

Article Type: Systematic review

Title Page

Title: Clinical guidelines for prevention and management of preterm birth: a systematic review

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Running title: Clinical practice guidelines for preterm birth

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## Abstract

**Background:** Clinical practice guidelines (CPG) endorse multiple strategies to prevent or manage preterm birth (PTB).

**Objectives:** To summarise CPG recommendations for PTB and identify areas of international consensus.

**Search strategy:** In June 2017 we searched for all CPG relevant to PTB without language restrictions.

**Selection criteria:** CPG were eligible if the following criteria were met:

- i. The guideline was published or current from June 2013
- ii. The guideline recommended practices for the prevention or management of PTB relevant to our pre-specified clinical questions for screening, medications or surgery and other interventions
- iii. Publications on methods of guideline development for eligible CPG were included to enable quality assessment

**Data collection and Analysis:** Two authors classified CPG recommendations relevant to pre-specified clinical questions. When more than 70% of CPGs reporting on a topic recommended or rejected an intervention we regarded this as consensus. We summarised recommendations in tables.

**Main results:** We identified 49 guidelines from 16 guideline developers. We found consensus for several clinical practices including cervical length screening for high risk women; short-term tocolysis; steroids for fetal lung maturation; and magnesium sulphate for fetal neuroprotection. We found discrepant recommendations for progesterone and fibronectin. No guideline identified an effective strategy for women with multiple pregnancy.

Conclusions: We identified interventions for which there is an international consensus of benefit for PTB. Systematic reviews of CPG using standardized methodology will help avoid duplication and target scarce resources for guideline developers globally.

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Keywords: Preterm birth, premature birth, clinical practice guideline.

Tweetable abstract: International clinical guidelines agree on the benefits and harms of several important interventions to prevent preterm birth.

## **Manuscript**

### **Introduction**

Complications from preterm births (PTB) are a primary cause of neonatal deaths worldwide, with surviving infants at risk of serious neonatal complications and long term disability [1]. The economic cost of PTB was estimated to be £2.9 billion for a single year in the UK [2; 3], with the psychological, social and financial costs to families no less profound [4; 5]. A World Health Organisation (WHO) priority-setting exercise identified PTB as a ‘top ten’ research priority to 2025 [6]. Discovery research to prevent PTB is also a key component of the global strategy to reduce new born deaths, as set out in the United Nations’ Sustainable Development Goals to 2030 [7].

Experts continue to debate the optimal clinical care of pregnant women to prevent or manage PTB.

Short and long term effects of diverse interventions must be set against women's individual histories and preferences. Clinical setting also has an important impact on cost-effectiveness. Even within the diverse individual, social and economic structures that shape women's antenatal care, it is now accepted that health-care providers can improve outcomes for pregnant women and their babies by following evidence-based guidelines [8; 9]. There is also widespread agreement that use of guidelines can improve efficient use of resources [10], but implementation remains difficult [11].

A recent study suggests that methods for guideline development have improved [12]. As the need for up-to-date guidance continues, efforts to reduce duplication, improve collaboration amongst guideline developers and establish methods for guideline adaptation and more efficient updating have received wider consideration [13, 14]. The objectives of this study are: to propose a methodology for reviewing the content of practice guidelines, and with these, to identify consensus and inconsistency in recommendations across the PTB-related guidelines. (286 words)

## **Methods**

We based our review methods on two systematic reviews of guidelines [8; 9].

### **Search Strategy**

In June 2016 we searched six online databases including Medline (Ovid) using a broad search strategy without language restrictions. We checked references for additional guidelines and hand searched the websites of professional societies. In May 2017 we repeated our hand searches and the Medline (Ovid) search, and we searched the online database Literatura Latino Americana en Ciências da Saúde virtual

health library (LILACS). All search strategies combined the keywords preterm or premature with birth, labour or delivery. Where possible we limited the search results of online databases to the article type 'practice guideline'. Full details of individual database search terms results appear in Appendix S1 and in a published protocol for this review [15].

We developed a list of clinical questions to inform the eligibility of practice guidelines and enable efficient searches of guidelines. The list emerged from the Cochrane Pregnancy and Childbirth review topic list and close readings of widely-known practice guidelines; the process was iterative. The finalised list of 27 clinical questions delineate the scope of this review (Table 1). We did not search for or summarise topics relevant to PTB beyond those pre-specified in our clinical questions. Eligible guidelines met the following criteria:

- i. The guideline was published or assessed as current from June 2013.
- ii. The guideline recommended clinical practices for the prevention or management of PTB relevant to our pre-specified questions on screening, medications or surgery and other interventions.
- iii. Guidelines targeted asymptomatic pregnant women, women with risk factors, or women presenting with clinical signs of preterm labour or birth as defined by the guideline. Women had singleton or multiple pregnancy.
- iv. Guidelines were written for single or multiple interventions.
- v. Publications on methodology of guideline development for eligible CPG were included to enable quality assessment.

Two researches completed eligibility assessment independently; we resolved conflicts through discussion. We sought help from native speakers with clinical expertise to assess the eligibility of several guidelines not published in English, as documented below in Acknowledgements. We did not complete duplicate assessment of foreign language guidelines.

### **Quality assessment**

We assessed guidelines' adherence to four of 13 Institute of Medicine (IOM) Standards for a Trustworthy Guideline [16; 17]. We choose four general standards prioritised by this review team: i) Did the guideline describe a development and funding process that was publicly accessible? ii) Did the guideline address gaps in evidence and summarised evidence for benefits and harms related to each recommendation? iii) Was the guideline based on a systematic review of available evidence? And iv) was the guideline developed by a multidisciplinary panel made up of clinical experts and included patients and/or other health consumers?

Most included guideline developers contributed more than one guideline to this review. Therefore, we summarised adherence to IOM standards for each included guideline developer (based on methodological papers and select guidelines) rather than for each of the 49 included guidelines. We conducted duplicate quality assessment with disagreement resolved by discussion.

### **Summarizing evidence**

To summarise guideline recommendations we divided the clinical questions into screening strategies, medications and surgical or other interventions. Two authors independently categorised recommendations according to the following scheme:

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- i. Yes – the guideline recommends the practice
  - ii. Conditional yes – the guideline recommends the practice for specific subgroups of women
  - iii. Consider – the guideline states that the practice may be considered under certain conditions or in subgroups
  - iv. No – the guideline recommends against the practice
  - v. The guideline states further research is needed or there is insufficient evidence to recommend
  - vi. The guideline does not mention the clinical question
  - vii. The guideline recommendation is unclear

For each clinical question we then reported the number of guidelines with relevant recommendations and used this number as a “denominator”. When a guideline’s recommendation for a specific clinical question was classified as ‘Yes’ or ‘Conditional yes’ for more than 70% of guidelines reporting on the question, we understood this as general support amongst guidelines and overall endorsement. This logic also applied to recommendations against an intervention to prevent or treat PTB. If more than 70% of reporting guidelines recommend against a clinical strategy with ‘No’ or ‘Not enough evidence,’ we recorded this as consensus against the intervention. We did not summarise guideline recommendations for health providers to ‘consider’ various treatments; neither did we summarise unclear recommendations. We noted specific clinical questions with no or very few guideline recommendations in the discussion below.

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## Results

Out of 750 screened records 639 were excluded as irrelevant or duplicate, 55 were not practice guidelines or were published before 2013. We included 56 articles (49 guidelines and 7 methods papers) produced by the 16 guideline developers listed below:

1. American Congress of Obstetricians and Gynecologists (ACOG)
2. Belgium Healthcare Knowledge Centre (KCE)
3. Chinese Society for Obstetrics and Gynecology
4. National College of Gynecologists and Obstetricians - France
5. International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)
6. Society of Obstetrics and Gynecology - Japan
7. King Edward Memorial Hospital Western Australia (WA)
8. National Institute for Clinical Excellence, UK (NICE)
9. New Zealand and Australian Clinical Practice Guidelines (NZA)
10. Queensland Australia
11. Royal College of Obstetrics and Gynaecology, UK (RCOG)
12. Royal Women's Hospital Australia
13. South Australia (SA)
14. Society of Obstetricians and Gynaecologists of Canada (SOGC)
15. University of Michigan Prenatal Care
16. World Health Organisation (WHO)

We identified 29 current guidelines via hand searches; such searches are particularly important for locating guideline updates because some professional societies, such as SOGC and ACOG, identified guidelines 'reaffirmed as current' only on their respective websites [18; 19]. Included practice guidelines

and reports on guideline methods are listed in the references to this paper [20-77]. We documented search results and eligibility decisions in Figure S1 PRISMA flow diagram and Appendix S2 Excluded studies.

Sixteen of the 49 included guidelines were written specifically for the prevention or management of PTB. Other guidelines covered the following topics: obstetric, antenatal or perinatal care (6); premature rupture of membranes (PROM) or preterm premature rupture of membranes (PPROM) (5); ultrasound in pregnancy (4); magnesium sulphate (4); multiple or twin pregnancy (3); screening during pregnancy (3); and cerclage (2). Single guidelines addressed antibiotics during pregnancy, nifedipine, tocolysis and progesterone.

We assessed development methodologies for adherence to four of 13 IOM indicators of quality [22; 23].

See Table S1 for complete assessments.

Seven guideline developers had clear and publically accessible funding processes. Four additional developers replied via email to describe their funding process (ACOG; China; SOGC; SA). Remaining guideline developers had no clear information regarding funding attached to publications or websites.

All guideline developers made efforts to assess gaps in evidence and consider both benefits and harms related to recommendations. Guideline developers based recommendations on formal systematic reviews of evidence, with the exception of two; both Michigan and The Royal Women's Hospital Australia drew evidence from a literature searches (which included Cochrane systematic reviews) [72; 69; 70]. Finally, nine guideline developers included patients or members of the public in interdisciplinary guideline panels. Two guideline developers reported (via email) that they involved no members of the public nor patients [China; SOGC]; remaining guidelines had no details.

The quality assessment validates our eligibility decisions. Included guidelines were overwhelmingly based on good-quality methods, including systematic reviews of available evidence and the consideration of harms as well as benefits of interventions. Just under half of the included guidelines made their funding process publicly available. More than half of the included guideline developers involved patients or members of the public.

### **Recommendations for clinical practice**

We summarised recommendations for clinical practice in tables (2, 3, 4, S3, S4). Where we identified conditional recommendations, we included the parameters in footnotes. All recommendations extracted for all included guidelines can be found in Table S2A -C.

Five of our clinical questions related to screening practices (See Table 2). We found consensus for two clinical scenarios. Guidelines reporting on cervical length (CL) screening for high risk women endorsed the practice for this subgroup. No guideline recommended against CL screening in high risk women. Just two guidelines reported on screening for asymptomatic bacteriuria to prevent PTB, but both recommended this strategy.

Most guidelines recommended against universal screening of CL in each pregnancy; just two of the eight guidelines reporting recommendations for this practice endorsed universal screening (Michigan; Japan).

A similar number of guidelines recommended against screening for bacterial vaginosis (BV) in pregnant women without signs of preterm labour or PPRM. Two guidelines argued for BV screening for women with a history of PTB or risk factors (Queensland; SOGC).

Guidelines disagreed on the appropriate use of fibronectin, with four guidelines endorsing its use in specific circumstances and three advising against.

Ten clinical questions related to the use of medications to prevent or manage PTB (See Table 3 and Table S3). Guidelines endorsed active strategies for five of these: the use of short term tocolysis; magnesium sulphate for fetal neuroprotection; antibiotics for women with PPROM; vaginal progesterone for women without symptoms or history of PTB but evident short cervix before 24 weeks' gestation; and steroids for women with threatened PTB.

Guidelines recommended against antibiotic prophylaxis for women with intact membranes but threatened PTB; against longer term tocolysis to prolong gestation; and against vaginal progesterone for women with twin pregnancy.

For two clinical questions we found recommendations both for and against with no overall consensus.

Guidelines were divided on whether or not to use vaginal progesterone in women with prior PTB but without short cervix. Ten guidelines reported recommendations on the use of a second dose of steroids for women who continue to be at risk of PTB; five guidelines endorsed a second dose and five recommended against.

Twelve clinical questions covered various surgical strategies to prevent or manage PTB (See Table 4 and Table S4). We found consensus for three questions. All guidelines reporting on cerclage agreed the procedure should be performed for women with short cervix and a previous PTB. Likewise, guidelines supported elective cerclage for women with multiple prior losses. Two guidelines also endorsed transabdominal cerclage after failed cervical cerclage. No other circumstances warranted cerclage. Guidelines advised against cerclage for women with short cervix but without prior PTB. Neither was cerclage endorsed for women with a single prior loss. Guidelines recommended against cerclage for women with twin pregnancy and for women with uterine anomalies or cervical surgery as the sole

indication. Guidelines recommended against the use of cervical pessary for women with singleton or multiple pregnancy; likewise, guidelines advised against combining progesterone with cervical cerclage.

There was very little guidance for two clinical questions. No included guideline addressed amnioinfusion in preterm premature rupture of membranes. Just two guidelines stated that there was insufficient evidence to make a recommendation for the use of emergency cerclage.

## **Discussion**

### **Main findings**

This review of PTB-related guidelines aimed to identify areas of international consensus as well as contested or understudied clinical strategies. We identified nine recommendations with consensus regarding benefit for PTB, namely: CL screening for high risk women; screening for asymptomatic bacteriuria; vaginal progesterone for women with a short cervix before 24 weeks' gestation; short-term tocolysis for women at risk of PTB; antibiotics for women with PPRM; magnesium sulphate for fetal neuroprotection; and steroids for women at risk of PTB. Guidelines also endorsed cerclage for women with multiple prior losses and for women with prior PTB and a short cervix before 24 weeks' gestation. Further, we found twelve interventions deemed ineffective which should not be supported, including antibiotics for women with intact membranes and signs of PTB; universal CL screening; and cerclage in women with a single prior loss, multiple pregnancy or no history of PTB. We found no intervention endorsed to prevent or manage PTB in multiple pregnancy. Importantly, for several clinical questions we found contradictory recommendations – on the use of fibronectin, vaginal progesterone and a second dose of steroids for women with continued risk of PTB. Recommendations for these clinical questions deserve further scrutiny. Finally, we found few or no guideline recommendations for cervical pessary,

for amnio-infusion for women with ruptured membranes or for emergency cerclage – these topics deserve further study.

### **Strengths and Limitations**

One strength of this project is the comprehensiveness of our searches (without language restrictions) and quality assessment, which confirmed that we summarised the most relevant, publicly-available practice recommendations. Another strength is the proposed methodology for guideline review, to encourage research collaboration and reduce waste by identifying areas of international consensus.

We based the scope of our review on pre-specified clinical questions and followed transparent, replicable methods to reduce bias. Though we considered the Cochrane Pregnancy & Childbirth topic list and well-known pregnancy guidelines to prioritise 27 clinical questions, our review of PTB guidance is not exhaustive. Other author teams may have prioritised different clinical questions or approached guidelines with different priorities. For example, peer reviewers of our paper felt strongly that we should have included diagnostic accuracy of tests for preterm labour and the role of low dose aspirin amongst our clinical questions. We chose not to deviate from the clinical questions described in our published protocol, but this criticism highlights the importance of a method to determine the scope of a review. For topics as wide-ranging as PTB prevention and treatment review teams may require significant input from a broad range of stakeholders to prioritise a clinical topic list and, thereby, enable the structured review of guidelines. Another criticism related to our failure to comply with the CROWN initiative and use the PTB core outcome set (COS) to structure data synthesis [76]. The methodology proposed here summarizes guideline recommendations for interventions rather than for specific outcomes. However, there is no question that trials' adherence to COS domains would improve the

quality of guidelines by strengthening the evidence base for key interventions and may also improve consistency of guideline recommendations.

There are several additional limitations to our synthesis. Ambiguous wording obstructs the implementation of guideline recommendations [14]. We took the view that the relatively frequent guideline recommendations to 'consider' various treatments were too vague to classify which may have underestimated the consensus amongst guidelines reported here. We chose not to evaluate the feasibility of recommendations in different settings or to search for relevant cost-effectiveness data or implementation strategies. Neither did we summarise guidelines' ratings of the quality of evidence supporting recommendations.

#### **Interpretation in light of other evidence**

To inform World Health Organisation (WHO) guideline development Abalos 2016 and Miller 2016 comprehensively reviewed CPG recommendations for antenatal care and routine maternity care [8; 9].

Both reviews noted discrepant recommendations. Miller 2016 also used AGREE II scores to select higher-quality guidelines for further analysis; they compared CPG recommendations to clinical practice using coverage rates for several recommended-for and recommended-against interventions. Neither WHO review evaluated the quality of the evidence supporting recommendations. Other systematic reviews of CPG for hypertension, sugar intake and antenatal infection screening reported similar methods [77; 78; 79]. However, none listed clinical questions a priori as we have done. Our proposed methodology renders the scope of the review transparent and reproducible, enables efficient searching of CPG, and, importantly, eliminates post-hoc or informal prioritisation.

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For clinical areas such as PTB prevention and management, where multiple clinical practice guidelines exist, funders should promote collaboration amongst guideline developers and encourage the adaptation of existing good-quality guidelines to fit local requirements [13; 14]. To facilitate this process, we urge funders and future guideline developers to systematically review all relevant clinical practice guidelines before embarking on new, resource-intensive guideline development projects.

### **Conclusion**

Effective strategies to avoid preterm birth are crucial for reducing newborn deaths worldwide. For clinical practice guidelines to improve health outcomes for women and babies, guidelines must present clear, credible and feasible recommendations. To avoid waste of scarce resources, we propose the method for systematic reviews of guidelines as a prudent first step in the development of practice guidelines and welcome suggestions for improvement of these methods. Researchers should also consider systematic reviews of guidelines as a strategy to identify research priorities and to improve efficiency and collaboration amongst guideline developers.

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## Disclosure of Interests

ZA is affiliated with the ISUOG guideline [75]. NM contributed to the WHO guideline [74]. ZA and NM may be authors of systematic reviews cited in included guidelines. BP and SM have no conflicts of interest to disclose. Completed ICMJE disclosure forms are available to view online as supporting information.

## Contribution to Authorship

ZA conceived the study, BP, SM and ZA created the list clinical questions. NM, BP and ZA conducted searches, applied eligibility criteria, classified guideline recommendations and created the summary tables. NM drafted the manuscript and BP, SM and ZA each contributed to writing the paper.

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## Ethics

No ethics approval was required or sought for this systematic review.

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**List of additional files:**

Table 1 Clinical questions

Table 2 Screening

Table 3 Drug therapy

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**Supporting information**

Appendix S1 Search strategies

Appendix S2 Excluded studies

Figure S1 PRISMA study flow diagram

Table S1 Quality assessment

Table S2A-C All guideline recommendations

Table S3 Medications

Table S4 Surgical and other therapy

Table 1 Clinical questions

1.	Should we use tocolysis long term to prolong the gestation in women in threatened preterm labour?
2.	Should we use tocolysis for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids?
3.	Should we use magnesium sulphate in women in threatened preterm labour?
4.	Should we use antibiotics as a prophylaxis in women with intact membranes but threatened preterm birth (PTB)?
5.	Should we use antibiotics in preterm prelabour rupture of membranes (PPROM) women?
6.	Should we use steroids in preterm birth?
7.	Should we use a second course of steroids?
8.	Should we use elective cervical cerclage in women with more than three preterm birth?
9.	Should we use cervical cerclage in women with history of one preterm birth before 34 weeks?
10.	Should we use cervical cerclage in women with a cervical length less than 25 mm detected between 16-24 weeks without history of PTB?
11.	Should we use cervical cerclage in women with a cervical length less than 25 mm detected before 24 weeks and previous preterm birth?
12.	Should we use cervical cerclage in high risk women (uterine anomalies or cervical surgery as sole indication)?
13.	Should we use cervical cerclage in twin pregnancy?
14.	Should we use transabdominal cerclage in women with history of cervix insufficiency with prior unsuccessful vaginal cervical cerclage?
15.	Should we use rescue cerclage in threatened preterm labour before 34 weeks?
16.	Should we use cervical length as universal screening in each pregnancy?
17.	Should we use cervical length as screening in high risk women?
18.	Should we screen for bacterial vaginosis to prevent PTB in women without signs of preterm labour or PPRM?
19.	Should we screen for asymptomatic bacteriuria to prevent PTB?
20.	Should we use vaginal progesterone supplementation between 16-24 weeks in women with prior preterm birth without short cervix?
21.	Should we use vaginal progesterone in asymptomatic women with cervical length less than 20 mm before or at 24 weeks without history of PTB?
22.	Should we use vaginal progesterone in twin pregnancy as a prevention of preterm labour?
23.	Should we use progesterone and cervical cerclage in high risk women of preterm labour?
24.	Should we use pessary to prevent preterm labour?
25.	Should we use pessary to prevent preterm labour in twin pregnancy?
26.	Should we use fibronectin as a screening in women at risk of preterm birth?
27.	Should we use amnioinfusion in PPRM during the labour?

Table 2: Screening strategies to prevent or manage preterm birth (columns report the number of guidelines making recommendations).

Key Recommendations:		Yes	Conditional Yes	No	Not enough evidence to recommend
Guidelines endorsed...	Cervical length as screening in high risk women only.	5	3 <sup>1</sup>	0	1
	Screening for asymptomatic bacteriuria to prevent PTB.	2	0	0	0
Guidelines recommended against...	Cervical length as universal screening in each pregnancy.	2	0	4	2
	Screening for bacterial vaginosis to prevent PTB in women without signs of PTL or PPROM.	0	2 <sup>2</sup>	5	0
Guidelines found little consensus on ...	Fibronectin as a screening in women at risk of PTB.	1	3 <sup>3</sup>	2	1

<sup>1</sup> ACOG advised against screening women with multiple pregnancy [27; 28]. SOGC also exempted twins [65]. The ISUOG guideline is written for twin pregnancy only (ie a high-risk group) and endorsed the practice [75].

<sup>2</sup> Queensland Australia targeted women with previous PTB [57]; SOGC targeted symptomatic women or those with risk factors for PTB [67].

<sup>3</sup> Belgium KCE targeted cervical length 16 to 29 mm [30]; Western Australia symptomatic women 24 to 36 weeks, intact membranes and cervical dilation less than 3cm [43]; SOGC symptomatic women 22 to 36 weeks with dilation less than 3cm [57].

Table 3 Medications to prevent or manage preterm birth (columns report the number of guidelines making recommendations).

Key Recommendations:		Yes	Conditional yes	No	Not enough evidence
Guidelines endorsed...	Tocolysis for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal steroids.	4	3 <sup>1</sup>	1	0
	Magnesium sulphate in women in threatened PTB.	1	9 <sup>2</sup>	0	0
	Antibiotics for women with PPROM.	8	2 <sup>3</sup>	1	0
	Vaginal progesterone in asymptomatic women without history of PTB who have cervical length of < 20 mm before or at 24 weeks' gestation.	8	0	0	0
	Steroids for women with threatened PTB.	1	11 <sup>4</sup>	0	1 <sup>5</sup>

<sup>1</sup> WA targeted women without contraindications and < 34 weeks' gestation [43]; Australia Royal Women's targeted PPROM [69]; France recommended Atosiban or Nifedipine for women with intact membranes [35].

<sup>2</sup> NICE targeted 24 to 29 weeks plus 6 days [49]; WA singleton or multiple pregnancy < 30 weeks [46]; Queensland 24 to 30 weeks [57]; Australia Royal Women's imminent PTB, singleton or multiple pregnancy and < 30 weeks [70]. WHO [74], Japan [20], S Australia [36] and France [35] all targeted women < 30 weeks gestation, while China stated less than 32 weeks and use only for less than 48 h [34].

<sup>3</sup> ACOG [22] targeted < 34 weeks. Australia Royal Women's targeted women up to 32 weeks without PTL or beyond 32 weeks if fetal lung maturity not proven or delivery not planned [69].

<sup>4</sup> Supplementary Table S3 has details of conditions placed on steroid use.

<sup>5</sup> Japan stated there was not enough evidence to recommend use for pregnant women before 24 weeks gestation (at 22 and 23 weeks' gestation). The guideline endorses use beyond 24 weeks (20).

Table 4 – Surgical and other interventions (columns report number of guidelines with recommendations)

Key Recommendations:		Yes	Conditional Yes	No	Not enough evidence
Guidelines endorsed...	Elective cervical cerclage in women with more than three PTB.	3	1 <sup>9</sup>	0	0
	Cervical cerclage in women with cervical length of <25 mm detected before 24 weeks and previous PTB.	5	0	0	0
	Transabdominal cerclage in women with history of cervical insufficiency with prior unsuccessful vaginal cervical cerclage.	2	0	0	0

<sup>9</sup> ACOG targets 1 or more painless losses due to cervical insufficiency and without abruption [24].