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PA Portfolio I – Spring 2023  
Mini-CAT Final

**Clinical Scenario:**

30 y/o F G4P1A2 presents 4 weeks pregnant and is wondering if there is anything that can be done to prevent her current pregnancy ending in a miscarriage, as her previous pregnancy ended in a miscarriage. The midwife mentions giving progesterone which can help decrease the likelihood of miscarriage.

**Search Question:**

In patients with recurrent miscarriages. Can giving progesterone prevent recurrent miscarriages and increase the likelihood of a full-term pregnancy that ends in a live birth?

**PICO Table:**

Population	Intervention	Comparison	Outcome(s)
Recurrent miscarriage	Progesterone	Placebo	Prevent miscarriage
Spontaneous abortion	Progestogen	No treatment	Prevent Spontaneous abortion
	vaginal progesterone		Increase live birth
	progesterone injection		Increase full-term pregnancy
			Decrease miscarriage

**Search Strategy and Databases Used:**

The best evidence when conducting research comes down to meta-analysis, and systemic review. If there are not sufficient articles from meta-analysis studies or systemic review, I will use RCT, this is because well conducted studies tend to have a large sample size and can compare treatment to alternative treatment, and placebos and draw a conclusion to see if a treatment is effective, harmful or has no use. If I am not able to find Meta-analysis studies, systemic reviews or RCT studies I will search for cohort studies to see how patients faired over time that were given progesterone.

### Results found:

All filters included meta-analysis, systematic review, Retrospective Cohort study and RCT, published in the last 10 years.

### PubMed:

((Recurrent miscarriage) AND (progesterone treatment)) AND (prevent miscarriage) → 66 results → Filter by RCT, Systemic Review, Clinical Trial, and Meta-analysis → 21 Results.

((spontaneous abortion) AND (Progestogen treatment)) AND (increase live birth) → 26 results → Filter by RCT, Systemic Review, Clinical Trial, and Meta-analysis → 16 results → filter by 5 years → 11 results.

(Progesterone treatment)) AND (full-term birth) → 0 Results

vaginal progesterone for recurrent miscarriage → 83 results → Filter by RCT, Systemic Review, Clinical Trial, and Meta-analysis → 22 Results → Filter by 5 years → 7 results

### Google Scholar.

Progestogen for preventing miscarriage → 6,060 Results → Since 2019 → 1,730 → Review Articles → 347 results.

The effects of Progestogen on miscarriage → 6,830 → Since 2019 → 1,920 → Reviewed articles → 378

Can progesterone prevent spontaneous abortions → 26,500 results → Since 2019 → 16,600 Results → Review Articles → 3,900 Results?

progesterone injection for miscarriage and increasing live birth → 19,500 results → Since 2019 → 7,170 results → Review Articles → 1,430 results.

### Cochrane Search-database:

Progesterone for miscarriage → Cochrane Review → 18 results → Publication Date 01/01/2019 – 03/25/2023 → 6 Results

Spontaneous abortions and progesterone treatment → Cochrane Review → 8 Results → Publication Date 01/01/2019 – 03/25/2023 → 0 Results

### CUNY YORK LIBRARY Search:

progesterone treatment for recurrent miscarriage → 364 Results → Filtered by years 2009 – 2023 → 148 results → Filter by Peer-Reviewed journals → 129 Results.

**Explanation:** When it came to choosing articles to research my topic on, I looked specifically for studies done in the United States which proved to be a challenge and opened my research to foreign studies but focused on countries such as Canada, and European countries because of their health-care system, and standard of research. I used Cochrane, Google scholar, York library and PubMed but Google Scholar, and PubMed yield me the most results possible, and from there I chose articles that were published within last 10 years, and looked for articles that compared progesterone against placebo, and narrowed my focus on articles that were RCT, and meta-analysis. I also made sure the articles included patients who had multiple miscarriages and from there I chose the best three articles that would help answer my question.

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**Title:** Progesterone for preventing miscarriage in women with recurrent miscarriage of unclear etiology.

**Type of Study:** RCT – Updated Review, and Meta-analysis.

**Citation:** Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev.* 2019 Nov 20;2019(11):CD003511. doi: 10.1002/14651858.CD003511.pub5. PMID: 31745982; PMCID: PMC6953238.

**Hyperlink:** <https://pubmed.ncbi.nlm.nih.gov/31745982/>

**Abstract:** Progesterone, a female sex hormone, is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilized egg. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone. Therefore, clinicians use progestogens (drugs that interact with the progesterone receptors), beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage.

**Materials and Methods:** The authors searched Cochrane library, Clinicaltrial.gov, and WHO International clinical trial registry. Randomized or quasi-randomized trials comparing progestogens with placebo or no treatment, given for the prevention of miscarriage, were eligible for inclusion. Women who were diagnosed with recurrent miscarriages (usually of unknown origin) and who began treatment with progestins in the

first trimester of pregnancy. Authors placed no restriction on the age of participants or past obstetric history otherwise. Where specified, authors limited the analysis to singleton pregnancies. Authors excluded women achieving pregnancy by in-vitro fertilization.

**Results:** The meta-analysis of all women, suggests that there may be a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo/controls (average risk ratio (RR) 0.73, 95% confidence interval (CI) 0.54 to 1.00, 10 trials, 1684 women, moderate-quality evidence). A subgroup analysis comparing placebo-controlled versus non-placebo-controlled trials, trials of women with three or more prior miscarriages compared to women with two or more miscarriages and different routes of administration showed no clear differences between subgroups for miscarriage. None of the trials reported on any secondary maternal outcomes, including severity of morning sickness, thromboembolic events, depression, admission to a special care unit, or subsequent fertility. There was a slight benefit for women receiving progestogen seen in the outcome of live birth rate (RR 1.07, 95% CI 1.00 to 1.13, 6 trials, 1411 women, moderate-quality evidence). No clear differences were seen for women receiving progestogen for the other secondary outcomes including neonatal death, fetal genital abnormalities, or stillbirth.

**Conclusion:** Patients with unexplained recurrent miscarriages, supplementation with progesterone therapy may reduce the rate of miscarriage in future pregnancy.

**Key points:**

- The secondary outcome of live birth rate was also probably improved with progesterone therapy.
- No trials reported any adverse maternal events.
- Results of this meta-analysis show that moderate-quality evidence demonstrates that progestogen supplementation probably reduces the miscarriage rate for women with recurrent miscarriage.

**Why I chose it:** I chose this article because it was RCT, and included studies from previous meta-analysis to answer the question if progesterone can help reduce miscarriage in patients who have had multiple miscarriage. This research paper was also a follow-up to a previous study published, and it has shown that progesterone does have a positive impact on patients who have had miscarriage in the past.

**Title:** PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomized, double-blind, placebo-controlled, international multicenter trial and economic evaluation:

**Type of Study:** RCT

**Citation:** Coomaraswamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, Gupta P, Dawood F, Koot YE, Atik RB, Bloemenkamp KW, Brady R, Briley A, Cavallaro R, Cheong YC, Chu J, Eapen A, Essex H, Ewies A, Hoek A, Kaaijk EM, Koks CA, Li TC, MacLean M, Mol BW, Moore J, Parrott S, Ross JA, Sharpe L, Stewart J, Trépel D, Vaithilingam N, Farquharson RG, Kilby MD, Khalaf Y, Goddijn M, Regan L, Rai R. PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. *Health Technol Assess.* 2016 May;20(41):1-92. doi: 10.3310/hta20410. PMID: 27225013; PMCID: PMC4904188.

**Hyperlink:** <https://pubmed.ncbi.nlm.nih.gov/27225013/>

**Abstract:** Progesterone is essential to maintain a healthy pregnancy. Guidance from the Royal College of Obstetricians and Gynecologists and a Cochrane review called for a definitive trial to test whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of unexplained recurrent miscarriage (RM). The PROMISE trial was conducted to answer this question. A concurrent cost-effectiveness analysis was conducted.

**Materials and Methods:** Randomized double-blinded, placebo-controlled international multicenter study, with economic evaluation, conducted in hospital settings across the UK (36 sites) and in the Netherlands (nine sites). Patients with unexplained recurrent miscarriage three or more first-trimester losses, between the ages of 18-39. Randomization, conceiving naturally and giving informed consent, received either micronized progesterone (Utrogestan<sup>®</sup>, Besins Healthcare) at a dose of 400 mg (two vaginal capsules of 200 mg) or placebo vaginal capsules twice daily, administered vaginally from soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) until 12 completed weeks of gestation (or earlier if the pregnancy ended before 12 weeks). Patients were randomized via a secure internet facility.

**Results:** 836 women were randomized, 404 received progesterone and 432 received placebo. The baseline data (age, body mass index, maternal ethnicity, smoking status and parity) of the participants were comparable in the two arms of the trial. The follow-up rate to primary outcome was 826 out of 836 (98.8%). The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3% (271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15;  $p = 0.45$ ). There was no evidence of a significant difference between the groups for any of the secondary outcomes.

**Conclusion:** There isn't evidence that first-trimester progesterone therapy improves outcome in patients with history of unexplained recurrent miscarriage.

**Key points:**

- The PROMISE trial found no evidence of significant differences in the rates of primary or secondary outcomes between the group randomized to receive progesterone and the group randomized to placebo during the study.
- Rates of miscarriage were not significantly different between the groups randomized to receive progesterone or placebo.
- Findings show that women with a history of unexplained RM do not benefit from first-trimester progesterone therapy for any of the key clinical outcomes that we observed.
- However, it is evident that progesterone at a dose of 400 mg twice daily appears safe to the mother and the fetus

**Why I chose it:** Despite this study being completed in Europe, I still chose this article because it is a RCT comparing progesterone to placebo when it came to patients with multiple miscarriages. Another reason I chose this study was that it was conducted across the U.K, and Netherlands, and researchers mentioned that other studies that showed potential benefit from progesterone were poorly conducted studies and overestimated the positive effect of progesterone.

**Title:** Progestogens for preventing miscarriage: a network

**Type of study:** Meta-Analysis

**Citation:** Devall AJ, Papadopoulou A, Podsek M, Haas DM, Price MJ, Coomarasamy A, Gallos ID. Progestogens for preventing miscarriage: a network meta-analysis. Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD013792. DOI: 10.1002/14651858.CD013792.pub2.

**Hyperlink:** <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/full>

**Abstract:** To investigate whether treatment with progestogens in the first trimester of pregnancy would decrease the incidence of miscarriage in women with a history of unexplained recurrent miscarriage.

**Materials and Methods:** The authors searched several databases Cochrane Central Register of Controlled Trials, Ovid MEDLINE(R), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of retrieved studies. They included all random controlled trials assessing the effectiveness or safety of progestogen treatment for the prevention of miscarriage. Cluster-randomized trials were eligible for inclusion. Randomized trials published only as abstracts were eligible if sufficient information could be retrieved. The authors excluded quasi- and non-randomized trials.

**Results: Women with Threatened Miscarriage:** Based on the relative effects from the pairwise meta-analysis, vaginal micronized progesterone (two trials, 4090 women, risk ratio (RR) 1.03, 95% confidence interval (CI) 1.00 to 1.07, high-certainty evidence), and dydrogesterone (one trial, 406 women, RR 0.98, 95% CI 0.89 to 1.07, moderate-certainty evidence) probably make little or no difference to the live birth rate when compared with placebo for women with threatened miscarriage.

**Women with recurrent Miscarriage:** Based on the results from one trial (826 women) vaginal micronized progesterone (RR 1.04, 95% CI 0.95 to 1.15, high-certainty evidence) probably makes little or no difference to the live birth rate when compared with placebo for women with recurrent miscarriage. The evidence for dydrogesterone compared with placebo for women with recurrent miscarriage is of very low-certainty evidence, therefore the effects remain unclear. No data are available to assess the effectiveness of 17- $\alpha$ -hydroxyprogesterone or oral micronized progesterone for the outcome of live birth in women with recurrent miscarriage.

**Conclusion:** The authors concluded that progestogens make little to no difference in live births rate for women with threatened or recurrent abortion.

**Key points:**

- Vaginal micronized progesterone made minor difference to the live birth rate when compared with placebo.
- There are likely no differences in adverse events associated with vaginal micronized progesterone

**Why I chose it:** I chose this article because it is a meta-analysis, and the authors chose to look at patients with recurrent miscarriages as well as patients with threatened miscarriages. Another reason I liked this meta-analysis is that it included different route progesterone that were given to patients and found that progesterone made no difference in reducing miscarriage.



**Title:** Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials

**Type of study:** Meta-Analysis and systemic review of RCT

**Citation:** Gabriele Saccone, Corina Schoen, Jason M. Franasiak, Richard T. Scott, Vincenzo Berghella,  
<https://doi.org/10.1016/j.fertnstert.2016.10.031>.

**Hyperlink:** [www.sciencedirect.com/science/article/pii/S0015028216629540](http://www.sciencedirect.com/science/article/pii/S0015028216629540)

**Abstract:** Miscarriage, defined as the spontaneous loss of a pregnancy before 24 weeks' gestation, is common with approximately 25% of women experiencing a miscarriage in their lifetime, and 15% to 20% of pregnancies ending in a miscarriage. Progesterone has an important role in maintaining a pregnancy, and supplementation with different progestogens in early pregnancy has been attempted to rescue a pregnancy in women with early pregnancy bleeding (threatened miscarriage), and to prevent miscarriages in asymptomatic women who have a history of three or more previous miscarriages (recurrent miscarriage).

**Materials and Methods:** The authors searched , and identified trials by searching independently the electronic databases MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, Scielo, and the Cochrane Central Register of Controlled Trials. The authors included RCTs comparing supplementation with progestogens (i.e., intervention group) in the first trimester of pregnancy with control (either placebo or no treatment) in women with a history of recurrent miscarriage, either consecutive or nonconsecutive. The definition of recurrent miscarriage was per the original trial design, which included either two or more or three or more losses. Trials in which recurrent miscarriage was defined as one miscarriage or more were excluded. All progestogens types were included, both natural P and synthetic progestogens (i.e., progestins), including but not limited to 17- $\alpha$ -hydroxyprogesterone-caproate (17-OHPC) and dydrogesterone. Studies in women with threatened miscarriage were excluded.

**Results:** Two RCTs used natural P, whereas the other eight studies used progestins: medroxyprogesterone, cyclopentylenol ether of progesterone, dydrogesterone, or 17-hydroxyprogesterone caproate. Pooled data from the 10 trials showed that women with a history of unexplained recurrent miscarriage who were randomized to the progestogens group in the first trimester and before 16 weeks had a lower risk of recurrent miscarriage (RR 0.72, 95% CI 0.53–0.97) and higher live birth rate (RR 1.07, 95% CI 1.02–1.15) compared with those who did not. No statistically significant differences were found in the other secondary outcomes, including preterm birth (RR 1.09, 95% CI 0.71–1.66), neonatal mortality (RR 1.80, 95% CI 0.44–7.34), and fetal genital abnormalities (RR 1.68, 95% CI 0.22–12.62).

**Conclusion:** The evidence that supplementation with progestogens may reduce the incidence of recurrent miscarriages and seems to be safe for fetuses. Synthetic progestogens, including weekly IM 17-hydroxyprogesterone caproate, but not natural P, were associated with a lower risk of recurrent miscarriage

**Key points:**

- 10 RCTs, including 1,586 women, showed that progestogens in women with at least two or three prior miscarriages were associated with lower risk of recurrent miscarriages and seemed to be safe to use during the first trimester.
- Synthetic progestogens therapy but not natural P supplementation was associated with a lower risk of recurrent miscarriage

**Why I chose it:** I chose this article because it's a meta-analysis of RCT, and it looked at first trimester pregnancy only because the majority of miscarriages occur during the first trimester. Additionally, the authors looked at different formulations of progesterone as well as synthetic progesterone. Along with my first article this article found that progesterone may help reduce miscarriages in patients with recurrent miscarriages, however the authors did point out that their meta-analysis does not include route, dosage, and timing of progesterone given, and the evidence maybe weak as well and more studies would need to be done.

## Summary of Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc. )	Outcomes Studied	Key Findings	Limitations and Biases
11/20/2019	Level 2-: Randomized or quasi-randomized controlled trials	<p>12 Trials, (1,856 women). 8 of the trials compared placebo, while 4 compared progesterone to no treatment (Met the inclusion criteria)</p> <p>Ten trials (1684 women) contributed data to the analyses.</p>	To assess the efficacy, and safety of progesterone as a preventive therapy against recurrent miscarriages.	<p>The data suggests there may be a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo/controls (average risk ratio (RR) 0.73, 95% confidence interval (CI) 0.54 to 1.00, 10 trials, 1684 women.</p> <p>Additionally, there slight benefit for women receiving progesterone with live births (RR 1.07, 95% CI 1.00 to 1.13, 6 trials, 1411 women)</p>	<p>The authors of the study took steps to minimize bias in the review process. The RCT the authors looked at varied one RCT was multi-center, few single centers and some of the number of centers was unclear. Also, the authors address those three trials used a computer-generated for randomization while other studies used different but adequate methods of randomization. The issue with this is that the methods weren't standardized and could've had bias for example one method was a created by statistician using a table which could have human error. Without consistent randomization it can't be guaranteed there weren't any biases.</p>

5/20/2016	Level 2-Randomized, double-blind, placebo-controlled, international multicenter trial	Patients with unexplained recurrent miscarriages are defined as 3 or more. Patients are between the ages of 18-39. Patients received either micronized progesterone (Utrogestan®), Besins Healthcare) at a dose of 400 mg (two vaginal capsules of 200 mg) or placebo vaginal capsules twice daily, administered vaginally from soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation). The study took place conducted in hospital settings across the UK (36 sites) and in the Netherlands (nine sites).	whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of unexplained recurrent miscarriage	838 patients were randomized with 404 receiving progesterone, and 432 receiving placebo. Baseline data such as age, BMI, maternal ethnicity smoking status, and parity of the participants were comparable in the two arms of the trial. The follow-up rate to the primary outcome was 826 out of 836 (98.8%). The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group, it was 63.3% (271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15; p = 0.45. A key finding is that there isn't much evidence that first-trimester progesterone will improve outcomes in patients with unexplained recurrent miscarriages.	One of the limitations of this study was that not all patients had polycystic ovaries, which may've had an impact on whether progesterone works. This is because patients with PCOS are at a higher risk of miscarriage, and the authors didn't address if patients with PCOS were on any other medications. A limitation of this study is that the studied population did not include serum progesterone at the time of randomization. None of the participants in the study with a history of recurrent miscarriage had checked progesterone levels before treatment as well. Also, the authors found that pill counting to be a poor tool for compliance assessment. Also, the authors only looked at the first trimester and didn't see if 2 <sup>nd</sup> or 3 <sup>rd</sup> -trimester recurrent miscarriages can be avoided.
4/19/2021	Level 1: Systematic review and meta-analysis of RCT	The author's search resulted in 1151 trials, and 1066 were screened, and excluded. The author's review includes seven two-arm randomized trials published between 1963 and 2020, involving 5,682 women. All studies were reported in English and were conducted in hospital settings across five countries: Australia, Germany, Hong Kong, the United Kingdom, and Singapore.	To see if different profiles of progesterone are a safe and effective treatment for threatened and recurrent miscarriage.	All trials took place in hospital settings.  Patients with threatened miscarriage: vaginal micronized progesterone (two trials, 4090 women, risk ratio (RR) 1.03, 95% confidence interval (CI) 1.00 to 1.07, high-certainty evidence), and dydrogesterone (one trial, 406 women, RR 0.98, 95% CI 0.89 to 1.07, moderate-certainty evidence) probably make little or no difference to the live birth rate when compared with placebo for women	Some limitations of this study are that the authors reviewed seven trials across five countries, and not all countries have similar healthcare systems, and standards of care which can affect the study outcome. Another limitation is that there was an indirect comparison between the different progesterone, but the authors concluded it was possible because they were compared to a placebo. It

				<p>with threatened miscarriage. In women with no previous miscarriages and early pregnancy bleeding, there is little or no improvement in the live birth rate (RR 0.99, 95% CI 0.95 to 1.04, high-certainty evidence) when treated with vaginal micronized progesterone compared to placebo.</p> <p>Patients with recurrent miscarriage:</p> <p>Results from one trial (826 women) In women with no previous miscarriages and early pregnancy bleeding, there is probably little or no improvement in the live birth rate (RR 0.99, 95% CI 0.95 to 1.04, high-certainty evidence) when treated with vaginal micronized progesterone compared to placebo.</p>	<p>would have been better to see if the different types of progesterone such as vaginal or oral were compared to each other to check for efficiency.</p>
2/2/2017	Level 1: Systematic review and meta-analysis of RCT	<p>The researchers identified RCT by searching electronic databases. The researchers included RCT that compared supplementation with progesterone in the first trimester. Different types of progesterone (<u>medroxyprogesterone</u>, cyclopentylenol ether of <u>progesterone</u>, <u>dydrogesterone</u>, or 17-hydroxyprogesterone caproate) were tested including natural, and synthetic</p>	<p>To see if treatment of progesterone in the first trimester of pregnancy would help decrease the incidence of miscarriage in patients with a history of recurrent miscarriage.</p>	<p>Ten trials including 1,586 women were analyzed. Eight studies used a placebo as a control and were double-blinded. Pooled data from the 10 trials showed that women with a history of unexplained recurrent miscarriage who were randomized to the progestogens group in the first trimester and before 16 weeks had a lower risk of recurrent miscarriage (RR 0.72, 95% CI 0.53–0.97) and higher live birth rate (RR 1.07, 95% CI 1.02–1.15) compared with those who did not</p>	<p>Some of the limitations of this systemic review are that a few RCTs was conducted before 1990 whereas before the days when randomized trials had any chance of being conducted to any degree of quality. Additionally, different preparation routes and dosages of progesterone as well as different durations were used. Thus, it is unclear which of these should be preferred.</p>

## - Weight of the evidence

**Article 1:** I chose this article because it was RCT, and included studies from previous meta-analysis to answer the question if progesterone can help reduce miscarriage in patients who have had multiple miscarriage. This research paper was also a follow-up to a previous study published, and it has shown that progesterone does have a positive impact on patients who have had miscarriage in the past.

**Article 2:** Despite this studying being completed in Europe, I still chose this article because it is a RCT comparing progesterone to placebo when it came to patients with multiple miscarriages. Another reason I chose this study was that it was done across the U.K, and Netherlands, and researchers mentioned that other studies that showed potential benefit from progesterone were poorly conducted studies and overestimated the positive effect of progesterone. Additionally, this study is the largest-ever randomized placebo-controlled clinical trial to report on the treatment effects of first-trimester progesterone therapy for pregnant women with a history of unexplained RM. It is, in fact, the largest randomized clinical trial ever conducted about recurrent pregnancy loss.

**Article 3:** I chose this article because it's a meta-analysis, and the authors chose to look at patients with recurrent miscarriages as well as patients with threatened miscarriages. Another reason why I liked this meta-analysis is that it included different route progesterone that were given to patients and found that progesterone made no difference in reducing miscarriage.

**Article 4:** I chose this article because it was a systemic review that looked at several different type of progesterone, and synthetic progesterone as well for first-trimester pregnancy, and found that it can be effective in reducing the risk of recurrent miscarriages.

### Conclusion From Each Article, and overarching conclusion:

*Progesterone is safe to use in patients who are pregnant as no side-effects have been reported. However, its use to prevent miscarriage is questionable, and thus should not be recommended as a way to prevent recurrent miscarriages.*

**Article 1:** Patients with unexplained recurrent miscarriages, supplementation with progesterone therapy may reduce rate of miscarriage in future pregnancy.

**Article 2:** There isn't evidence that first-trimester progesterone therapy improves outcome in patients with history of unexplained recurrent miscarriage.

**Article 3:** The authors concluded that progestogens make little to no difference in live births rate for women with threatened or recurrent abortion.

**Article 4:** Based off the findings supplementation with progestogens can reduce incidence of recurrent miscarriage.

### Magnitude of effects/statistical significance:

**Article 1:** There was probably a slight benefit for women receiving progestogen seen in the outcome of live birth rate (RR 1.07, 95% CI 1.00 to 1.13, 6 trials, 1411 women, moderate-quality evidence. No clear differences were seen for women receiving progestogen for the other secondary outcomes including neonatal death, fetal genital abnormalities, or stillbirth.

**Article 2:** The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3% (271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15;  $p = 0.45$ ). There was no evidence of a significant difference between the groups for any of the secondary outcomes.

**Article 3: Women with Recurrent Miscarriage:** Based on the results from one trial (826 women) vaginal micronized progesterone (RR 1.04, 95% CI 0.95 to 1.15, high-certainty evidence) makes little or no difference to the live birth rate when compared with placebo for women with recurrent miscarriage.

**Women with Threatened Miscarriage:** meta-analysis, vaginal micronized progesterone (two trials, 4090 women, risk ratio (RR) 1.03, 95% confidence interval (CI) 1.00 to 1.07, high-certainty evidence), and dydrogesterone (one trial, 406 women, RR 0.98, 95% CI



0.89 to 1.07, moderate-certainty evidence) probably make little or no difference to the live birth rate when compared with placebo for women with threatened miscarriage.

**Article 4:** 10 trials showed that women with a history of unexplained recurrent miscarriage who were randomized to the progestogens group in the first trimester and before 16 weeks had a lower risk of recurrent miscarriage (RR 0.72, 95% CI 0.53–0.97) and higher live birth rate (RR 1.07, 95% CI 1.02–1.15) compared with those who did not

### **Clinical Bottom Line**

Out of the four articles I researched, only two found that progesterone is beneficial at reducing the risk of miscarriage in patients. My second article, which was an RCT, found no benefit of progesterone reducing the risk of miscarriage, but did find that progesterone is safe for patients, and the fetus. The third article, a meta-analysis, found no difference in using progesterone when compared to placebo in reducing the risk of miscarriage. My last article found that progesterone is beneficial in the first-trimester, but there are some limitations to this meta-analysis with the RCT's being done prior to there being a standardized way to randomize patients, and the dosage, and route of administration of progesterone was not measured to which make it's hard to recommend progesterone to patients. My final article found that progesterone is safe and can help reduce miscarriages in patients with recurrent miscarriage, however the authors do note that further research is needed. The PROMISE trial, which is the largest ever randomized placebo-controlled clinical trial found no evidence of progesterone reducing miscarriages, and that 80% of miscarriages occur in the first trimester. Given the evidence that I have researched progesterone is not something as clinicians we should recommend to patients with recurrent miscarriages instead alternative methods should be investigated.



## Foreign Study:

	Cultural Context:	Social Context	Economic Context	Language
<p><b>Article 2:</b>            PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomized, double-blind, placebo-controlled, international multicenter trial and economic evaluation:</p>	<p>This study was done across U.K, and Netherlands, but the study was funded by NIH in the U.K. In England and Netherlands offer similar screening methods for pregnant patients, such as Ultrasound, testing for Hep B, syphilis, HIV, and down syndrome. This is also true for the Netherlands; there prenatal care is similar to the United States.</p>	<p>The study was overseen by an ethics board as well. The sponsors in the U.K. reported to the Medicines and Healthcare Products Regulatory Agency (MHRA), and in the Netherlands Research Ethics Committee (REC). Both bodies are equivalent to ensuring the study was conducted in an ethical manner. The United Kingdom, The Netherlands, and United States share similar ethical bodies when governing studies have regulatory bodies that are similar when it comes to approving medicine. Also, the United Kingdom, and the Netherlands have Physician Associate/Assistant as well</p>	<p>United Kingdom along with Netherlands are developed nations with universal healthcare, and both countries are economically developed like the United States. The research was funded by NIH, which is the British government's major funder of clinical, public health, social care research. The study was conducted in hospital settings. The trial coordinator monitored the quantity of supplies held by each dispensing pharmacy in comparison with the number and rate of randomizations undertaken and liaised with Besins Healthcare to ensure adequate supplies in the UK and the Netherlands.</p>	<p>English is the predominant language in the U.K, where the study was funded. Dutch is the common language in the Netherlands, and the researchers translated participant information sheet, and consent form from English to Dutch, so the patients in Netherlands, and U.K were given the same information when it came to participating in this clinical trial.</p>

### Sources:

<https://www.nhs.uk/pregnancy/your-pregnancy-care/your-antenatal-care/#:~:text=If%20you're%20pregnant%20in,syphilis%2C%20HIV%20and%20hepatitis%20B>

<https://www.iamexpat.nl/expat-info/family-kids/pregnancy/prenatal-care-netherlands>

<https://www.napa.nl/english-information/>

<https://www.aapa.org/news-central/2019/10/british-government-recognizes-physician-associate-profession>

