Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

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

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.[5] It assists in maintaining pregnancy by suppressing smooth muscle activity in the uterus and keeping the uterus quiescent until term.[2,6] 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.[6] 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.[7] 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.

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

Population	Pregnant women
Intervention	Micronized progesterone capsule (Prometrium) administered vaginally
Comparator	Placebo, No treatment
Outcomes	Prevention of miscarriage, preterm birth, membrane rupture, adverse events
Study Designs	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 progestrerone 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[8] was used for systematic reviews and the Downs and Black checklist[9] 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[6] and two RCTs[10,11] 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

<u>Systematic review</u>

One relevant systematic review[6] 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[10,11] 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[10] 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[11] 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[10] also reported on miscarriage, intrauterine death, tocolytic therapy, corticosteroid treatment of fetal lung maturation, adverse events and infant death. One RCT[11] reported on hospitalization and delivery mode.

Summary of Critical Appraisal

Systematic review

The included systematic review[6] 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.

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Randomized controlled trial

In both included RCTs,[10,11] 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[10] was double blinded and one RCT[11] 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 Ceasarian 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 to1.27] and 0.88 [0.79 to0.98]). 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[10] 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[11] 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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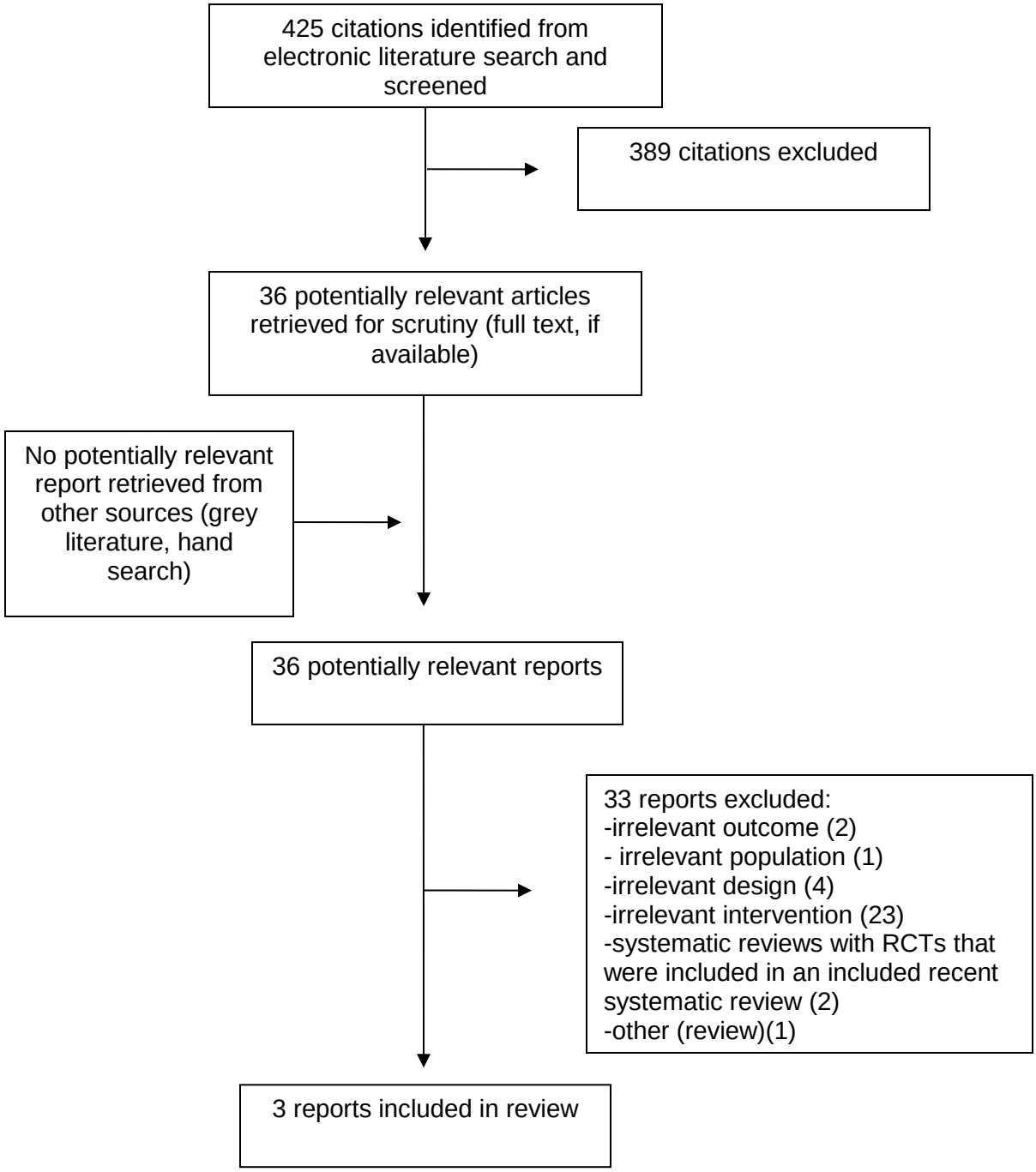
ABBREVIATIONS

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

First Author, Publication Year, Country	Study Design,	Patient Characteristics, Sample Size (N)	Comparison	Outcomes Measured
Systematic review				
Dodd, [6] 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
Randomized controlled trial				
Rode,[10] 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,[11] 2009, India	Single centre RCT; blinding not reported	Women at high risk[a] 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)		

NICU = neonatal intensive care unit
[a]High risk: history of at least once prior spontaneous preterm birth of singleton infant > 20 weeks and < 37 weeks as a result of spontaneous labour or preterm rupture of fetal membranes

APPENDIX 3: Summary of Study Strengths and Limitations

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

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

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Systematic reviews</td><td></td></tr>
<tr><td>Dodd, [6] 2013, Cochrane collaboration</td><td>
Main Findings:

Maternal outcomes
<table>
<tr><td>Outcome</td><td>Study</td><td></td><td></td></tr>
<tr><td></td><td>Fonesca 2007 N=250</td><td>Majhi 2009 N=100</td><td>Rode 2011 N=675</td></tr>
<tr><td></td><td colspan="3">RR (95% CI)</td></tr>
<tr><td>Preterm birth<28 weeks</td><td>NR</td><td>NR</td><td>1.31 (0.49, 3.48)</td></tr>
<tr><td>Preterm birth<34 weeks</td><td>0.58 (0.38, 0.87)</td><td>0.67 (0.12, 3.82)</td><td>0.83 (0.59, 1.16)</td></tr>
<tr><td>Preterm birth<37 weeks</td><td>NR</td><td>0.32 (0.14, 0.72)</td><td>0.90 (0.77, 1.05)</td></tr>
<tr><td>Caesarian section</td><td>NR</td><td>0.57 (0.18, 1.83)</td><td>0.91 (0.81, 1.01)</td></tr>
<tr><td>Spontaneous vaginal delivery</td><td>NR</td><td>1.07 (0.93, 1.23)</td><td>NR</td></tr>
<tr><td>Intrauterine fetal death</td><td>1.01 (0.06, 16.06)</td><td>NR</td><td>0.61 (0.15, 2.55)</td></tr>
<tr><td>Antenatal tocolysis</td><td>NR</td><td>NR</td><td>0.70 (0.48, 1.01)</td></tr>
<tr><td colspan="4">CI = confidence interval, NR = not reported, RR = relative risk</td></tr>
</table>
Neonatal outcomes
<table>
<tr><td>Outcome</td><td>Study</td><td></td><td></td></tr>
<tr><td></td><td>Fonesca 2007 N=250</td><td>Majhi 2009 N=100</td><td>Rode 2011 N=675</td></tr>
<tr><td></td><td colspan="3">RR (95% CI)</td></tr>
<tr><td>Birth weight < 2500 g</td><td>0.96 (0.73, 1.27)</td><td>NR</td><td>0.88 (0.79, 0.98)</td></tr>
<tr><td>Perinatal death</td><td>0.38 (0.10, 1.40)</td><td>NR</td><td>1.46 (0.56, 3.81)</td></tr>
<tr><td>Neonatal sepsis</td><td>0.28 (0.08, 0.97)</td><td>0.14 (0.01, 2.70)</td><td>1.14 (0.61, 2.13)</td></tr>
<tr><td>Neonatal death</td><td>0.29 (0.06, 1.37)</td><td>NR</td><td>3.57 (0.75, 17.14)</td></tr>
<tr><td>NICU</td><td>NR</td><td>0.11 (0.01, 2.01)</td><td>0.89 (0.79, 0.99)</td></tr>
<tr><td>Respiratory distress syndrome</td><td>0.59 (0.29, 1.19)</td><td>NR</td><td>1.08 (0.79, 1.48)</td></tr>
<tr><td>Need for assisted ventilation</td><td>0.65 (0.36, 1.16)</td><td>NR</td><td>1.02 (0.46, 2.26)</td></tr>
<tr><td>Intraventricular hemorrhage</td><td>0.51 (0.05, 5.53)</td><td>NR</td><td>1.70 (0.62, 4.66)</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

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)
Apgar score < 7 at 5 min	NR	NR	0.74 (0.33, 1.65)
CI = confidence interval, NR = not reported, RR = relative risk			

Authors' Conclusion:
"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

(Note: Above conclusion by author is based on various routes of administration and forms of progesterone)

Randomized controlled trial

Rode,[10] 2011, UK (study -PREDICT)

Main Findings:

Maternal outcomes (twin pregnancy)

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[a]	2 (0.6)	2 (0.6)	1.0 (0.1, 7.3)
Corticosteroid treatment for fetal lung maturation[b]	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)
Maternal adverse outcomes[c]			
- 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

CI = confidence interval; OR = odds ratio; NA = not applicable
[a] In all cases, death of one twin only
[b] For this outcome number used for analysis in progesterone group was 333
[c] For these outcomes, number used for analysis in progesterone group was 332

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Maternal side effects by organ type

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)
Gasterointestinal	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)

Neonatal outcomes (twin pregnancy)

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 enterocolotis	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)

CI = confidence interval; CPAP = continuous positive airway pressure; OR = odds ratio; NA = not applicable; NICU = neonatal intensive care unit

[a] In all cases, death of one twin only

Authors' Conclusion:

"Progesterone treatment did not prevent preterm delivery in twin gestations. There were no harmful effects to fetuses and infants of maternal progesterone treatment." P. 272

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Majhi,[11] 2009, India</td><td>

Main Findings:

Maternal outcomes (singleton pregnancy)

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)
CI = confidence interval; LCSC = lower segment ceasarian section; RR = relative risk			

Neonatal outcomes

Outcome	Progesterone	No progesterone	RR (95% CI)[a]
Birth weight (g) (mean ± SD)	2813 ± 501	2599 ± 421	214.38 (30.66, 398.09)[b]
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)[b]
CI = confidence interval; g = gram; RR = relative risk; SD = standard deviation [a] Unless otherwise mentioned [b] Mean difference (95% CI)			

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Authors' Conclusion:

"We conclude intravaginal administration of 100 mg of natural micronised progesterone significantly reduced the incidence of pre-term birth <37 weeks in women with one prior pre-term birth. Future research is warranted to assess the long-term safety and efficacy of progesterone." P.493

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