane database of systematic reviews
10 2012;4:CD008991.
11
12
13 9. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women
14 with an asymptomatic sonographic short cervix in the midtrimester decreases preterm
15 delivery and neonatal morbidity: a systematic review and metaanalysis of individual
16 patient data. *Am J Obstet Gynecol* 2012;206(2):124 e1-19.
17
18
19
20
21 10. Dodd JM, Jones L, Flenady V, et al. Prenatal administration of progesterone for
22 preventing preterm birth in women considered to be at risk of preterm birth. The
23 Cochrane database of systematic reviews 2013;7:CD004947.
24
25
26
27 11. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate
28 of preterm birth in women with a sonographic short cervix: a multicenter,
29 randomized, double-blind, placebo-controlled trial. *Ultrasound in obstetrics &*
30 *gynecology : the official journal of the International Society of Ultrasound in*
31 *Obstetrics and Gynecology* 2011;38(1):18-31.
32
33
34
35
36 12. Bazian. Screening for Preterm Labour in asymptomatic, low-risk women. External
37 review against programme appraisal criteria for the UK National Screening
38 Committee (UK NSC): UK National Screening Committee, 2014.
39
40
41
42 13. Norman JE, Marlow N, Messow CM, et al. Vaginal progesterone prophylaxis for
43 preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial.
44 *Lancet* 2016.
45
46
47
48 14. Goya M, Pratcorona L, Merced C, et al. Cervical pessary in pregnant women with
49 a short cervix (PECEP): an open-label randomised controlled trial. *Lancet*
50 2012;379(9828):1800-6.
51
52
53
54 15. Nicolaides KH, Syngelaki A, Poon LC, et al. A Randomized Trial of a Cervical
55 Pessary to Prevent Preterm Singleton Birth. *N Engl J Med* 2016;374(11):1044-52.
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

16. Rafael TJ, Berghella V, Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. The Cochrane database of systematic reviews 2014;9:CD009166.

17. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG : an International Journal of Obstetrics and Gynaecology 2014; 122(1):27-37.

18. Liem S, Schuit E, Hegeman M, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. Lancet 2013;382(9901):1341-9.

19. Nicolaides KH, Syngelaki A, Poon LC, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. Am J Obstet Gynecol 2016;214(1):3 e1-9.

20. Goya M, de la Calle M, Pratcorona L, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). Am J Obstet Gynecol 2016;214(2):145-52.

21. Crowe S US, Duley L, Oliver S. . Description of a workshop to set research priorities in preterm birth. James Lind Alliance 2014.

Contributors

SJS and KMKI planned the organization, content, and structure of the article. SJS performed the literature search and drafted the article, with crucial edits and additions from KMKI. Both authors participated in subsequent revisions. KMKI is guarantor.

Disclosure Statement

1
2
3
4
5
6 We have read and understood the BMJ policy on declaration of interests and declare
7 the following interests: SJS is an unpaid representative on Scottish Governmental
8 Advisory Groups, and a member of the RCOG Preterm Birth Clinical Study Group
9 and has received travel expenses to attend meetings relating to these roles. SJS is
10 chief investigator and a co-investigator in trials relating to preterm birth funded by
11 NIHR HTA, and the institution she works at has also received research funding from
12 Sparks, Tommy's and the British Maternal and Fetal Medicine (BMFMS) Society.
13 SJS has been provided with ultrasound equipment and software for use in studies of
14 preterm birth research from GE and Philips. SJS has received Honoraria for
15 contributing to book chapters, and travel and accommodation expenses as an invited
16 speaker at conferences and academic institutions. KMKI is chief investigator for C-
17 STICH, funded by NIHR HTA. KMKI receives travel and accommodation expenses
18 as an invited speaker at conferences and academic institutions; however, honoraria or
19 royalty fees generated from academic activities funds academic activities related to
20 women's health. The authors had no support from any organization for the submitted
21 work. The authors grant the publishers a worldwide license.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 **Acknowledgments**

40 The authors would like to thank members of the RCOG Preterm birth Clinical Study
41 Group for advice on future research recommendations and information on ongoing
42 trials.
43
44
45
46
47
48

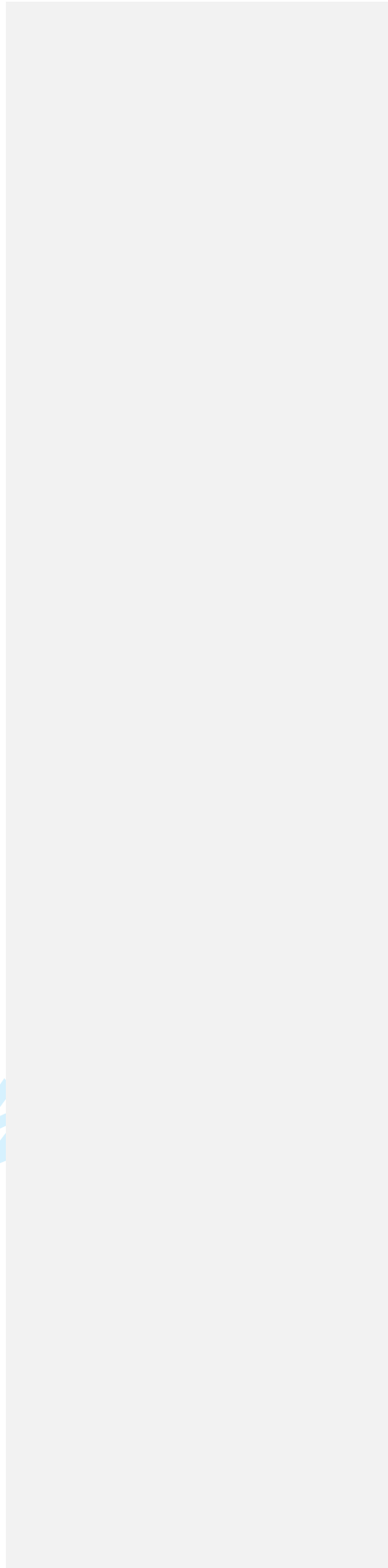
49 **Licence for Publication**

50 The Corresponding Author has the right to grant on behalf of all authors and does
51 grant on behalf of all authors, an exclusive licence (or non exclusive for government
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in BMJ and any other BMJ PGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (<http://group.bmj.com/products/journals/instructions-for-authors/licence-forms>).

Confidential: For Review



Tables

Table 1

Treatment	What is it?	Usual Timing	Evidence and Guidance for use
Cervical Cerclage	A purse string suture that strengthens and tightens the cervix. Usually inserted under regional (spinal) or general anaesthesia.	Inserted between 12 and 24 weeks gestation, and removed at 37 weeks gestation or if there are signs of labour before this.	Current NICE guideline recommends offering cerclage to women with a clinical risk factor (Box 1) and a short cervix on ultrasound (<25mm) but mainly low or moderate quality evidence.
Progesterone supplements	Intravaginal progesterone is the only formulation available in the UK. Usually prescribed as once daily pessaries.	Commenced between 16 and 22 weeks gestation, and continued to 34-36 weeks gestation.	Current NICE guideline recommends offering vaginal progesterone to women with a clinical risk factor (Box 1) and/or a short cervix on ultrasound (<25mm) but mainly low or moderate quality evidence.
Cervical Pessary (Arabin)	A silicon ring that sits over the cervix and works by supporting the cervix and tilting it posteriorly. No anaesthesia or analgesia is required for insertion. There is only one cervical pessary on the market – Arabin.	Inserted between 18 and 22 weeks gestation, and removed at 37 weeks gestation or if there are signs of labour before this.	Not reviewed in current NICE guideline.

Table 1: Treatment options for preterm birth

Comment [SS1]: Images for each sent in separate file of supplementary material

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Confidential
Review

Table 2

	Study design	Population	Intervention/ Comparator	Reduction in PTB?	Reduction in Perinatal Mortality?	Reduction in Adverse Neonatal Outcome?
Cervical Cerclage	Systematic review and IPD level meta-analysis (5 trials; 504 women/infants) [7]	Cervical length less than 25mm	Cervical Cerclage/Expectant Management	Yes <35 weeks 28.4% vs 41.3% RR 0.70 95% CI 0.55–0.89 (5 trials; n=504)	No 8.8% vs 13.8% RR 0.65 95% CI 0.40–1.07 (5 trials; n=504)	Yes 12.8% vs 20.1% RR 0.64 95% CI 0.43-0.96 (5 trials; n=504)
	Systematic review and meta-analysis of summary statistics (8 trials; 2392 women, 2391 infants) [8]	High risk of preterm birth (history and/or short cervix)	Cervical Cerclage/Expectant Management	Yes <34 weeks 17.6% vs 23.1% RR 0.79 95% CI 0.68-0.93 (8 trials; n=2392)	No 8.4% vs 10.7% RR 0.78 95% CI 0.61-1.00 (8 trials; n=2391)	No 17.5% vs 23.2% RR 0.82 95% CI 0.61, 1.09 (4 trials; n=817)
Vaginal Progesterone	Systematic review and IPD level meta-analysis (5 trials; 775 women, 827 infants) [9] **	Cervical length of ≤25mm	Vaginal Progesterone/ Placebo	Yes <34weeks 16.0% vs 27.1% RR 0.61 95% CI 0.47–0.81 (5 trials; n= 775)	No 3.4% vs 5.3% RR 0.63 95% CI 0.34-1.18 (5 trials; n= 827)	Yes 9.7% vs 17.3% RR, 0.57 95% CI, 0.40-0.81 (5 trials; n= 827)
	Systematic review and meta-analysis of summary statistics (5 trials; 1165 women/infants) [10]	Previous preterm delivery	Vaginal Progesterone*/Placebo or no treatment	Yes <34 weeks 3.5% vs 21.7% RR 0.21	No 3.7% vs 5.6% RR 0.67 95% CI 0.34- 1.29	-

				95% CI 0.10-0.44 (4 trials; n=454)	(2 trials; n=752)	
	Systematic review and meta-analysis of summary statistics (2 trials; 732 women/infants) [10]	Ultrasound identified short cervix	Vaginal Progesterone*/ Placebo	Yes <34 weeks 20.8% vs 36% RR 0.58 95% CI 0.38-0.87 (1 trial ; n=250)	No 3.0% vs 5.3% RR 0.56 95% CI 0.27-1.17 (2 trials; n=732))	-
	Randomised Control Trial (1228 women/infants) [13]	High risk of PTB (history &/or short cervix or positive fetal fibronectin + clinical risk factor)	Vaginal Progesterone/ Placebo	No <34 weeks 18% vs 16% Adjusted OR 0.86 95% CI 0.61-1.22	No 1% vs 1% Unadjusted OR 1.14 95% CI 0.41-3.17	No Adjusted OR 0.62 10% vs 7% 95% CI 0.38-1.03
Cervical Pessary	Randomised Trial (1 trial; 385 women/infants) [14]	High risk of preterm birth (history and/or short cervix)	Cervical Pessary/ Expectant Management	Yes <34 weeks 6.3% vs 26.8% RR 0.24 95% CI 0.13-0.43 (1 trial; n=385)	No 0 vs 0.5% RR 0.0 95% CI [0.0-0.0] (1 trial; n=385)	-
	Randomised Trial (932 women/infants) [15]	Ultrasound identified short cervix (<25mm)	Cervical Pessary/ Expectant Management (Progesterone was given if cervical length <15mm in either group)	No <34 weeks 12.0% vs 10.8%, OR 1.12 95% CI 0.75 –1.69	No 3.2% vs 2.4% OR 1.38 95% CI 0.63-3.4	No 6.7% vs 5.7%, OR 1.18 95% CI 0.69-2.03

Summary data of Systematic Reviews of Randomised Trials of Interventions to Prevent Preterm Birth (PTB) in Women with Risk Factors and Singleton Pregnancy.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

We performed searches in Medline and the Cochrane Libraries using search terms for PTB combined with terms for progesterone, cervical pessary, Arabin and cervical cerclage and a filter for systematic reviews of randomized control trials restricted to studies in humans.

*This review included data from trials of intramuscular 17 alpha hydroxyprogesterone acetate, which is not available in the UK. Data presented here are restricted to those relating to vaginal progesterone.

** review included some multiple pregnancies

IPD : Individual patient level data meta-analysis

RR: Risk Ratio

OR: Odds Ratio

CI: Confidence Interval

Yes and No indicate statistically significant difference in outcome

Confidential: For Review Only

Table 3 (online only)

	Study design	Population	Intervention/Comparator	Reduction in PTB?	Reduction in Perinatal Mortality?	Reduction in Adverse Neonatal Outcome?
Cervical Cerclage	Systematic review and meta-analysis of summary statistics (5 trials, 128 women, 262 infants) [16]	Multiple pregnancy	Cervical Cerclage vs Expectant Management	No 46.2% vs 31.8% RR 1.16 95% CI 0.44-3.06 (4 trials; n = 83)	No 19.2% vs 9.5%; RR 1.74 95% CI 0.92-3.28 (5 trials, n =262)	No 40.4% vs 20.3% RR 1.54 95% CI 0.58 -4.11, (3 trials; n = 116)
Vaginal Progesterone	Systematic review and IPD level meta-analysis (7 trials; 1,735 women, 3470 infants) [17]	Multiple pregnancy	Vaginal Progesterone* / Expectant Management	Yes <35 weeks 26% vs 28% RR 0.94 95% CI 0.8-1.1 (7 trials; n=1,735)	No 2% vs 2% RR 0.97 95% CI 0.65-1.4 (7 trials; n=3470)	No 13% vs 13% RR 0.97 RR 0.96 95% CI 0.83-1.1 (7 trials; n=3470) -----** Short cervix subgroup 26.8% vs 63.5%; RR 0.57 95% CI 0.47-0.70 (n=116)
Cervical Pessary	Randomised Trial (808 women; 1634 infants) [18]	Multiple pregnancy	Cervical Pessary vs Expectant Management		No 4% vs 4% RR 0.83 95% CI 0.41-1.68 [1 trial; n=1,634]	No 13% vs 14% RR 0.98, 95% CI 0.69-1.39 [1 trial; n=1,634] Short cervix subgroup 12% vs 29%

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

						RR 0.40 95% CI 0.19-0.83 (n=133)
Randomised Trial (1,180 women; 2,354 infants)[19]	Twins	Cervical Pessary vs Expectant Management	No <34 weeks 13.6% vs. 12.9% RR 1.05 95% CI 0.79-1.41	No 2.5% vs. 2.7% RR 0.91 95% CI 0.55-1.49	No 10.0 vs. 9.2% RR 1.09 95% CI 0.85-1.41	Short cervix subgroup 17.1% vs 14.7% RR 1.20 95% CI 0.77-1.89 (n=396)
Randomised Trial (137 women; 274 infants) [20]	Twins and short cervix (≤25mm)	Cervical Pessary vs Expectant Management	Yes <34 weeks 16.2% vs 39.4% RR 0.41 95% CI 0.22-0.76	No No deaths in either group	No 5.9% vs 9.1% RR 0.64 95% CI 0.27-1.50	

Table 3: Summary data of Systematic Reviews of Randomised Trials of Interventions to Prevent Preterm Birth (PTB) in Women with Risk

Factors and Multiple Pregnancy.

We performed searches in Medline and the Cochrane Libraries using search terms for PTB combined with terms for progesterone, cervical pessary, Arabin and cervical cerclage and a filter for systematic reviews of randomized control trials restricted to studies in humans.

1
2
3
4
5
6
7
8
9 *This review included data from trials of intramuscular 17 alpha hydroxyprogesterone acetate, which is not available in the UK. Data presented
10 here are restricted to those relating to vaginal progesterone.
11

12
13 IPD : Individual patient level data meta-analysis
14

15 RR: Risk Ratio
16

17 OR: Odds Ratio
18

19 CI: Confidence Interval
20

21 Yes and No indicate statistically significant difference in outcome
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Table 4: Ongoing relevant trials

Title Setting [Trial Registration or ID] Funder	Population	Intervention	Comparator(s)	Primary Outcome	Comments
C-STITCH: Cerclage suture Type for an Insufficient Cervix and its effect on Health outcomes UK Multicentre [ISRCTN15373349] NIHR HTA	Women with singleton pregnancy and indication for cervical cerclage (n=900).	Cervical cerclage using monofilament (nylon) suture	Cervical cerclage using multifilament (Mersilene tape) suture	Pregnancy loss rate (miscarriage and perinatal mortality, defined as any still birth or neonatal death in the first week of life)	Primary outcome influenced by patient and public involvement group, and chosen as most relevant to pregnant women.
MAVRIC: A multicentre randomised controlled trial of transabdominal versus transvaginal cervical cerclage UK Multicentre [ISCTRN33404560] The Moulton Charitable Foundation	Women with singleton pregnancy and previous failed vaginal cerclage (n=133)	Abdominal Cerclage	High or Low Vaginal Cerclage	Spontaneous PTB < 32 weeks	Recruitment closed and reports in preparation
STOPPIT-2: An open randomised trial of the Arabin pessary to prevent preterm birth in twin pregnancy, with health economics and acceptability UK Multicentre [ISCTRN02235181] NIHR HTA	Women with multiple pregnancy and a short cervix	Cervical (Arabin) Pessary	Standard care	Obstetric: Spontaneous PTB <34 weeks. Neonatal: Composite morbidity and mortality	Includes a neonatal primary outcome.
SuPPoRT: Stitch, Progesterone or Pessary: a Randomised Trial UK Multicentre [EudraCT 2015-000456-15] NIHR Research Fellowship	Women with singleton pregnancy at high risk of spontaneous preterm birth with a short cervix (<25mm) (n=540)	Cervical Cerclage	Vaginal Progesterone 200mg or Cervical Pessary	Delivery <37 weeks	2 trials comparing interventions in women with risk factors for PTB.
ReCAP: Randomised Trial into Prevention of Preterm Birth: Feasibility Study UK 2 Centres [UKCRN ID 18675]	Women with singleton pregnancies at high risk of spontaneous preterm birth with a short cervix	Cervical Cerclage	Vaginal Progesterone 200mg or Cervical		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

NIHR RfPB	(<3 rd centile) (Feasibility – no specified sample size)		Pessary		
-----------	---	--	---------	--	--

Abbreviations: HTA: Health Technology Assessment, RfPB: Research for Patient Benefit, PTB: Preterm Birth

Confidential: For Review Only

