



**TITLE: Vaginal Micronized Progesterone Capsules for the Prevention of Miscarriage and Preterm Birth: A Review of the Clinical Evidence**

**DATE:** 28 April 2014

## **CONTEXT AND POLICY ISSUES**

Miscarriage is defined as spontaneous loss of pregnancy before 24 weeks of gestation.<sup>1</sup> Preterm birth is defined as delivery before 37 weeks of gestation.<sup>2</sup> The incidence of preterm birth ranges between 5% and 10% in resource rich countries and is on the rise in many countries<sup>3</sup>. Preterm birth is a major cause of perinatal morbidity and mortality.<sup>4</sup> It can lead to medical problems in the newborn including death and long-term medical issues or disability.<sup>2</sup> The 2011 estimates for total births and fetal deaths (stillbirths) in Canada were respectively 380,454 and 2,818.<sup>1</sup>

Various drugs have been used to delay the premature onset of labor and prevent preterm birth. Included among these drugs is progesterone which is indicated for a variety of conditions. It has been used for prevention of endometrial hyperplasia, for treatment of amenorrhea and abnormal uterine bleeding, and as part of assisted reproductive technology for infertile women.<sup>5</sup> It assists in maintaining pregnancy by suppressing smooth muscle activity in the uterus and keeping the uterus quiescent until term.<sup>2,6</sup> It is available in different doses, different forms and for different routes of administration such as oral, intramuscular and vaginal. The different formulations and routes of administration result in different absorption rates and consequently potentially different treatment efficacy.<sup>6</sup> Vaginal progesterone is available in various forms such as gel, suppositories, or capsules. Prometrium, a micronized progesterone capsule, is indicated for women with intact uterus, as an adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma.<sup>7</sup> However, it is being used off-label for prevention of miscarriage and preterm birth, hence the need to assess its clinical efficacy and safety for these indications.

The purpose of this report is to review the available evidence on the clinical efficacy and safety of vaginally administered micronized progesterone capsules for the prevention of miscarriage and preterm birth.

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**RESEARCH QUESTION**

1. What is the clinical efficacy of vaginal use of micronized progesterone capsules to prevent miscarriage and preterm birth?

**KEY FINDINGS**

Limited evidence suggests that the risks of preterm birth < 37 weeks or < 34 weeks may be lower with micronized progesterone capsules compared with placebo or no treatment. However, there were inconsistencies with respect to statistical significance and results need to be interpreted with caution. One study suggested that the risk of miscarriage in women with singleton pregnancy who had a history of preterm birth was similar for treatment with either micronized progesterone capsule or placebo. There was no statistically significant difference in risk of neonatal complications between micronized progesterone capsule and placebo. Information on long term efficacy and safety of micronized progesterone capsules are lacking.

**METHODS**

**Literature Search Strategy**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 26, 2014.

**Selection Criteria and Methods**

One reviewer screened the titles and abstracts of the retrieved publications, selected potentially relevant articles for retrieval of full-text publications for further investigation. A second reviewer evaluated the full-text publications for final selection, according to the criteria listed in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Pregnant women
<b>Intervention</b>	Micronized progesterone capsule (Prometrium) administered vaginally
<b>Comparator</b>	Placebo, No treatment
<b>Outcomes</b>	Prevention of miscarriage, preterm birth, membrane rupture, adverse events
<b>Study Designs</b>	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT) and non-randomized studies

**Exclusion Criteria**

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009 or duplicate publications of the same study and did not provide

additional relevant information. Studies on vaginally administered progesterone that did not specifically indicate the progesterone type as micronized capsules were excluded. Studies on progesterone that did not report results separately for vaginally administered Prometrium or micronized progesterone capsules were excluded. Studies that did not report quantitative results, were excluded. Individual studies that were included in at least one of the included systematic reviews were excluded unless there was additional data in the study report. Systematic reviews in which all included studies were included in a more recent or comprehensive systematic reviews or health technology assessments were excluded.

### **Critical Appraisal of Individual Studies**

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist<sup>8</sup> was used for systematic reviews and the Downs and Black checklist<sup>9</sup> for RCTs.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

## **SUMMARY OF EVIDENCE**

### **Quantity of Research Available**

The literature search yielded 425 articles. Upon screening titles and abstracts, 389 articles were excluded and 36 potentially relevant articles were selected for full-text review. No potentially relevant article was identified from the grey literature. Of these 36 articles, 33 did not satisfy the inclusion criteria and were excluded. One systematic review<sup>6</sup> and two RCTs<sup>10,11</sup> were selected for inclusion. No relevant health technology assessment or non-randomized study was identified. Details of the study selection process are outlined in Appendix 1.

### **Summary of Study Characteristics**

Characteristics of the included systematic review and RCTs are summarized below and details are provided in Appendix 2

#### Systematic review

One relevant systematic review<sup>6</sup> on the pre-natal administration of progesterone for preventing preterm birth published in 2013 by the Cochrane collaboration was identified. This systematic review had a broad scope and assessed various types of progesterone and routes of administration. Of the 36 RCTs included in this systematic review, results from three RCTs were relevant and the results were presented separately. The publication dates for these three RCTs were 2007, 2009 and 2011. Of these three RCTs on micronized progesterone capsules, two RCTs compared it with placebo and one RCT compared it with no treatment. The number of patients in the RCTs ranged between 100 and 677. Outcomes reported included preterm birth, delivery mode, intrauterine death, antenatal tocolysis, birth weight, admission to neonatal intensive care unit [NICU], perinatal death, neonatal death, and perinatal complications.

### Randomized controlled trial

Two relevant RCTs<sup>10,11</sup> on vaginally administered micronized progesterone capsule were selected for inclusion even though they were included in the systematic review described above, as the study reports contained additional information on adverse effects relevant for this report. One RCT<sup>10</sup> was a multi-center double blind placebo controlled study, published in 2011 from Europe and involved 677 women of mean age 32 years and with twin pregnancies. One RCT<sup>11</sup> was a single center study, published in 2009 from India, and involved 100 women of mean age 26 years with previous history of preterm birth and currently with singleton pregnancies. It compared micronized progesterone capsule with no treatment. Both studies reported on preterm birth, birth weight, admission to the NICU, and perinatal complications. One RCT<sup>10</sup> also reported on miscarriage, intrauterine death, tocolytic therapy, corticosteroid treatment of fetal lung maturation, adverse events and infant death. One RCT<sup>11</sup> reported on hospitalization and delivery mode.

## **Summary of Critical Appraisal**

### Systematic review

The included systematic review<sup>6</sup> was well conducted. The objectives, inclusion and exclusion criteria were stated. Multiple databases were searched. Article selection, data extraction and quality assessment were done in duplicate. Lists of included and excluded studies were provided. Characteristics of the individual studies were provided. Publication bias was explored and there was suggestion of potential bias. Authors declared their conflict of interest and there appeared to be none.

### Randomized controlled trial

In both included RCTs,<sup>10,11</sup> the objectives, inclusion and exclusion criteria, patient characteristics, interventions and outcomes and sample size calculations were explicitly described. Intent-to-treat (ITT) analysis was performed and P-values or 95% confidence intervals (CIs) were provided. Randomization was appropriately conducted. One RCT<sup>10</sup> was double blinded and one RCT<sup>11</sup> did not report on blinding.

Strengths and limitations of individual studies are provided in Appendix 3.

## **Summary of Findings**

The overall findings from the systematic review and RCTs are summarized below and details are available in Appendix 4.

### What is the clinical efficacy of vaginal use of micronized progesterone capsules to prevent miscarriage and preterm birth?

### Systematic review

The relative risk (RR) for preterm birth < 37 weeks was lower with micronized progesterone capsule compared to placebo or no treatment in two RCTs but statistically significant in one and did not reach statistical significance in the other (RR 0.32, 95% CI [confidence interval] 0.14 to

0.72 and RR 0.90, 95% CI 0.77 to 1.05). The RR for preterm birth < 34 weeks was lower with progesterone compared with placebo or no treatment, in three RCTs but statistically significant in one RCT and did not reach statistical significance in two RCTs (RR [95% CI]: 0.58 [0.38 to 0.87], 0.67 [0.12 to 3.82] and 0.83 [0.59 to 1.16]). The RR for micronized progesterone capsule compared with placebo or no treatment did not reach statistical significance for Cesarean section delivery, vaginal delivery, fetal death, antenatal tocolysis, perinatal death, neonatal death, and neonatal outcomes (respiratory distress syndrome, need for assisted ventilation, intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis and Apgar score < 7 at 5 minutes). The RR for micronized progesterone capsule compared with placebo for birth weight <2,500 g was statistically significant in one study and not statistically significant in one study (RR [95% CI]: 0.96 [0.73 to 1.27] and 0.88 [0.79 to 0.98]). The RR for micronized progesterone capsule compared with placebo or no treatment for admission to NICU was statistically significant in one study and not statistically significant in one study (RR [95% CI]: 0.11 [0.01 to 2.01] and 0.89 [0.79 to 0.99]) The RRs for micronized progesterone capsule compared with placebo for maternal adverse events (gestational diabetes and pre-eclampsia) were not statistically significant.

### Randomized controlled trial

Two relevant RCTs were identified. As these RCTs were also included in the included systematic review, only results that were not described in the systematic review will be presented here.

In one RCT<sup>10</sup> the rate of miscarriage was similar in both the micronized progesterone capsule and placebo groups (RR [95% CI]: 1.0 [0.1 to 16.4]). The RRs for micronized progesterone capsule compared with placebo for maternal adverse events (gestational diabetes and pre-eclampsia) were not statistically significant. There was greater risk of increase in liver enzymes with micronized progesterone capsule compared with placebo (RR [95% CI]: 0.4 [0.2 to 0.9]).

In one RCT<sup>11</sup> the risk of hospitalization was lower with micronized progesterone capsule compared with no treatment but not statistically significant (RR [95% CI]: 0.33 [0.04 to 3.096]).

### **Limitations**

The included systematic review had a broad scope and hence presented pooled results of studies using different forms of progesterone. Since the focus of the current report is micronized progesterone capsules, pooled results presented in the systematic review could not be used. However, the results of individual studies were presented separately and are included here.

It was difficult to compare results across studies as the populations varied. Of the two included RCTs one study involved women with singleton pregnancy and one study involved women with twin pregnancy. The mechanism of initiation of preterm labour may be different in twin pregnancies and singleton pregnancies and this could affect treatment results.

Results for some outcomes were sometimes statistically significant and sometimes not, hence results need to be interpreted with caution.

Not all studies reported all outcomes. Information on long term infant and childhood outcomes were lacking.



None of the included studies were conducted in Canada hence results may not be generalizable to the Canadian setting.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

Limited evidence suggests that the risks of preterm birth < 37 weeks or < 34 weeks may be lower with micronized progesterone capsules compared with placebo or no treatment. However, there were inconsistencies with respect to statistical significance and results need to be interpreted with caution. One study suggested that the risk of miscarriage in women with singleton pregnancy who had a history of preterm birth was similar for treatment with either micronized progesterone capsule or placebo. There was no statistically significant difference in risk of neonatal complications between micronized progesterone capsule and placebo. Results across studies with respect to birth weight <2,500 g, neonatal sepsis, and admission to NICU were inconsistent. Information on long term efficacy and safety of micronized progesterone capsules are lacking.

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REFERENCES

1. Live births and fetal deaths (stillbirths), by type (single or multiple), Canada, provinces and territories. Table 102-4515 [Internet]. Ottawa: Statistics Canada; 2013 Mar 18. [cited 2014 Apr 17]. Available from: <http://www5.statcan.gc.ca/cansim/a05?lang=eng&id=1024515&pattern=1024515&searchTypeByValue=1&p2=35>
2. Su LL, Samuel M, Chong YS. Progestational agents for treating threatened or established preterm labour. Cochrane Database Syst Rev [Internet]. 2014 [cited 2014 Mar 31];1:CD006770. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006770.pub3/pdf>
3. Haas DM. Preterm birth. Clin Evid [Internet]. 2011 [cited 2014 Apr 17];2011:1404. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217816/pdf/2011-1404.pdf>
4. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol [Internet]. 2012 Feb [cited 2014 Mar 31];206(2):124-19. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437773>
5. Progesterone: drug information. 2014 [cited 2014 Apr 25]. In: UpToDate [Internet]. Version 17.0. Waltham (MA): UpToDate; c2005 - . Available from: [www.uptodate.com](http://www.uptodate.com) Subscription required.
6. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev [Internet]. 2013 [cited 2014 Mar 31];7:CD004947. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004947.pub3/pdf>
7. PrPrometrium® (progesterone capsules) 100mg progestin [product monograph]. Kirkland (QC): Merck Canada Inc.; 2013 Aug 28.
8. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2014 Apr 17];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>
9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Apr 9];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>
10. Rode L, Klein K, Nicolaides KH, Krampfl-Bettelheim E, Tabor A, PREDICT Group. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. Ultrasound

Obstet Gynecol [Internet]. 2011 Sep [cited 2014 Mar 31];38(3):272-80. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/uog.9093/pdf>

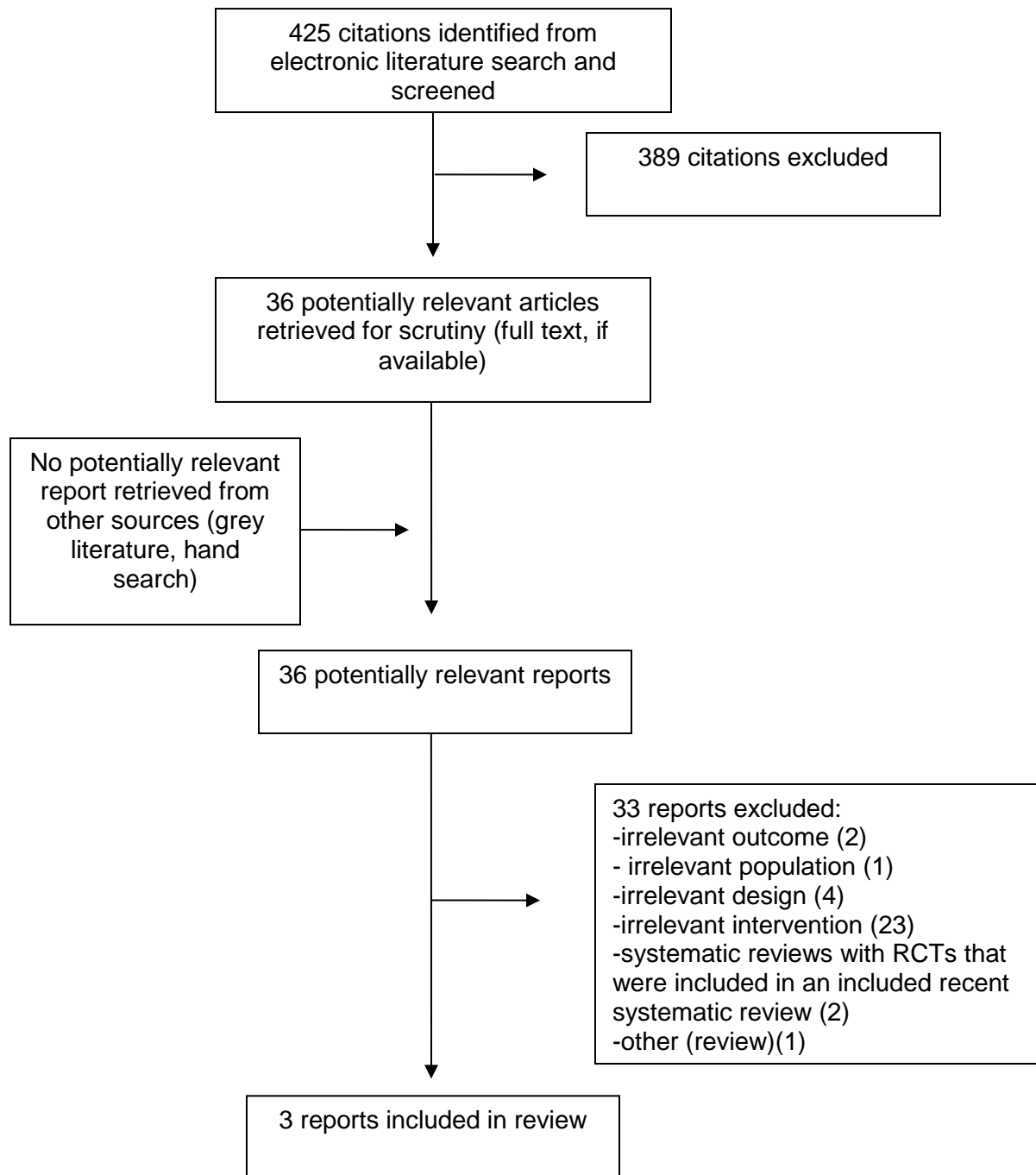
11. Majhi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronised progesterone to prevent pre-term birth: a randomised trial in India. J Obstet Gynaecol. 2009 Aug;29(6):493-8.



## ABBREVIATIONS

CI	confidence interval
ITT	intent-to-treat
NICU	neonatal intensive care unit
NR	not reported
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation

APPENDIX 1: Selection of Included Studies



**APPENDIX 2: Characteristics of Included Studies**

<b>First Author, Publication Year, Country</b>	<b>Study Design,</b>	<b>Patient Characteristics, Sample Size (N)</b>	<b>Comparison</b>	<b>Outcomes Measured</b>
<b>Systematic review</b>				
Dodd, <sup>6</sup> 2013, Cochrane collaboration	Systematic review (included 36 RCTs of which 3 RCTs were relevant for this report)	Women with singleton or multiple pregnancy with previous history of prior spontaneous preterm birth or ultrasound identified short cervix  N = 1027 (250+ 677+ 100) for the 3 relevant RCTs	Progesteron (different forms and different routes of administration) versus placebo or no treatment.  Only the relevant comparisons (comparison of micronized progesterone capsule versus placebo or no treatment) are considered here	Preterm birth, delivery mode, fetal death, antenatal tocolysis.  Birth weight, perinatal death, neonatal sepsis, neonatal death, admission to NICU, perinatal complications
<b>Randomized controlled trial</b>				
Rode, <sup>10</sup> 2011, Europe (study - PREDICT)	Multi-centre, double blind RCT	Women with live, diamniotic twin pregnancy and chorionicity assessed by ultrasound before 16 weeks' gestation.  N = 677  Age in years (mean± SD): 32.0± 4.5 (progesterone), 31.9± 4.4 (placebo)	Micronized progesterone capsule (200 mg) versus placebo; both administered vaginally	Preterm birth, miscarriage, intrauterine death, tocolytic therapy, corticosteroid treatment for fetal lung maturation, adverse events.  Birth weight, infant death, admission to NICU, perinatal complications
Majhi, <sup>11</sup> 2009, India	Single centre RCT; blinding not reported	Women at high risk <sup>a</sup> of preterm birth, having a singleton pregnancy.  N =100  Age in years	Micronized progesterone capsule (100mg) inserted vaginally once daily at bedtime versus no treatment	Preterm birth, delivery mode, hospitalization  Birth weight, admission to NICU, perinatal complications

First Author, Publication Year, Country	Study Design,	Patient Characteristics, Sample Size (N)	Comparison	Outcomes Measured
		(mean± SD): 26.56± 3.5 (progesterone), 26.42± 3.2 (no treatment)		
<p>NICU = neonatal intensive care unit  <sup>a</sup>High risk: history of at least once prior spontaneous preterm birth of singleton infant &gt; 20 weeks and &lt; 37 weeks as a result of spontaneous labour or preterm rupture of fetal membranes</p>				

**APPENDIX 3: Summary of Study Strengths and Limitations**

First Author, Publication Year, Country	Strengths	Limitations
<b>Systematic review</b>		
Dodd, <sup>6</sup> 2013, Cochrane collaboration	<ul style="list-style-type: none"> <li>• The objective was clearly stated.</li> <li>• The inclusion and exclusion criteria were stated.</li> <li>• Multiple databases searched, as well as hand searching of relevant journals and major conference proceedings</li> <li>• Study selection was described</li> <li>• List of included and excluded studies provided</li> <li>• Article selection and data extraction were done in duplicate</li> <li>• Characteristics of the individual studies were provided</li> <li>• Quality assessments of studies were conducted in duplicate</li> <li>• Publication bias was explored with Funnel plot. There was considerable asymmetry in the Funnel plot, suggesting potential for bias.</li> <li>• Conflict of interest was declared and there appeared to be none</li> </ul>	<ul style="list-style-type: none"> <li>• A flow chart of study selection was not presented but the selection process was described.</li> </ul>
<b>Randomized controlled trial</b>		
Rode, <sup>10</sup> 2011, UK (study -PREDICT)	<ul style="list-style-type: none"> <li>• Objectives were clearly stated.</li> <li>• Inclusion/ exclusion criteria were stated.</li> <li>• Patient characteristics, interventions, and outcomes were described.</li> <li>• Randomized by creating a randomized sequence and using a interactive voice-response randomization system; patients and study personnel were blinded,</li> <li>• Number lost to follow up were reported (0.2%)</li> <li>• Sample size calculation was described</li> <li>• ITT analysis</li> <li>• 95% confidence intervals provided</li> </ul>	<ul style="list-style-type: none"> <li>• Generalizability limited; population restricted to women with twin pregnancy and were from hospitals in Denmark and Austria</li> </ul>
Majhi, <sup>11</sup> 2009, India	<ul style="list-style-type: none"> <li>• Objectives were clearly stated.</li> <li>• Inclusion/ exclusion criteria were stated.</li> </ul>	<ul style="list-style-type: none"> <li>• Blinding not reported; control group received no treatment so participants would have been</li> </ul>

First Author, Publication Year, Country	Strengths	Limitations
	<ul style="list-style-type: none"> <li>• Patient characteristics, interventions, and outcomes were described.</li> <li>• Randomized using computer generated random numbers tables; investigators were not involved in randomization procedure</li> <li>• None lost to follow up</li> <li>• Sample size calculation was described</li> <li>• ITT analysis</li> <li>• P value or 95% confidence intervals provided</li> </ul>	<ul style="list-style-type: none"> <li>• aware of assignment.</li> <li>• Generalizability limited; population restricted to women with singleton pregnancy and previous history of preterm birth from a single center in India</li> </ul>



**APPENDIX 4: Main Study Findings and Authors' Conclusions**

First Author, Publication Year, Country	Main Findings and Authors' Conclusion																																																																																							
<b>Systematic reviews</b>																																																																																								
Dodd, <sup>6</sup> 2013, Cochrane collaboration	<p><b>Main Findings:</b></p> <p><b>Maternal outcomes</b></p> <table border="1" data-bbox="472 541 1377 1136"> <thead> <tr> <th data-bbox="472 541 753 667">Outcome</th> <th colspan="3" data-bbox="753 541 1377 575">Study</th> </tr> <tr> <td data-bbox="472 575 753 667"></td> <td data-bbox="753 575 940 667">Fonesca 2007 N=250</td> <td data-bbox="940 575 1167 667">Majhi 2009 N=100</td> <td data-bbox="1167 575 1377 667">Rode 2011 N=675</td> </tr> <tr> <td data-bbox="472 667 753 701"></td> <td colspan="3" data-bbox="753 667 1377 701">RR (95% CI)</td> </tr> </thead> <tbody> <tr> <td data-bbox="472 701 753 758">Preterm birth&lt;28 weeks</td> <td data-bbox="753 701 940 758">NR</td> <td data-bbox="940 701 1167 758">NR</td> <td data-bbox="1167 701 1377 758">1.31 (0.49, 3.48)</td> </tr> <tr> <td data-bbox="472 758 753 814">Preterm birth&lt;34 weeks</td> <td data-bbox="753 758 940 814">0.58 (0.38, 0.87)</td> <td data-bbox="940 758 1167 814">0.67 (0.12, 3.82)</td> <td data-bbox="1167 758 1377 814">0.83 (0.59, 1.16)</td> </tr> <tr> <td data-bbox="472 814 753 871">Preterm birth&lt;37 weeks</td> <td data-bbox="753 814 940 871">NR</td> <td data-bbox="940 814 1167 871">0.32 (0.14, 0.72)</td> <td data-bbox="1167 814 1377 871">0.90 (0.77, 1.05)</td> </tr> <tr> <td data-bbox="472 871 753 928">Caesarian section</td> <td data-bbox="753 871 940 928">NR</td> <td data-bbox="940 871 1167 928">0.57 (0.18, 1.83)</td> <td data-bbox="1167 871 1377 928">0.91 (0.81, 1.01)</td> </tr> <tr> <td data-bbox="472 928 753 984">Spontaneous vaginal delivery</td> <td data-bbox="753 928 940 984">NR</td> <td data-bbox="940 928 1167 984">1.07 (0.93, 1.23)</td> <td data-bbox="1167 928 1377 984">NR</td> </tr> <tr> <td data-bbox="472 984 753 1041">Intrauterine fetal death</td> <td data-bbox="753 984 940 1041">1.01 (0.06, 16.06)</td> <td data-bbox="940 984 1167 1041">NR</td> <td data-bbox="1167 984 1377 1041">0.61 (0.15, 2.55)</td> </tr> <tr> <td data-bbox="472 1041 753 1098">Antenatal tocolysis</td> <td data-bbox="753 1041 940 1098">NR</td> <td data-bbox="940 1041 1167 1098">NR</td> <td data-bbox="1167 1041 1377 1098">0.70 (0.48, 1.01)</td> </tr> </tbody> </table> <p data-bbox="472 1136 1377 1169">CI = confidence interval, NR = not reported, RR = relative risk</p> <p><b>Neonatal outcomes</b></p> <table border="1" data-bbox="472 1230 1377 1879"> <thead> <tr> <th data-bbox="472 1230 753 1356">Outcome</th> <th colspan="3" data-bbox="753 1230 1377 1264">Study</th> </tr> <tr> <td data-bbox="472 1264 753 1356"></td> <td data-bbox="753 1264 940 1356">Fonesca 2007 N=250</td> <td data-bbox="940 1264 1167 1356">Majhi 2009 N=100</td> <td data-bbox="1167 1264 1377 1356">Rode 2011 N=675</td> </tr> <tr> <td data-bbox="472 1356 753 1390"></td> <td colspan="3" data-bbox="753 1356 1377 1390">RR (95% CI)</td> </tr> </thead> <tbody> <tr> <td data-bbox="472 1390 753 1446">Birth weight &lt; 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	Retinopathy of prematurity	5.07 (0.25, 104.70)	NR	1.02 (0.26, 4.07)																																																												
	Necrotizing enterocolitis	0.34 (0.01, 8.23)	NR	0.51 (0.05, 5.63)																																																												
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	<p><b>Authors' Conclusion:</b>                      "The use of progesterone is associated with benefits in infant health following administration in women considered to be at increased risk of preterm birth due either to a prior preterm birth or where a short cervix has been identified on ultrasound examination. However, there is limited information available relating to longer-term infant and childhood outcomes, the assessment of which remains a priority.                      Further trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone therapy when given to women considered to be at increased risk of early birth." P.2</p> <p>(Note: Above conclusion by author is based on various routes of administration and forms of progesterone)</p>																																																															
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Rode, <sup>10</sup> 2011, UK (study -PREDICT)	<p><b>Main Findings:</b></p> <p><b>Maternal outcomes ( twin pregnancy)</b></p> <table border="1" data-bbox="472 1142 1433 1713"> <thead> <tr> <th data-bbox="472 1142 846 1236">Outcome</th> <th data-bbox="846 1142 1029 1236">Progesterone N=334 n (%)</th> <th data-bbox="1029 1142 1203 1236">Placebo N= 341 n (%)</th> <th data-bbox="1203 1142 1433 1236">OR (95% CI)</th> </tr> </thead> <tbody> <tr> <td data-bbox="472 1236 846 1268">Preterm birth &lt; 22 weeks )</td> <td data-bbox="846 1236 1029 1268">1 (0.3)</td> <td data-bbox="1029 1236 1203 1268">1 (0.3)</td> <td data-bbox="1203 1236 1433 1268">1.0 (0.1, 16.4)</td> </tr> <tr> <td data-bbox="472 1268 846 1299">Preterm birth &lt; 28 weeks</td> <td data-bbox="846 1268 1029 1299">9 (2.7)</td> <td data-bbox="1029 1268 1203 1299">7 (2.1)</td> <td data-bbox="1203 1268 1433 1299">1.3 (0.5, 3.6)</td> </tr> <tr> <td data-bbox="472 1299 846 1331">Preterm birth &lt; 32 weeks</td> <td data-bbox="846 1299 1029 1331">24 (7.2)</td> <td data-bbox="1029 1299 1203 1331">31 (9.1)</td> <td data-bbox="1203 1299 1433 1331">0.8 (0.4, 1.3)</td> </tr> <tr> <td data-bbox="472 1331 846 1362">Preterm birth &lt; 34 weeks</td> <td data-bbox="846 1331 1029 1362">51 (15.3)</td> <td data-bbox="1029 1331 1203 1362">63 (18.5)</td> <td data-bbox="1203 1331 1433 1362">0.8 (0.5, 1.2)</td> </tr> <tr> <td data-bbox="472 1362 846 1394">Preterm birth &lt; 37 weeks</td> <td data-bbox="846 1362 1029 1394">158 (47.3)</td> <td data-bbox="1029 1362 1203 1394">179 (52.5)</td> <td data-bbox="1203 1362 1433 1394">0.8 (0.6, 1.1)</td> </tr> <tr> <td data-bbox="472 1394 846 1425">Miscarriage</td> <td data-bbox="846 1394 1029 1425">1 (0.3)</td> <td data-bbox="1029 1394 1203 1425">1 (0.3)</td> <td data-bbox="1203 1394 1433 1425">1.0 (0.1, 16.4)</td> </tr> <tr> <td data-bbox="472 1425 846 1457">Intrauterine death<sup>a</sup></td> <td data-bbox="846 1425 1029 1457">2 (0.6)</td> <td data-bbox="1029 1425 1203 1457">2 (0.6)</td> <td data-bbox="1203 1425 1433 1457">1.0 (0.1, 7.3)</td> </tr> <tr> <td data-bbox="472 1457 846 1520">Corticosteroid treatment for fetal lung maturation<sup>b</sup></td> <td data-bbox="846 1457 1029 1520">76 (22.8)</td> <td data-bbox="1029 1457 1203 1520">97 (28.4)</td> <td data-bbox="1203 1457 1433 1520">0.7 (0.5, 1.0)</td> </tr> <tr> <td data-bbox="472 1520 846 1551">Tocolytic therapy</td> <td data-bbox="846 1520 1029 1551">41 (12.3)</td> <td data-bbox="1029 1520 1203 1551">60 (17.6)</td> <td data-bbox="1203 1520 1433 1551">0.7 (0.4, 1.0)</td> </tr> <tr> <td data-bbox="472 1551 846 1583"><b>Maternal adverse outcomes<sup>c</sup></b></td> <td data-bbox="846 1551 1029 1583"></td> <td data-bbox="1029 1551 1203 1583"></td> <td data-bbox="1203 1551 1433 1583"></td> </tr> <tr> <td data-bbox="472 1583 846 1614">- Gestational diabetes</td> <td data-bbox="846 1583 1029 1614">16 (4.8)</td> <td data-bbox="1029 1583 1203 1614">12 (3.5)</td> <td data-bbox="1203 1583 1433 1614">1.4 (0.6, 3.0)</td> </tr> <tr> <td data-bbox="472 1614 846 1646">- Increased liver enzymes</td> <td data-bbox="846 1614 1029 1646">11 (3.3)</td> <td data-bbox="1029 1614 1203 1646">25 (7.3)</td> <td data-bbox="1203 1614 1433 1646">0.4 (0.2, 0.9)</td> </tr> <tr> <td data-bbox="472 1646 846 1677">- Pre-eclampsia</td> <td data-bbox="846 1646 1029 1677">27 (8.1)</td> <td data-bbox="1029 1646 1203 1677">30 (8.8)</td> <td data-bbox="1203 1646 1433 1677">0.9 (0.5, 1.5)</td> </tr> <tr> <td data-bbox="472 1677 846 1709">- Thromboembolic event</td> <td data-bbox="846 1677 1029 1709">0 (0)</td> <td data-bbox="1029 1677 1203 1709">1 (0.3)</td> <td data-bbox="1203 1677 1433 1709">NA</td> </tr> </tbody> </table> <p data-bbox="472 1713 1433 1745">CI = confidence interval; OR = odds ratio; NA = not applicable</p> <p data-bbox="472 1745 1433 1776"><sup>a</sup> In all cases, death of one twin only</p> <p data-bbox="472 1776 1433 1808"><sup>b</sup> For this outcome number used for analysis in progesterone group was 333</p> <p data-bbox="472 1808 1433 1860"><sup>c</sup> For these outcomes, number used for analysis in progesterone group was 332</p>				Outcome	Progesterone N=334 n (%)	Placebo N= 341 n (%)	OR (95% CI)	Preterm birth < 22 weeks )	1 (0.3)	1 (0.3)	1.0 (0.1, 16.4)	Preterm birth < 28 weeks	9 (2.7)	7 (2.1)	1.3 (0.5, 3.6)	Preterm birth < 32 weeks	24 (7.2)	31 (9.1)	0.8 (0.4, 1.3)	Preterm birth < 34 weeks	51 (15.3)	63 (18.5)	0.8 (0.5, 1.2)	Preterm birth < 37 weeks	158 (47.3)	179 (52.5)	0.8 (0.6, 1.1)	Miscarriage	1 (0.3)	1 (0.3)	1.0 (0.1, 16.4)	Intrauterine death <sup>a</sup>	2 (0.6)	2 (0.6)	1.0 (0.1, 7.3)	Corticosteroid treatment for fetal lung maturation <sup>b</sup>	76 (22.8)	97 (28.4)	0.7 (0.5, 1.0)	Tocolytic therapy	41 (12.3)	60 (17.6)	0.7 (0.4, 1.0)	<b>Maternal adverse outcomes<sup>c</sup></b>				- Gestational diabetes	16 (4.8)	12 (3.5)	1.4 (0.6, 3.0)	- Increased liver enzymes	11 (3.3)	25 (7.3)	0.4 (0.2, 0.9)	- Pre-eclampsia	27 (8.1)	30 (8.8)	0.9 (0.5, 1.5)	- Thromboembolic event	0 (0)	1 (0.3)	NA
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	<p><b>Maternal side effects by organ type</b></p> <table border="1" data-bbox="472 369 1425 716"> <thead> <tr> <th>Outcome</th> <th>Progesterone N=334 n (%)</th> <th>Placebo N= 341 n (%)</th> </tr> </thead> <tbody> <tr> <td>Central nervous system</td> <td>32 (9.6)</td> <td>39 (11.4)</td> </tr> <tr> <td>Skin</td> <td>11 (3.3)</td> <td>10 (2.9)</td> </tr> <tr> <td>Gastrointestinal</td> <td>13 (3.9)</td> <td>21 (6.2)</td> </tr> <tr> <td>Reproductive system and breast (includes as well vaginal discharge and itching)</td> <td>194 (58.1)</td> <td>213 (62.5)</td> </tr> <tr> <td>Miscellaneous</td> <td>13 (3.9)</td> <td>16 (4.7)</td> </tr> </tbody> </table> <p><b>Neonatal outcomes ( twin pregnancy)</b></p> <table border="1" data-bbox="472 835 1425 1472"> <thead> <tr> <th>Outcome</th> <th>Progesterone n/N</th> <th>Placebo n/N</th> <th>OR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Birth weight &lt;2500g</td> <td>306/659</td> <td>357/677</td> <td>0.8 (0.6, 1.0)</td> </tr> <tr> <td>Birth weight &lt;1500g</td> <td>36/659</td> <td>48/677</td> <td>0.8 (0.4,1.4)</td> </tr> <tr> <td>Infant death</td> <td>9/664</td> <td>8/678</td> <td>1.2 (0.3, 4.0)</td> </tr> <tr> <td>Congenital or chromosomal anomalies</td> <td>25/663</td> <td>27/677</td> <td>1.0 (0.5, 1.7)</td> </tr> <tr> <td>Perinatal complications</td> <td></td> <td></td> <td></td> </tr> <tr> <td>-Hypoglycemia</td> <td>30/659</td> <td>48/674</td> <td>0.6(0.4, 1.1)</td> </tr> <tr> <td>-Intraventricular hemorrhage</td> <td>10/659</td> <td>6/674</td> <td>1.7 (0.5, 5.6)</td> </tr> <tr> <td>-Jaundice</td> <td>106/659</td> <td>116/674</td> <td>0.9 (0.6, 1.3)</td> </tr> <tr> <td>-Necrotizing enterocolitis</td> <td>1/659</td> <td>2/674</td> <td>0.5 (0.0, 5.6)</td> </tr> <tr> <td>-Patent ductus arteriosus</td> <td>12/659</td> <td>19/674</td> <td>0.6 (0.3, 1.5)</td> </tr> <tr> <td>-Respiratory syndrome</td> <td>73/659</td> <td>69/674</td> <td>1.1 (0.7, 1.7)</td> </tr> <tr> <td>-Retinopathy of prematurity</td> <td>4/659</td> <td>4/674</td> <td>1.0 (0.2, 4.8)</td> </tr> <tr> <td>-Septicemia</td> <td>20/659</td> <td>18/674</td> <td>1.1 (0.5, 2.4)</td> </tr> <tr> <td>Admission to NICU</td> <td>307/664</td> <td>354/678</td> <td>0.8 (0.6, 1.1)</td> </tr> <tr> <td>CPAP treatment of at least 24 h</td> <td>105/659</td> <td>121/674</td> <td>0.9 (0.6, 1.13)</td> </tr> <tr> <td>Respirator treatment</td> <td>12/659</td> <td>12/674</td> <td>1.0 (0.4, 2.6)</td> </tr> </tbody> </table> <p>CI = confidence interval; CPAP = continuous positive airway pressure; OR = odds ratio; NA = not applicable; NICU = neonatal intensive care unit  <sup>a</sup> In all cases, death of one twin only</p>				Outcome	Progesterone N=334 n (%)	Placebo N= 341 n (%)	Central nervous system	32 (9.6)	39 (11.4)	Skin	11 (3.3)	10 (2.9)	Gastrointestinal	13 (3.9)	21 (6.2)	Reproductive system and breast (includes as well vaginal discharge and itching)	194 (58.1)	213 (62.5)	Miscellaneous	13 (3.9)	16 (4.7)	Outcome	Progesterone n/N	Placebo n/N	OR (95% CI)	Birth weight <2500g	306/659	357/677	0.8 (0.6, 1.0)	Birth weight <1500g	36/659	48/677	0.8 (0.4,1.4)	Infant death	9/664	8/678	1.2 (0.3, 4.0)	Congenital or chromosomal anomalies	25/663	27/677	1.0 (0.5, 1.7)	Perinatal complications				-Hypoglycemia	30/659	48/674	0.6(0.4, 1.1)	-Intraventricular hemorrhage	10/659	6/674	1.7 (0.5, 5.6)	-Jaundice	106/659	116/674	0.9 (0.6, 1.3)	-Necrotizing enterocolitis	1/659	2/674	0.5 (0.0, 5.6)	-Patent ductus arteriosus	12/659	19/674	0.6 (0.3, 1.5)	-Respiratory syndrome	73/659	69/674	1.1 (0.7, 1.7)	-Retinopathy of prematurity	4/659	4/674	1.0 (0.2, 4.8)	-Septicemia	20/659	18/674	1.1 (0.5, 2.4)	Admission to NICU	307/664	354/678	0.8 (0.6, 1.1)	CPAP treatment of at least 24 h	105/659	121/674	0.9 (0.6, 1.13)	Respirator treatment	12/659	12/674	1.0 (0.4, 2.6)
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Majhi, <sup>11</sup> 2009, India	<p><b>Main Findings:</b></p> <p><b>Maternal outcomes (singleton pregnancy)</b></p> <table border="1" data-bbox="472 432 1425 747"> <thead> <tr> <th>Outcome</th> <th>Progesterone N=50 n (%)</th> <th>No progesterone N=50 n (%)</th> <th>RR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Preterm birth ≤ 34 weeks</td> <td>2 (4)</td> <td>3 (6)</td> <td>0.67 (0.12, 3.82)</td> </tr> <tr> <td>Preterm birth &lt; 37 weeks</td> <td>6 (12)</td> <td>19 (38)</td> <td>0.32 (0.14, 0.72)</td> </tr> <tr> <td>Hospitalization</td> <td>1 (2)</td> <td>3 (6)</td> <td>0.33 (0.04, 3.096)</td> </tr> <tr> <td>Vaginal delivery</td> <td>46 (92)</td> <td>43 (86)</td> <td>1.07 (0.93, 1.23)</td> </tr> <tr> <td>LSCS</td> <td>4 (8)</td> <td>7 (14)</td> <td>0.57 (0.18, 1.83)</td> </tr> </tbody> </table> <p>CI = confidence interval; LCSC = lower segment cesarian section; RR = relative risk</p> <p><b>Neonatal outcomes</b></p> <table border="1" data-bbox="472 898 1425 1245"> <thead> <tr> <th>Outcome</th> <th>Progesterone</th> <th>No progesterone</th> <th>RR (95% CI)<sup>a</sup></th> </tr> </thead> <tbody> <tr> <td>Birth weight (g) (mean ± SD)</td> <td>2813 ± 501</td> <td>2599 ± 421</td> <td>214.38 (30.66, 398.09)<sup>b</sup></td> </tr> <tr> <td>NICU</td> <td>0 (0)</td> <td>4 (8)</td> <td>P = 0.12</td> </tr> <tr> <td>Sepsis</td> <td>0 (0)</td> <td>3 (6)</td> <td>P = 0.16</td> </tr> <tr> <td>Hyperbilirubinaemia</td> <td>1 (2)</td> <td>3 (6)</td> <td>0.33 (0.04, 3.09)</td> </tr> <tr> <td>Necrotising enterocolitis</td> <td>0 (0)</td> <td>1 (2)</td> <td>P = 0.31</td> </tr> <tr> <td>Cord pH (mean ± SD)</td> <td>7.257 ± 0.047</td> <td>7.262 ± 0.045</td> <td>0.005 (-0.013, 0.023)<sup>b</sup></td> </tr> </tbody> </table> <p>CI = confidence interval; g = gram; RR = relative risk; SD = standard deviation  <sup>a</sup> Unless otherwise mentioned  <sup>b</sup> Mean difference (95% CI)</p>	Outcome	Progesterone N=50 n (%)	No progesterone N=50 n (%)	RR (95% CI)	Preterm birth ≤ 34 weeks	2 (4)	3 (6)	0.67 (0.12, 3.82)	Preterm birth < 37 weeks	6 (12)	19 (38)	0.32 (0.14, 0.72)	Hospitalization	1 (2)	3 (6)	0.33 (0.04, 3.096)	Vaginal delivery	46 (92)	43 (86)	1.07 (0.93, 1.23)	LSCS	4 (8)	7 (14)	0.57 (0.18, 1.83)	Outcome	Progesterone	No progesterone	RR (95% CI) <sup>a</sup>	Birth weight (g) (mean ± SD)	2813 ± 501	2599 ± 421	214.38 (30.66, 398.09) <sup>b</sup>	NICU	0 (0)	4 (8)	P = 0.12	Sepsis	0 (0)	3 (6)	P = 0.16	Hyperbilirubinaemia	1 (2)	3 (6)	0.33 (0.04, 3.09)	Necrotising enterocolitis	0 (0)	1 (2)	P = 0.31	Cord pH (mean ± SD)	7.257 ± 0.047	7.262 ± 0.045	0.005 (-0.013, 0.023) <sup>b</sup>
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