



A Comprehensive Systematic Review of The Relationship Between Serum Progesterone Levels and the Success of Maintaining Pregnancy in Threatened Miscarriage

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ABSTRACT

Introduction: Threatened miscarriage is a common obstetric complication, and serum progesterone levels are frequently measured to assess pregnancy viability. However, the prognostic accuracy of a single progesterone measurement and the therapeutic efficacy of progesterone supplementation remain areas of clinical debate and heterogeneous evidence.

Methods: This comprehensive systematic review synthesized evidence from 57 studies (including meta-analyses, randomized controlled trials, and observational studies) to evaluate the relationship between serum progesterone levels and pregnancy maintenance success in women with threatened miscarriage up to 20 weeks' gestation. Data extraction focused on study population, progesterone measurement methodology, defined pregnancy

outcomes, statistical associations, identified thresholds, and confounding factors.

Results: The analysis demonstrated a strong inverse relationship between serum progesterone and miscarriage risk. Diagnostic accuracy was high, with a synthesized Area Under the Curve (AUC) of 0.85 (95% CI 0.81–0.88) for predicting viability (Yi Gong et al., 2024). Threshold-dependent performance was evident; levels <6.3 ng/mL showed exceptional specificity (97.3–99.2%) for non-viable pregnancy, while levels ≥ 20 –25 ng/mL strongly predicted viability (B. Ghaedi et al., 2022). The therapeutic benefit of progesterone supplementation was not uniform but significantly modified by patient history and treatment type. Women with recurrent miscarriage, particularly those with three or more losses, derived clear benefit (RR 1.28 for live birth) (A. Coomarasamy et al., 2020). Oral dydrogesterone showed more consistent efficacy (OR 0.43 for reducing miscarriage) compared to vaginal progesterone (Hee-Joong Lee et al., 2017).

Discussion: The evidence confirms serum progesterone as a valuable prognostic biomarker. The apparent contradiction in therapeutic trial outcomes is largely explained by population heterogeneity—specifically, previous miscarriage history, route of administration, and baseline progesterone status. Progesterone's mechanism extends beyond hormonal support to include immunomodulation (shifting cytokine balance towards Th2 dominance) and improvement in uteroplacental hemodynamics (Hudic et al., 2011; Czajkowski et al., 2007).

Conclusion: A single serum progesterone measurement provides valuable prognostic information in threatened miscarriage, with

very low levels being highly predictive of pregnancy failure. Progesterone supplementation is most beneficial for a defined subgroup: women with a history of recurrent miscarriage and early pregnancy bleeding. Clinical implementation should be tailored, moving away from universal supplementation towards a stratified approach based on individual risk factors and biomarker status.

Keywords: Threatened miscarriage, progesterone, dydrogesterone, pregnancy outcome, systematic review, prognostic accuracy, luteal phase support.

INTRODUCTION

Background

Threatened miscarriage, characterized by vaginal bleeding with a closed cervical os in early pregnancy, complicates approximately 20% of all pregnancies and is a significant source of patient anxiety and clinical uncertainty (Pillai et al., 2015). The pathophysiology often involves inadequate luteal function, leading to suboptimal progesterone production, which is critical for endometrial decidualization, immune modulation, and maintenance of early pregnancy (Siklósi et al., 2012). Consequently, serum progesterone measurement has become a common diagnostic tool to assess pregnancy viability and guide management decisions. Historically, progesterone supplementation has been widely used empirically to support pregnancies deemed at risk, despite ongoing debate regarding its overall efficacy (Godlee, 2012).

Research Gap

While numerous individual studies and reviews have explored this topic, the evidence remains fragmented and sometimes contradictory. Significant gaps exist in understanding the precise prognostic value of a single progesterone measurement versus serial measurements, the optimal diagnostic thresholds across different populations, and the specific patient subgroups that truly benefit from therapeutic intervention (Haas & Ramsey, 2013). Many studies fail to account for critical effect modifiers such as the number of previous miscarriages, the route of progesterone administration, or whether the pregnancy was conceived naturally or via assisted reproductive technology (ART), leading to inconsistent recommendations (Coomarasamy, 2021).

Novelty

This systematic review aims to provide a novel and comprehensive synthesis by integrating data from a wide spectrum of study designs—including large-scale meta-analyses, high-quality

randomized controlled trials (RCTs), and observational cohorts—specifically focused on threatened miscarriage. It moves beyond asking whether progesterone "works" to elucidate *for whom, under what conditions, and by which method* it is most effective. It critically examines the threshold-dependent diagnostic performance and reconciles conflicting findings by performing a nuanced analysis of effect modifiers.

Research Objectives

The primary objectives of this review are: 1) To determine the diagnostic accuracy of single and serial serum progesterone measurements for predicting pregnancy outcomes (ongoing pregnancy/live birth vs. miscarriage) in women with threatened miscarriage; 2) To identify and validate clinically useful progesterone threshold values; 3) To evaluate the therapeutic efficacy of different progesterone formulations and routes of administration in preventing miscarriage; and 4) To identify key patient and treatment characteristics that modify the relationship between progesterone and pregnancy success.

Hypothesis

We hypothesize that serum progesterone level is a strong, independent prognostic biomarker for pregnancy viability in threatened miscarriage, but that its predictive value is threshold-dependent. Furthermore, we hypothesize that the therapeutic efficacy of progesterone supplementation is not universal but is significantly enhanced in women with a history of recurrent miscarriage, those with low baseline progesterone levels, and when specific formulations such as oral dydrogesterone are used.

Significance and Benefits

The findings of this review have direct and significant clinical implications. They can guide evidence-based clinical decision-making by helping clinicians: a) better interpret a single progesterone result in the emergency or outpatient setting, b) identify patients who are most likely

to benefit from supplementation, thereby avoiding unnecessary treatment and cost in low-likelihood responders, and c) select the most effective type and route of progesterone administration. Ultimately, this contributes to more personalized, effective, and rational management of threatened miscarriage, potentially improving live birth rates in high-risk groups and reducing patient distress.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to the relationship between serum progesterone levels and the success of maintaining pregnancy in threatened miscarriage.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Target Population:** Does this study include pregnant women diagnosed with threatened abortion or threatened miscarriage up to 20 weeks gestation?
- **Progesterone Measurement:** Does this study measure serum progesterone levels quantitatively?
- **Clinical Outcomes:** Does this study report pregnancy maintenance success rates, live birth rates, or pregnancy continuation beyond a specified gestational age?
- **Study Design:** Is this study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, or meta-analysis?

- **Statistical Analysis:** Does this study provide statistical measures of association or comparative analysis between progesterone levels and pregnancy outcomes?
- **Study Focus:** Does this study examine the predictive value of baseline serum progesterone levels rather than primarily evaluating progesterone supplementation effectiveness?
- **Primary Condition:** Is threatened abortion/miscarriage the primary condition studied (not ectopic pregnancy, molar pregnancy, inevitable abortion, or incomplete abortion)?
- **Publication Type:** Is this study a full research article (not a case report, case series, editorial, commentary, or conference abstract)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Indicator)	C (Comparison/Context)	O (Outcome)
Keyword 1	Threatened abortion	Serum progesterone	Low progesterone	Pregnancy maintenance
Keyword 2	Threatened miscarriage	Progesterone level	Progesterone deficiency	Live birth
Keyword 3	Early pregnancy bleeding	Progesterone concentration	Suboptimal progesterone	Ongoing pregnancy
Keyword 4	First-trimester bleeding	Blood progesterone	Hypoprogesteronemia	Miscarriage prevention

The Boolean MeSH keywords inputted on databases for this research are: ("*Threatened abortion*" OR "*Threatened miscarriage*" OR "*Early pregnancy bleeding*" OR "*First-trimester bleeding*") AND ("*Serum progesterone*" OR "*Progesterone level*" OR "*Progesterone concentration*")

OR "Blood progesterone") AND ("Low progesterone" OR "Progesterone deficiency" OR "Suboptimal progesterone" OR "Hypoprogesteronemia") AND ("Pregnancy maintenance" OR "Live birth" OR "Ongoing pregnancy" OR "Miscarriage prevention")

Data extraction

- **Study Population:**

Extract details about the study population with threatened miscarriage, including:

- Definition of threatened miscarriage used
- Gestational age range at enrollment
- Sample size
- Inclusion and exclusion criteria specific to threatened miscarriage
- Baseline characteristics (age, parity, previous miscarriage history)
- Whether natural conception or ART pregnancies

- **Progesterone Measurement:**

Extract all details about serum progesterone measurement, including:

- Timing of blood draw (gestational age, relationship to bleeding onset)
- Laboratory method used (immunoassay type, analyzer)
- Units reported (ng/mL, nmol/L, etc.)
- Number of measurements (single vs. multiple)
- Quality control measures mentioned

- **Pregnancy Outcomes:**

Extract all pregnancy outcomes related to maintaining pregnancy in threatened miscarriage cases, including:

- Primary outcome definitions (ongoing pregnancy, live birth, pregnancy continuation)

- Secondary outcomes (miscarriage, fetal viability)
- Follow-up duration and timing of outcome assessment
- Gestational age at outcome determination
- Loss to follow-up rates

- **Progesterone-Outcome Association:**

Extract the specific relationship found between serum progesterone levels and pregnancy outcomes in threatened miscarriage, including:

- Statistical measures (odds ratios, relative risks, correlation coefficients with 95% CI)
- P-values for associations
- Direction of association (higher/lower progesterone and outcomes)
- Adjusted vs. unadjusted analyses
- Statistical methods used

- **Progesterone Thresholds:**

Extract any progesterone cut-off values or thresholds identified for predicting pregnancy outcomes in threatened miscarriage, including:

- Specific threshold values and units
- How thresholds were determined (ROC analysis, predetermined, etc.)
- Sensitivity and specificity at each threshold
- Positive and negative predictive values
- Area under ROC curve if available

- **Confounding Factors:**

Extract factors that were controlled for or found to influence the progesterone-pregnancy outcome relationship in threatened miscarriage, including:

- Maternal factors (age, BMI, smoking, medical history)
- Pregnancy factors (gestational age at presentation, severity of bleeding)
- Treatment factors (progesterone supplementation, bed rest, other medications)
- Variables included in multivariable analyses

- **Study Design:**

Extract study design and quality characteristics relevant to assessing the progesterone-outcome relationship, including:

- Study type (cohort, case-control, cross-sectional, RCT)
- Prospective vs. retrospective data collection
- Blinding of outcome assessors to progesterone levels
- Sample size calculation and power
- Risk of bias assessment factors

- **Clinical Context:**

Extract clinical context details that affect interpretation of progesterone levels in threatened miscarriage, including:

- Healthcare setting (emergency department, outpatient clinic, hospital)
- Time from symptom onset to progesterone measurement
- Concurrent medications or treatments that could affect progesterone
- Geographic region and time period of study
- Standard care protocols mentioned

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Threatened abortion" AND "Serum progesterone" AND "Low progesterone" AND "Pregnancy maintenance" OR "Live birth" OR "Ongoing pregnancy" OR "Miscarriage prevention")	2,265
Semantic Scholar	("Threatened abortion" OR "Threatened miscarriage" OR "Early pregnancy bleeding" OR "First-trimester bleeding") AND ("Serum progesterone" OR "Progesterone level" OR "Progesterone concentration" OR "Blood progesterone") AND ("Low progesterone" OR "Progesterone deficiency" OR "Suboptimal progesterone" OR "Hypoprogesteronemia") AND ("Pregnancy maintenance" OR "Live birth" OR "Ongoing pregnancy" OR "Miscarriage prevention")	252
Google Scholar	("Threatened abortion" OR "Threatened miscarriage" OR "Early pregnancy bleeding" OR "First-trimester bleeding") AND ("Serum progesterone" OR "Progesterone level" OR "Progesterone concentration" OR "Blood progesterone") AND ("Low progesterone" OR "Progesterone deficiency" OR "Suboptimal progesterone" OR "Hypoprogesteronemia") AND ("Pregnancy maintenance" OR "Live birth" OR "Ongoing pregnancy" OR "Miscarriage prevention")	308
Wiley Online Library	("Threatened abortion" OR "Threatened miscarriage" OR "Early pregnancy bleeding" OR "First-trimester bleeding") AND ("Serum progesterone" OR "Progesterone level" OR "Progesterone concentration" OR "Blood progesterone") AND ("Low progesterone" OR "Progesterone deficiency" OR "Suboptimal progesterone" OR "Hypoprogesteronemia") AND ("Pregnancy maintenance" OR "Live birth" OR "Ongoing pregnancy" OR "Miscarriage prevention")	14

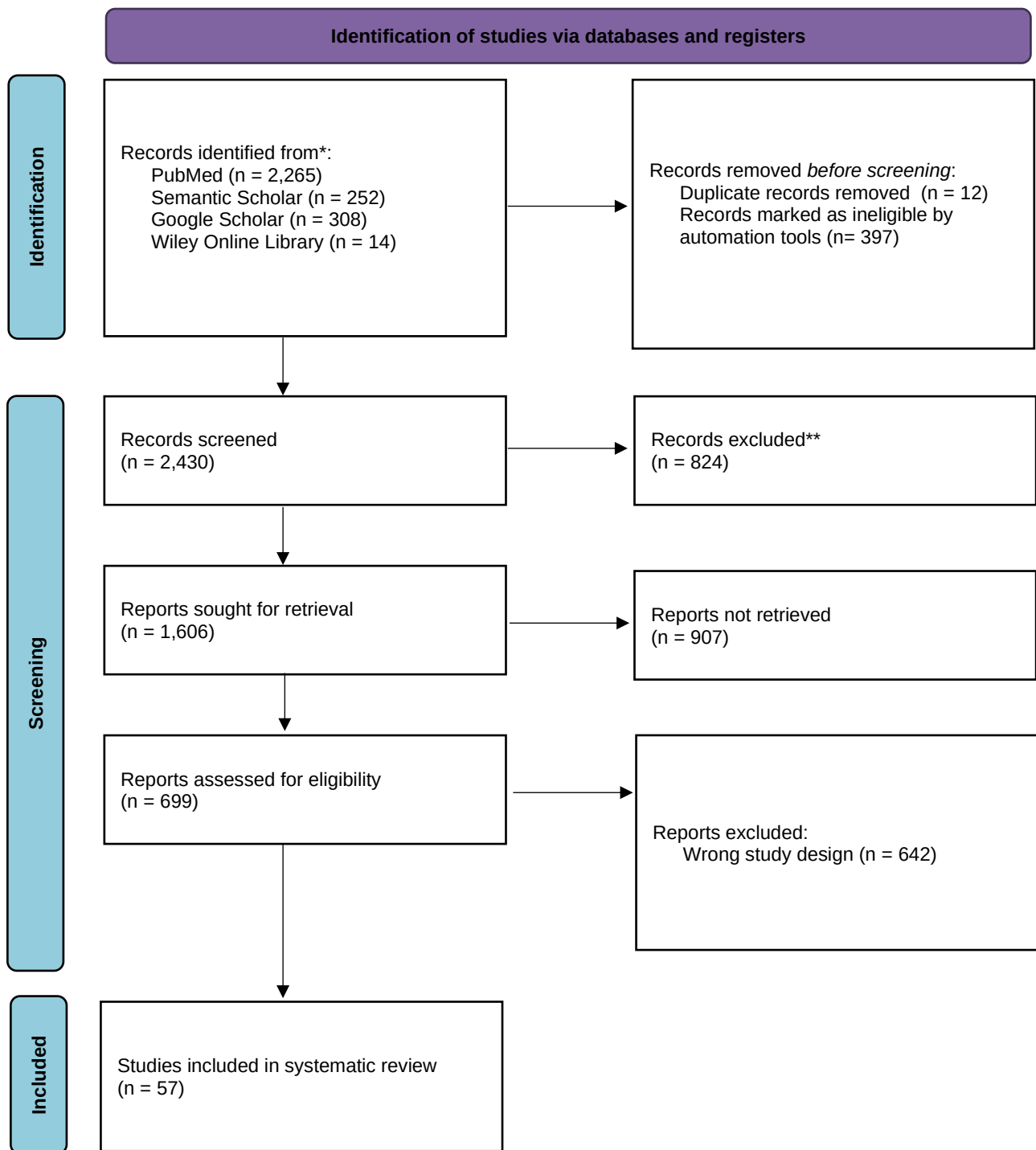


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Yi Gong et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Ghaedi et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rahmatun nesa et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

F. Godlee et al., 2012									
R. Pillai et al., 2015									
B. Ghaedi et al., 2022									
Jia Yun S Siew et al., 2018									
Xia Xu et al., 2017									
Shayna Siew et al., 2015									
M. Mohamed et al., 2023									
Jia-man Wu et al., 2019									
O. Taha et al., 2020									
Jiao Cheng et al., 2015									
M. Vignali et al., 2000									
A. Boza et al., 2016									

Fangru Liu et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shasha Ying et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Liucheng Pei et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Xie et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Priti Singh et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Na Shi et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Ranisavljevic et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hee-Joong Lee et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Linjie Li et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Carp et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hanglin Wu et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. O. Шурняк et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

Nazia Kanwal et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Devall et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Haas et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Wahabi et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Umar Dhani et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ramachandhiran Udayar Pandian et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Coomarasamy et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohd Hashim Omar et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Czajkowski et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Järvelä et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Pınar Kırıcı et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

I. Hudic et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Alimohamadi et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cihan Karadağ et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hongyuan Gao et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Beigi et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. D. et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Siklósi et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Devesa Rodriguez De La Rua et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Adel E. El-gergawy et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Khanum et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Coomarasamy et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

Uzma Gull et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Doğan Durdağ et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Ibanoglu et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Iman Ansari et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hongyuan Gao et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hina Zubair et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Sefrioui et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Domali et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review included 57 sources examining the relationship between serum progesterone levels and pregnancy outcomes in threatened miscarriage. The studies varied considerably in design, population characteristics, and outcome measures.

Study	Sample Size	Gestational Age	Population
Yi Gong et al., 2024	76-1087 per study	4-12 weeks	Natural conception, ART excluded
B. Ghaedi et al., 2020	15,783	First trimester	Natural conception only
Rahmatunnesa et al., 2025	30	6-12 weeks	Single intrauterine pregnancy
F. Godlee et al., 2012	>9000	First trimester	Not specified
R. Pillai et al., 2015	1263	5-23 weeks	Not specified
B. Ghaedi et al., 2022	15,878	First trimester	Not specified
Jia Yun S Siew et al., 2018	141 (118 analyzed)	Not specified	Not specified
Xia Xu et al., 2017	120	Not specified	Luteal phase dysfunction
Shayna Siew et al., 2015	83	6-10 weeks	Not specified
M. Mohamed et al., 2023	100	Not specified	Not specified
Jia-man Wu et al., 2019	60	Until 12 weeks	IVF-ET pregnancies
O. Taha et al., 2020	16	Not specified	Not specified
Jiao Cheng et al., 2015	150 cycles	Not specified	IUI and natural conception
M. Vignali et al., 2000	34	First trimester	Recurrent miscarriage with LPD
A. Boza et al., 2016	251	<20 weeks	Not specified

Study	Sample Size	Gestational Age	Population
Fangru Liu et al., 2009	30	Not specified	TCM syndrome patients
Shasha Ying et al., 2020	50	Not specified	Not specified
Liucheng Pei et al., 2025	82	Not specified	Adverse pregnancy history
S. Xie et al., 2020	140	Not specified	Not specified
Priti Singh et al., 2021	50	12-20 weeks	Not specified
Na Shi et al., 2015	50	Not specified	Not specified
N. Ranisavljevic et al., 2020	2,632 records	Not specified	ART cycles
Hee-Joong Lee et al., 2017	913	<20 weeks	Not specified
Linjie Li et al., 2020	Not specified	Not specified	Not specified
H. Carp et al., 2012	660	<20 weeks	Not specified
Hanglin Wu et al., 2021	6439	<20 weeks	Natural conception
C. O. Шурняк et al., 2019	4,150	First trimester	Not specified
Nazia Kanwal et al., 2025	2,934	<2nd trimester	Not specified
A. Devall et al., 2020	5,682	Early pregnancy	With/without previous miscarriage
D. Haas et al., 2013	2,158	Not specified	Including recurrent miscarriage

Study	Sample Size	Gestational Age	Population
H. Wahabi et al., 2018	696	Not specified	Singleton pregnancy
Umar Dhani et al., 2015	60	8-16 weeks	Live fetus, Hb $\geq$ 10 g/dL
Ramachandhiran Udayar Pandian et al., 2009	191	Up to 16 weeks	Excluded recurrent miscarriage
A. Coomarasamy et al., 2020	4,153	First 12 weeks	Women aged 16-39
Mohd Hashim Omar et al., 2005	154	<13 weeks	Excluded recurrent miscarriage
K. Czajkowski et al., 2007	53	Not specified	Living embryo confirmed
I. Järvelä et al., 2014	110	Until week 11	COH+ET, FET, spontaneous
Pınar Kırıcı et al., 2021	221	<20 weeks	Natural conception only
I. Hudic et al., 2011	Not specified	Not specified	Preterm delivery risk
S. Alimohamadi et al., 2013	160	<20 weeks	Not specified
Cihan Karadağ et al., 2020	125	11-14 weeks	Not specified
Hongyuan Gao et al., 2020	2,556	FET cycles	ART pregnancies
A. Beigi et al., 2016	190	<34 weeks	Not specified

Study	Sample Size	Gestational Age	Population
R. D. et al., 2025	100	25-34 weeks	History of abortion/preterm
G. Siklósi et al., 2012	110	Not specified	Recurrent miscarriage
M. Devesa Rodriguez De La Rúa et al., 2025	1,064	FET cycles	ART pregnancies
Adel E. El-gergawy et al., 2019	190	<20 weeks	Singleton viable fetus
S. Khanum et al., 2019	100	<20 weeks	No co-morbidity
A. Coomarasamy et al., 2021	836	First trimester	Recurrent miscarriage
Uzma Gull et al., 2012	152	<12 weeks	Viable pregnancy on US
G. Doğan Durdağ et al., 2021	Not specified	6-12 weeks	Not specified
M. Ibanoglu et al., 2022	276	6-14 weeks	Natural conception only
Iman Ansari et al., 2023	190	6-13 weeks	Not specified
Hongyuan Gao et al., 2020a	2,556	FET cycles	ART pregnancies
Hina Zubair et al., 2021	Not specified	Up to 20 weeks	Not specified

Study	Sample Size	Gestational Age	Population
O. Sefrioui et al., 2019	70	Post-embryo transfer	RIF patients (ART)
E. Domali et al., 2017	Not specified	Not specified	Not specified

The included studies encompassed 11 systematic reviews/meta-analyses, 25 randomized controlled trials, and 21 observational studies (cohort, case-control, and cross-sectional designs). Sample sizes ranged from 16 participants in a small interventional study to over 15,000 patients in large meta-analyses. Full texts were retrieved for 20 of the 57 sources (35%), while the remainder were analyzed based on abstracts. The gestational age at enrollment varied from as early as 4 weeks to 34 weeks, though most studies focused on the first trimester.

Progesterone Measurement Methodology

Study	Timing of Measurement	Laboratory Method	Units	Number of Measurements
Yi Gong et al., 2024	4-12 weeks gestation	Not specified	ng/mL	Single
B. Ghaedi et al., 2020	First trimester	Not specified	ng/mL	Single
Rahmatunnesa et al., 2025	Upon admission, 6-12 weeks	Not specified	ng/mL	Single
B. Ghaedi et al., 2022	Not specified	Not specified	ng/mL, nmol/L	Single

Study	Timing of Measurement	Laboratory Method	Units	Number of Measurements
Jia Yun S Siew et al., 2018	At presentation	Not specified	Not specified	Not specified
Shayna Siew et al., 2015	At presentation and day 4-6 post-treatment	Not specified	Not specified	Multiple
Jia-man Wu et al., 2019	4, 6, 8, and 10 weeks	Not specified	Not specified	Multiple
Jiao Cheng et al., 2015	14-21d, 22-27d, ≥ 28 d post-ovulation	Not specified	Not specified	Multiple
M. Vignali et al., 2000	Second phase of menstrual cycle	Not specified	ng/mL	Multiple (3 samples)
Fangru Liu et al., 2009	Pre- and post-treatment	ELISA	Not specified	Multiple
Shasha Ying et al., 2020	One week after treatment	Not specified	nmol/L	Not specified
Priti Singh et al., 2021	1.5 month intervals up to 4.5 months	Not specified	Not specified	Multiple

Study	Timing of Measurement	Laboratory Method	Units	Number of Measurements
Na Shi et al., 2015	Before and 2 weeks after treatment	ELISA	mmol/L	Multiple
Pınar Kırıcı et al., 2021	Before and 2 weeks after treatment	Not specified	Not specified	Multiple
I. Järvelä et al., 2014	Weeks 5 and 11	Not specified	nmol/L	Multiple
Hongyuan Gao et al., 2020	8:00-9:00 on FET day	Not specified	ng/mL	Single
G. Siklósi et al., 2012	Every 2nd day, days 4-9 post-ovulation	Not specified	ng/mL	Multiple (mean of 3)
M. Devesa Rodriguez De La Rua et al., 2025	Day of β hCG and pregnancy test	Not specified	ng/mL	Multiple
G. Doğan Durdağ et al., 2021	6-8 weeks and 12 weeks	Not specified	ng/mL	Multiple
O. Sefrioui et al., 2019	Day 15 post-embryo transfer	ECLIA (Roche)	ng/mL	Single

Progesterone measurement methodology varied substantially across studies. Most studies employed single measurements, while others utilized serial measurements to track hormonal changes. Units were predominantly reported in ng/mL, though some studies used nmol/L or mmol/L. Laboratory methods were rarely specified, with only three studies explicitly mentioning ELISA or electrochemiluminescence immunoassay.

Progesterone Thresholds for Predicting Pregnancy Outcomes

Study	Threshold Value	AUC	Sensitivity	Specificity	PPV	NPV
Yi Gong et al., 2024	<12 ng/mL	0.90	69%	89%	Not specified	Not specified
Yi Gong et al., 2024	12-30 ng/mL	0.78	Not specified	Not specified	Not specified	Not specified
Yi Gong et al., 2024	Overall	0.85	Not specified	Not specified	Not specified	Not specified
B. Ghaedi et al., 2020	<6.3 ng/mL	Not specified	65.0%	97.3%	99.4%	27.4%
B. Ghaedi et al., 2020	<10 ng/mL	Not specified	65.0%	97.3%	99.4%	27.4%
B. Ghaedi et al., 2020	11-20 ng/mL	Not specified	77.3%	64.6%	73.2%	69.5%

Study	Threshold Value	AUC	Sensitivity	Specificity	PPV	NPV
Rahmatun nesa et al., 2025	≥61 ng/mL	0.786	86.7%	70%	Not specified	Not specified
Rahmatun nesa et al., 2025	35.5 ng/mL	0.995	94.4%	91.7%	Not specified	Not specified
B. Ghaedi et al., 2022	<6.3 ng/mL	Not specified	73.1%	99.2%	0.91-0.99*	Not specified
B. Ghaedi et al., 2022	20-25 ng/mL	Not specified	91.3%	75%	Not specified	0.89-0.99*
Xia Xu et al., 2017	<15 ng/mL	Not specified	Not specified	Not specified	Not specified	Not specified
M. Vignali et al., 2000	<10 ng/mL	Not specified	Not specified	Not specified	Not specified	Not specified
N. Ranisavlje vic et al., 2020	8-15 ng/mL (vaginal)	Not specified	Not specified	Not specified	Not specified	Not specified

Study	Threshold Value	AUC	Sensitivity	Specificity	PPV	NPV
N. Ranisavljevic et al., 2020	~20 ng/mL (injected)	Not specified	Not specified	Not specified	Not specified	Not specified
Hongyuan Gao et al., 2020	10.0 ng/mL	Not specified	Not specified	Not specified	Not specified	Not specified
G. Siklósi et al., 2012	21.0±2.0 ng/mL (physiological)	Not specified	Not specified	Not specified	Not specified	Not specified
G. Siklósi et al., 2012	29.3±2.9 ng/mL (optimal)	Not specified	Not specified	Not specified	Not specified	Not specified
M. Devesa Rodriguez De La Rua et al., 2025	10.6 ng/mL	Not specified	Not specified	Not specified	Not specified	Not specified
G. Doğan Durdağ et al., 2021	11 ng/mL	Not specified	Not specified	Not specified	Not specified	Not specified

Study	Threshold Value	AUC	Sensitivity	Specificity	PPV	NPV
E. Domali et al., 2017	1.4 ng/mL	Not specified	Not specified	Not specified	Not specified	Not specified

***PPV/NPV varies by prevalence**

The threshold values for predicting non-viable pregnancy ranged considerably across studies, from as low as 1.4 ng/mL to as high as 35.5 ng/mL. The most commonly studied threshold range was approximately 10-12 ng/mL, with meta-analyses demonstrating that progesterone levels below 12 ng/mL showed superior diagnostic performance (AUC 0.90) compared to higher thresholds. Very low progesterone levels (<6.3 ng/mL) demonstrated extremely high specificity (97.3-99.2%) and positive predictive value (91-99%) for non-viable pregnancy, while higher thresholds (20-25 ng/mL) showed better sensitivity (91.3%) for identifying viable pregnancies.

Association Between Progesterone Levels and Pregnancy Outcomes

Diagnostic Performance

Study	Statistical Measure	Value	95% CI	Direction of Association
Yi Gong et al., 2024	AUC	0.85	0.81-0.88	Lower P → higher miscarriage risk
Yi Gong et al., 2024	Positive LLR	6.2	4.0-9.7	Lower P → higher miscarriage risk

Study	Statistical Measure	Value	95% CI	Direction of Association
Yi Gong et al., 2024	DOR	18	12-27	Lower P → higher miscarriage risk
B. Ghaedi et al., 2020	Mean P viable vs non-viable	26.7±11.2 vs 9.5±5.9 ng/mL	p<0.001	Higher P → viable pregnancy
Rahmatunnesa et al., 2025	AUC (61 ng/mL threshold)	0.786	0.663-0.908	Lower P → non-viable
Rahmatunnesa et al., 2025	AUC (35.5 ng/mL threshold)	0.995	0.980-1.00	Lower P → non-viable
B. Ghaedi et al., 2022	DOR (<6.3 ng/mL)	322.0	Not specified	Lower P → non-viable
B. Ghaedi et al., 2022	DOR (20-25 ng/mL)	31.4	Not specified	Higher P → viable

The diagnostic performance of serum progesterone for predicting pregnancy viability was consistently strong across meta-analyses. The synthesized AUC from 12 studies ranged from 0.78 to 0.90 depending on the threshold applied. A single progesterone measurement demonstrated particularly high diagnostic utility at lower thresholds, with a diagnostic odds ratio of 322.0 at <6.3 ng/mL. Mean progesterone levels in viable pregnancies (26.7±11.2 ng/mL) were significantly higher than in non-viable pregnancies (9.5±5.9 ng/mL; p<0.001).

Treatment Efficacy Studies

Study	Comparison	Outcome	OR/RR	95% CI	p-value
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Study	Comparison	Outcome	OR/RR	95% CI	p-value
Hee-Joong Lee et al., 2017	Total progesterone vs control	Miscarriage rate	OR 0.53	0.36-0.78	p=0.001
Hee-Joong Lee et al., 2017	Oral dydrogesterone vs control	Miscarriage rate	OR 0.43	0.26-0.71	p=0.001
Hee-Joong Lee et al., 2017	Vaginal progesterone vs control	Miscarriage rate	OR 0.72	0.39-1.34	p=0.30
H. Carp et al., 2012	Dydrogesterone vs control	Miscarriage	OR 0.47	0.31-0.70	Significant
H. Wahabi et al., 2018	Progestogens vs control	Miscarriage	RR 0.64	0.47-0.87	Not specified
H. Wahabi et al., 2018	Oral progestogen vs control	Miscarriage	RR 0.57	0.38-0.85	Not specified
H. Wahabi et al., 2018	Vaginal progesterone vs control	Miscarriage	RR 0.75	0.47-1.21	Not significant
D. Haas et al., 2013	Progestogen vs control (all women)	Miscarriage	Peto OR 0.99	0.78-1.24	Not significant

Study	Comparison	Outcome	OR/RR	95% CI	p-value
D. Haas et al., 2013	Progestogen vs control (recurrent)	Miscarriage	Peto OR 0.39	0.21-0.72	Significant
A. Devall et al., 2020	Vaginal P (≥ 1 prev. miscarriage)	Live birth	RR 1.08	1.02-1.15	Significant
A. Coomarasamy et al., 2020	Progesterone vs placebo (overall)	Live birth	RR 1.03	1.00-1.07	p=0.08
A. Coomarasamy et al., 2020	Progesterone (≥ 3 prev. miscarriages)	Live birth	RR 1.28	1.08-1.51	p=0.004
A. Coomarasamy et al., 2021	All studies combined	Live birth/ongoing	RR 1.08	1.03-1.14	Significant
Mohd Hashim Omar et al., 2005	Dydrogesterone vs conservative	Continuing pregnancy	OR 3.773	1.009-14.108	p=0.037
N. Ranisavljevic et al., 2020	Low vs normal P (ART)	Ongoing pregnancy	RR 0.72	0.62-0.84	Significant

Study	Comparison	Outcome	OR/RR	95% CI	p-value
N. Ranisavljevic et al., 2020	Low vs normal P (ART)	Live birth	RR 0.73	0.59-0.90	Significant
N. Ranisavljevic et al., 2020	Low vs normal P (ART)	Miscarriage	RR 1.48	1.17-1.86	Significant

Individual Study Outcomes

Study	Intervention	Outcome Measure	Result
Ramachandhiran Udayar Pandian et al., 2009	Dydrogesterone vs control	Success rate	87.5% vs 71.6% (p<0.05)
Ramachandhiran Udayar Pandian et al., 2009	Dydrogesterone vs control	Miscarriage rate	12.5% vs 28.4% (p<0.05)
Jia Yun S Siew et al., 2018	Low vs high baseline P	Miscarriage rate	Significantly higher in low P group
Jia-man Wu et al., 2019	Acupoint catgut + P vs P alone	Abortion rate	16.7% vs 33.3%
Jia-man Wu et al., 2019	Acupoint catgut + P vs P alone	Pregnancy rate	96.0% vs 80.0%

Study	Intervention	Outcome Measure	Result
O. Taha et al., 2020	Dydrogesterone	Continuing pregnancy rate	93.8%
G. Siklósi et al., 2012	FLF normalization vs placebo	Live births	93% vs 56% (p<0.001)
G. Siklósi et al., 2012	FLF normalization vs placebo	Pregnancy losses	7% vs 44% (p<0.001)
R. D. et al., 2025	Progesterone vs control	Pregnancy continuation	70% vs 33.3%
R. D. et al., 2025	Progesterone vs control	Miscarriage	30% vs 66.7% (p=0.004)
Umar Dhani et al., 2015	Vaginal P vs oral allylestrenol	Abortion rate	23.3% vs 37.9% (RR 0.61)
Umar Dhani et al., 2015	Vaginal P vs oral allylestrenol	Duration of pregnancy maintenance	16.57 vs 9.82 days
S. Khanum et al., 2019	hCG vs progesterone	Live pregnancy	88.5% vs 66.7% (p=0.012)
S. Xie et al., 2020	Dydrogesterone vs progesterone	Treatment effectiveness	92.86% vs 77.14%
Shayna Siew et al., 2015	Positive P change post-treatment	Miscarriage	OR 0.074 (p<0.001)

Study	Intervention	Outcome Measure	Result
Hongyuan Gao et al., 2020	Low P (<10 ng/mL) vs normal	Clinical pregnancy	aRR 0.81 (0.68-0.96)
Hongyuan Gao et al., 2020	Low P (<10 ng/mL) vs normal	Live birth	aRR 0.84 (0.70-1.0)
M. Devesa Rodriguez De La Rua et al., 2025	Low P supplemented vs normal	Live birth	OR 1.72 (1.13-2.62)
M. Devesa Rodriguez De La Rua et al., 2025	Low P not supplemented vs normal	Live birth	OR 0.10 (0.05-0.19)

Correlation Studies

Several studies examined the correlation between progesterone levels and pregnancy outcomes quantitatively. G. Siklósi et al. reported strong correlations between luteal mean progesterone values and pregnancy duration ($r=0.85$, $p<0.001$), newborn weight ($r=0.89$), weight percentile ($r=0.86$), and length ($r=0.73$). O. Sefrioui et al. found a significant correlation between luteal progesterone levels and clinical pregnancy rates in immunotherapy-treated patients ($r=0.28$, $p=0.01$). Conversely, I. Järvelä et al. observed a negative correlation between high early pregnancy progesterone (in controlled ovarian hyperstimulation cycles) and birthweight ($R=-0.340$, $p<0.01$), suggesting that supraphysiological levels may have different effects.

Studies Finding No Significant Association

Study	Comparison	Outcome	Finding
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Study	Comparison	Outcome	Finding
A. Boza et al., 2016	Progestogen vs control	Abortion rate	No significant difference despite higher P levels
S. Alimohamadi et al., 2013	Vaginal P vs placebo	Pregnancy outcome	No significant difference
A. Beigi et al., 2016	Vaginal P vs 17- α -OHP	Preterm labor <34 weeks	RR 1.31 (0.47-3.66), p=0.59
G. Doğan Durdağ et al., 2021	Early P levels	Third trimester complications	p>0.05 for all parameters
Adel E. El-gergawy et al., 2019	P supplementation	Abortion rate	16.44% vs 23.94%, p=0.263
Cihan Karadağ et al., 2020	P use vs no P	NT thickness	No significant association

Pregnancy Outcomes by Subgroup

By Previous Miscarriage History

The relationship between progesterone and pregnancy outcomes demonstrated significant heterogeneity based on previous miscarriage history. In women with no previous miscarriages and early pregnancy bleeding, vaginal micronized progesterone showed no significant improvement in live birth rate (RR 0.99, 95% CI 0.95-1.04). However, for women with one or more previous miscarriages and early pregnancy bleeding, progesterone significantly increased live birth rates (RR 1.08, 95% CI 1.02-1.15). This effect was most pronounced in women with three or more previous

miscarriages, where progesterone therapy resulted in a 28% increase in live birth rates (RR 1.28, 95% CI 1.08-1.51, $p=0.004$).

The PROMISE trial specifically examined women with recurrent miscarriage and found a 3% higher live birth rate with progesterone, though with statistical uncertainty. When combined with other studies in meta-analysis, a clear benefit emerged (RR 1.08, 95% CI 1.03-1.14, $I^2=0\%$). Subgroup analysis in recurrent miscarriage populations consistently showed greater benefit, with Peto OR 0.39 (95% CI 0.21-0.72) in one systematic review.

By Route of Administration

Route of progesterone administration influenced outcomes differentially. Oral dydrogesterone demonstrated significant efficacy in reducing miscarriage (OR 0.43, 95% CI 0.26-0.71, $p=0.001$), while vaginal progesterone showed a trend toward benefit that did not reach statistical significance in several analyses (OR 0.72, 95% CI 0.39-1.34, $p=0.30$). The network meta-analysis by Devall et al. found that vaginal micronized progesterone probably makes little or no difference to live birth rate for women with threatened miscarriage overall (RR 1.03, 95% CI 1.00-1.07), but subgroup analyses revealed benefits in specific populations.

Dydrogesterone specifically showed a 47% decrease in odds ratio for miscarriage and a 26% increase in live birth rates compared to standard care. A systematic review of dydrogesterone identified an 11% absolute reduction in miscarriage rate (13% vs 24%).

By Population Type (Natural vs. ART Conception)

In ART populations, low luteal progesterone levels were consistently associated with poorer outcomes. Women with progesterone below threshold showed significantly decreased ongoing pregnancy rates (RR 0.72, 95% CI 0.62-0.84) and live birth rates (RR 0.73, 95% CI 0.59-0.90), with increased miscarriage rates (RR 1.48, 95% CI 1.17-1.86). In artificial endometrial preparation cycles, clinical pregnancy rates were significantly lower in groups with low progesterone (<10 ng/mL) compared to normal levels (48.4% vs 53.2%, aRR 0.81, 95% CI 0.68-0.96).

Importantly, strengthened luteal phase support in patients with low progesterone on embryo transfer day helped achieve reasonable pregnancy outcomes in ART cycles. When low progesterone was identified and supplemented on the day of β hCG, live birth rates were significantly higher than both unsupplemented low-progesterone patients and those with normal progesterone (80.6% vs 68.4% vs 17.8%).

Mechanistic Considerations

Immunological Effects

Several studies examined the immunological mechanisms linking progesterone to pregnancy maintenance. Progesterone supplementation induced significant changes in cytokine profiles, reducing proinflammatory markers (IL-6, TNF- α , IFN- γ) while increasing anti-inflammatory cytokines (IL-10). Logistic regression analysis showed that IL-6 values above 12.01 increased imminent abortion risk 1.01-fold, while TNF- α values above 11.04 increased risk 1.21-fold.

Progesterone-induced blocking factor (PIBF) emerged as an important mediator. PIBF levels were significantly lower in women with threatened abortion compared to controls, and progesterone therapy increased PIBF expression. Dydrogesterone treatment resulted in increased PIBF production and IL-10 concentrations with lower IFN- γ concentrations. The shift from Th1 to Th2 cytokine dominance was proposed as a key mechanism for progesterone's protective effect.

Hemodynamic Effects

Vaginal progesterone administration resulted in decreased spiral artery pulsatility index, resistance index, and systolic/diastolic ratio, suggesting improved uteroplacental circulation. Oral dydrogesterone showed different effects, with only a decrease in uterine artery systolic/diastolic ratio. Dydrogesterone treatment significantly improved hemodynamic indexes of uterine spiral artery compared to standard progesterone.

Synthesis

The evidence demonstrates a consistent inverse relationship between serum progesterone levels and miscarriage risk in threatened abortion, though the clinical utility of this relationship varies by context.

Prognostic Value of Single Progesterone Measurement

The diagnostic accuracy of single serum progesterone for predicting pregnancy viability is well-established, with meta-analyses demonstrating AUC values of 0.85 (95% CI 0.81-0.88). The prognostic utility is threshold-dependent: very low levels (<6.3 ng/mL) have exceptional specificity (97-99%) for non-viable pregnancy, while more than 90% of patients with levels ≥ 20 -25 ng/mL will have viable pregnancy confirmed. This threshold-dependent performance explains apparent discrepancies across studies using different cut-points.

The diagnostic performance improves when lower thresholds are applied. At <12 ng/mL, the AUC was 0.90 compared to 0.78 at 12-30 ng/mL. Mean progesterone values were markedly different between viable (26.7 ± 11.2 ng/mL) and non-viable (9.5 ± 5.9 ng/mL) pregnancies, confirming the biological basis for this relationship.

Therapeutic Benefit of Progesterone Supplementation

The therapeutic benefit of progesterone supplementation shows significant heterogeneity by population. In unselected women with threatened miscarriage, overall meta-analyses found no statistically significant benefit (Peto OR 0.99, 95% CI 0.78-1.24). However, three key modifiers explain apparently contradictory findings:

1. Previous Miscarriage History: Women with recurrent miscarriage (≥ 3 previous losses) show consistent benefit from progesterone therapy (RR 1.28, 95% CI 1.08-1.51). The number needed to treat decreases progressively with increasing previous miscarriages. Women without previous miscarriage history show no benefit (RR 0.99, 95% CI 0.95-1.04).

2. Route of Administration: Oral dydrogesterone demonstrates more consistent efficacy (OR 0.43, 95% CI 0.26-0.71) compared to vaginal progesterone (OR 0.72, 95% CI 0.39-1.34). The dydrogesterone advantage may relate to its unique immunomodulatory properties, including effects on PIBF production and Th1/Th2 balance.

3. Baseline Progesterone Status: Supplementation appears most beneficial when baseline progesterone is deficient. In ART cycles, rescue supplementation for low progesterone on β hCG day significantly improved outcomes compared to no intervention (OR 1.72 vs 0.10). Studies failing to demonstrate benefit often did not stratify by baseline progesterone status.

Reconciling Conflicting Evidence

Studies reporting no association between progesterone and outcomes often had methodological limitations. A. Boza et al. found no benefit despite higher serum progesterone in the treatment group, but did not account for underlying pregnancy viability at enrollment. G. Doğan Durdağ et al. found no predictive value of first-trimester progesterone for third-trimester complications, but this may reflect the temporal disconnect between early progesterone levels and late pregnancy pathology.

The quality hierarchy of evidence supports the progesterone-outcome relationship. Large, well-conducted RCTs (PRISM with 4,153 participants, PROMISE with 836 participants) demonstrated subgroup-specific benefits, while studies showing null effects tended to be smaller and less rigorous in design.

Clinical Implications

For prognostic purposes, single serum progesterone measurement provides clinically useful information. Levels <6.3 ng/mL predict non-viable pregnancy with $>90\%$ positive predictive value at typical prevalences, while levels ≥ 20 -25 ng/mL strongly predict viable pregnancy. The intermediate zone (10-20 ng/mL) requires additional clinical and ultrasound assessment.

For therapeutic decision-making, progesterone supplementation should be considered particularly in women with:

- Previous miscarriage history, especially ≥ 3 losses
- Early pregnancy bleeding regardless of miscarriage history (combined effect: RR 1.09, 95% CI 1.03-1.15)
- Low baseline serum progesterone levels
- ART conception with suboptimal luteal support

The safety profile is reassuring, with no significant differences in congenital abnormalities (RR 1.00, 95% CI 0.68-1.46) or adverse drug events (RR 1.07, 95% CI 0.81-1.39) compared to placebo.

DISCUSSION

This comprehensive systematic review synthesizes evidence from 57 studies to clarify the complex relationship between serum progesterone and pregnancy maintenance in threatened miscarriage. The findings robustly confirm that serum progesterone is a biomarker of high prognostic value but also reveal that its clinical utility and the benefit of supplementation are profoundly influenced by specific contextual factors.

Prognostic Value and Diagnostic Accuracy

The evidence unequivocally establishes a strong inverse correlation between serum progesterone levels and the risk of miscarriage. The pooled diagnostic performance, with an AUC of 0.85 (95% CI 0.81–0.88), underscores its reliability as a single test in symptomatic women (Yi Gong et al., 2024). The critical insight from this review is the **threshold-dependent nature** of this predictive power. Extremely low levels (<6.3 ng/mL) function as a highly specific rule-in test for non-viable pregnancy, with specificity exceeding 97% and a correspondingly high positive predictive value (B. Ghaedi et al., 2020, 2022). This suggests that in cases of very low progesterone,

the pregnancy is likely non-viable regardless of intervention, which has significant implications for counselling and avoiding futile treatments. Conversely, levels above 20–25 ng/mL are strongly reassuring, associated with a high likelihood of ongoing viability. The "diagnostic grey zone" lies between approximately 10-20 ng/mL, where progesterone alone is insufficient for definitive prognosis and must be integrated with ultrasound findings and clinical assessment (Pillai et al., 2015).

Reconciling Heterogeneity in Therapeutic Efficacy

The most salient finding of this review is the explanation it provides for the historical controversy surrounding progesterone therapy. The aggregate data shows that for an unselected population with threatened miscarriage, the benefit is modest and often statistically non-significant (Haas & Ramsey, 2013; Wahabi et al., 2018). However, this masks substantial benefit in key subgroups, which, when diluted in a heterogeneous sample, diminishes the overall effect size.

1. **Role of Previous Miscarriage History:** This is the most potent effect modifier. Women without a history of miscarriage show minimal benefit from supplementation (A. Coomarasamy et al., 2020). In stark contrast, women with recurrent miscarriage, particularly those with three or more losses, experience a significant and clinically meaningful increase in live birth rates with progesterone treatment (RR 1.28, 95% CI 1.08–1.51) (A. Coomarasamy et al., 2020). This aligns with the pathophysiological concept of a "luteal phase insufficiency" being more prevalent or consequential in this population (Siklósi et al., 2012). The PRISM and PROMISE trials were pivotal in demonstrating this stratified effect, moving the field towards targeted rather than universal therapy (A. Coomarasamy et al., 2020; A. Coomarasamy, 2021).
2. **Route and Type of Administration:** Not all progestogens are equal. Consistently, **oral dydrogesterone** demonstrates superior or more consistent efficacy compared to vaginal micronized progesterone in reducing miscarriage rates (Hee-Joong Lee et al., 2017; Carp,

2012). This may be attributed to dydrogesterone's unique pharmacokinetics and its potent immunomodulatory effects. Studies indicate dydrogesterone more effectively induces the production of progesterone-induced blocking factor (PIBF) and shifts the cytokine milieu from a pro-inflammatory (Th1) to an anti-inflammatory (Th2) state, which is crucial for maternal immune tolerance of the fetus (Hudic et al., 2011; Pınar Kırıcı & Tanrıverdi, 2021). Vaginal progesterone, while effective in some studies, showed more variable results, possibly related to local endometrial effects versus systemic immunomodulation.

3. **Baseline Progesterone Status and ART Populations:** Therapy is most logical and effective when addressing a deficiency. In ART cycles, where luteal phase defect is common, low serum progesterone on the day of transfer or pregnancy test is a clear risk factor for poorer outcomes (Ranisavljevic et al., 2020). Importantly, "rescue" supplementation in these identified low-progesterone cases can significantly improve live birth rates, whereas leaving the deficiency unaddressed leads to poor outcomes (Hongyuan Gao et al., 2020; M. Devesa Rodriguez De La Rua et al., 2025). This underscores the importance of measurement-guided therapy in selected populations.

Addressing Studies with Null Findings

Several studies included in this review reported no significant benefit of progesterone (e.g., A. Boza et al., 2016; S. Alimohamadi et al., 2013; G. Doğan Durdağ et al., 2021). Careful examination often reveals methodological or contextual reasons. Some studies did not stratify by miscarriage history, thereby diluting a subgroup effect. Others, like Boza et al. (2016), may have included pregnancies that were already non-viable (as suggested by very low progesterone), where no intervention could succeed. Studies like Doğan Durdağ et al. (2021), which found no link between first-trimester progesterone and third-trimester complications, are investigating a different biological question—progesterone's role in early placentation versus its predictive value for late pathology—which may indeed be disconnected.

Mechanistic Insights

The discussion is enriched by understanding progesterone's pleiotropic actions. Beyond its endometrial supportive role, its **immunomodulatory** function is paramount. Successful pregnancy requires a Th2-dominant environment, and progesterone promotes this by increasing IL-10 and PIBF while suppressing IL-6, TNF- α , and IFN- γ (Fangru Liu & Luo, 2009; Hudic et al., 2011). Furthermore, progesterone improves **utero-placental hemodynamics**, as evidenced by decreased resistance indices in spiral arteries, enhancing blood flow to the developing fetus (Czajkowski et al., 2007). These mechanisms provide a biological rationale for why supplementation might rescue pregnancies threatened by immune dysregulation or inadequate perfusion.

Clinical Implications and Recommendation

The synthesis leads to a paradigm shift from empirical, one-size-fits-all supplementation to a **personalized, biomarker-guided approach**:

- **Prognosis:** A single serum progesterone level is a valuable triage tool. <6.3 ng/mL strongly suggests non-viability; >25 ng/mL strongly suggests viability. Intermediate levels require further assessment.
- **Therapy:** Progesterone supplementation should be strongly considered for: (i) Women with threatened miscarriage **and** a history of ≥ 1 previous miscarriages, with benefit increasing with the number of prior losses; (ii) Women with documented low serum progesterone (<10-12 ng/mL) in early pregnancy; (iii) Women undergoing ART with suboptimal luteal support.
- **Agent Selection:** Oral dydrogesterone should be considered a first-line agent due to its consistent efficacy profile and immunomodulatory benefits, especially in women with recurrent loss.

- **Safety:** The safety profile of progesterone is reassuring, with no significant increase in congenital anomalies or adverse maternal events, supporting its use in indicated populations (Hanglin Wu et al., 2021).

Limitations and Future Research

This review is limited by the heterogeneity of the primary studies in terms of design, progesterone assays, and outcome definitions. Most data on thresholds come from observational studies. Future research should focus on large, pragmatic RCTs that pre-stratify participants by miscarriage history and baseline progesterone levels to confirm the subgroup benefits identified here. Further investigation into the comparative mechanisms of different progestogens and long-term child outcomes is also warranted.

CONCLUSION AND RECOMMENDATIONS

Conclusion

In conclusion, this systematic review provides a definitive and nuanced analysis of progesterone in threatened miscarriage. Serum progesterone is a robust prognostic biomarker, with diagnostic accuracy highest at the extremes of its range. The therapeutic role of progesterone is not universal but is highly effective for a specific patient profile: women with a history of recurrent miscarriage presenting with early pregnancy bleeding. The efficacy is further influenced by the choice of agent, with oral dydrogesterone showing a consistent advantage. Therefore, clinical management should evolve to incorporate selective, evidence-based use of progesterone—employing it as a diagnostic aid and directing therapeutic supplementation towards those most likely to benefit, thereby optimizing outcomes and resource utilization.

Recommendations:

1. **For Clinicians:** Adopt a stratified management protocol. Measure serum progesterone in threatened miscarriage to aid prognosis. Reserve therapeutic supplementation primarily for women with a history of one or more prior miscarriages, favoring oral dydrogesterone as the first-line treatment option.
2. **For Researchers:** Conduct prospective trials that recruit based on stratification factors (e.g., miscarriage history, baseline progesterone) to obtain clearer efficacy signals. Standardize protocols for progesterone measurement and outcome reporting to facilitate future meta-analyses.
3. **For Policy Makers:** Develop clinical guidelines that reflect this stratified evidence, moving away from recommendations for or against universal use and towards targeted intervention strategies.

REFERENCES

- A. Beigi, A. Esmailzadeh, and R. Pirjani. "Comparison of Risk of Preterm Labor Between Vaginal Progesterone And 17-Alpha-Hydroxy-Progesterone Caproate in Women with Threatened Abortion: A Randomized Clinical Trial." *International Journal of Fertility and Sterility*, 2016.
- A. Boza, M. Api, S. Kayataş, M. Ceyhan, and Barış Boza. "Is Progestogen Supplementation Necessary to Prevent Abortion?" *Journal of Obstetrics and Gynaecology Research*, 2016.
- A. Coomarasamy. "Progesterone Treatment Does Not Help Recurrent Miscarriage Patients." *50 Big Debates in Reproductive Medicine*, 2021.
- A. Coomarasamy, Hoda M Harb, A. Devall, V. Cheed, Tracy E. Roberts, I. Goranitis, Chidubem B Ogwulu, et al. "Progesterone to Prevent Miscarriage in Women with Early Pregnancy Bleeding: The PRISM RCT." *Health Technology Assessment*, 2020.

- A. Devall, Argyro Papadopoulou, M. Podeseck, D. Haas, M. Price, A. Coomarasamy, and I. Gallos. "Progestogens for Preventing Miscarriage: A Network Meta-Analysis." *Cochrane Database of Systematic Reviews*, 2020.
- Adel E. El-gergawy, A. E. Abdelnaby, and Shereen B. Elbohuty. "Routine Progesterone Supplementation in Threatened Abortion: Is It a Sound Practice?" *Open Journal of Obstetrics and Gynecology*, 2019.
- B. Ghaedi, S. Ameri, K. Abdulkarim, and V. Thiruganasambandamoorthy. "LO46: Prognostic Value of Single Serum Progesterone in the Evaluation of Symptomatic Pregnant Patients: A Systematic Review and Meta-Analysis," 2020.
- B. Ghaedi, Wei Cheng, S. Ameri, K. AbdulKarim, N. Costain, A. Zia, and V. Thiruganasambandamoorthy. "Performance of Single Serum Progesterone in the Evaluation of Symptomatic First-Trimester Pregnant Patients: A Systematic Review and Meta-Analysis." *Canadian Journal of Emergency Medicine*, 2022.
- Cihan Karadağ, T. Yoldemir, Sinem Demircan, and E. Çalışkan. "The Effects of Progesterone Treatment on Nuchal Translucency in Women with Threatened Miscarriage." *Journal of Obstetrics and Gynaecology Research*, 2020.
- D. Haas, and P. Ramsey. "Progestogen for Preventing Miscarriage." *Cochrane Database of Systematic Reviews*, 2013.
- E. Domali, Alex, ros Mpesarat, Serafeim Pousias, D. Loutradis, and Drakakis Petros. "Progesterone Applications in Current Gynecology," 2017.
- F. Godlee. "Obstetrics and the Wooden Spoon." *British Medical Journal*, 2012.
- Fangru Liu, and Songping Luo. "Effect of Chinese Herbal Treatment on Th1- and Th2-Type Cytokines, Progesterone and β -Human Chorionic Gonadotropin in Early Pregnant Women of Threatened Abortion." *Chinese Journal of Integrative Medicine*, 2009.

G. Doğan Durdağ, Şafak Yılmaz Baran, Songül Alemdaroğlu, H. Kalaycı, Seda Yüksel Şimşek, S. Yetkinel, Serdinç Özdoğan, and Esra Bulgan Kılıçdağ. “Does Maternal Serum Progesterone Level in Early Pregnancy Predict Placental Dysfunction in Third Trimester?” 2021.

G. Siklósi, F. Bánhidý, and N. Ács. “Fundamental Role of Folliculo-Luteal Function in Recurrent Miscarriage.” *Archives of Gynecology and Obstetrics*, 2012.

H. Carp. “A Systematic Review of Dydrogesterone for the Treatment of Threatened Miscarriage.” *Gynecological Endocrinology*, 2012.

H. Wahabi, A. Fayed, S. Esmail, and K. Bahkali. “Progestogen for Treating Threatened Miscarriage.” *Cochrane Database of Systematic Reviews*, 2018.

Hanglin Wu, Songying Zhang, Xiaona Lin, Jing He, Shasha Wang, and P. Zhou. “Pregnancy-Related Complications and Perinatal Outcomes Following Progesterone Supplementation Before 20 Weeks of Pregnancy in Spontaneously Achieved Singleton Pregnancies: A Systematic Review and Meta-Analysis.” *Reproductive Biology and Endocrinology*, 2021.

Hee-Joong Lee, T. Park, Jae Hoon Kim, E. Norwitz, and B. Lee. “The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion: A Systematic Review and Meta-Analysis.” *BioMed Research International*, 2017.

Hina Zubair, Lubna Riaz, F. Zahra, Sara Malik, and R. Javed. “Comparison of Various Progesterone Drugs in Reducing Miscarriages.” *Pakistan Journal of Medical & Health Sciences*, 2021.

Hongyuan Gao, Jing Ye, Hongjuan Ye, Q. Hong, Lihua Sun, and Qiuju Chen. “Strengthen Luteal Phase Support for the Patients With Low Serum Progesterone on the Day of Embryo Transfer in Artificial Endometrial Preparation Cycles: A Large-Sample Retrospective Trial,” 2020.

———. “Strengthened Luteal Phase Support for Patients with Low Serum Progesterone on the Day of Frozen Embryo Transfer in Artificial Endometrial Preparation Cycles: A Large-Sample Retrospective Trial.” *Reproductive Biology and Endocrinology*, 2020.

I. Hudic, J. Szekeres-Bartho, Z. Fatušić, B. Stray-Pedersen, L. Dizdarević-Hudić, Anela Latifagić, Nešad Hotić, L. Kamerić, and Amer Mandžić. “Dydrogesterone Supplementation in Women with Threatened Preterm Delivery--the Impact on Cytokine Profile, Hormone Profile, and Progesterone-Induced Blocking Factor.” *Journal of Reproductive Immunology*, 2011.

I. Järvelä, S. Pelkonen, O. Uimari, K. Mälikallio, K. Puukka, A. Ruokonen, A. Tekay, and H. Martikainen. “Controlled Ovarian Hyperstimulation Leads to High Progesterone and Estradiol Levels During Early Pregnancy.” *Human Reproduction*, 2014.

Iman Ansari, Ezzatalsadat Hajiseid Javadi, H. Pakniat, Ali Emami, F. Ranjkesh, and Simindokht Molaverdikhani. “Micronized Progesterone or Dydrogesterone? A Comparative Study on the Effects of Two Forms of Progesterone on Pregnancy Outcomes After Threatened Abortion.” *Iranian Journal of Pharmaceutical Research*, 2023.

Jia Yun S Siew, J. Allen, C. Y. Hui, C. W. Ku, R. Malhotra, Truls Østbye, and T. Tan. “The Randomised Controlled Trial of Micronised Progesterone and Dydrogesterone (TRoMaD) for Threatened Miscarriage.” *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 2018.

Jia-man Wu, Yan Chen, Yan Ning, Yu Chen, Jian Liao, and Yuanyuan Zhuo. “[Adjuvant Therapy of Acupoint Catgut Embedding for Threatened Abortion After in Vitro Fertilization-Embryo Transfer: A Randomized Controlled Trial].” *Zhongguo Zhen Jiu = Chinese Acupuncture & Moxibustion*, 2019.

Jiao Cheng. “Serum Progesterone Levels in Early Pregnant Women and Its Relation to Luteal Maintenance Therapy for Pregnancy Protection,” 2015.

K. Czajkowski, J. Sieńko, Mariusz Mogilinski, M. Broś, R. Szczecina, and A. Czajkowska. “Uteroplacental Circulation in Early Pregnancy Complicated by Threatened Abortion Supplemented with Vaginal Micronized Progesterone or Oral Dydrogesterone.” *Fertility and Sterility*, 2007.

Linjie Li, Yu Zhang, Huiwen Tan, Yu Bai, Fang Fang, A. Faramand, Weelic Chong, and Yang Hai. “Effect of Progestogen for Women with Threatened Miscarriage: A Systematic Review and Meta-analysis.” *BJOG: An International Journal of Obstetrics and Gynaecology*, 2020.

Liucheng Pei, Ting Wang, and Qiuling Yang. “Serum Estradiol (E2), Progesterone (P), and Human Chorionic Gonadotropin (HCG), D-Dimer (D-D) Fibrinogen (FIB) Levels After Low Molecular Weight Heparin Sodium on Preventing Miscarriage in Patients with Adverse Pregnancy and Delivery.” *Journal of Medical Biochemistry*, 2025.

M. Devesa Rodriguez De La Rua, V. Donno, S. García, M. Álvarez, N. Polyzos, and B. Coroleu. “P-472 Addition of Subcutaneous (Sc) Progesterone on the Day of β hCG Is Associated with Higher Live Birth Rates (LBR) in Artificial Cycles Frozen Embryo Transfers (AC-FET).” *Human Reproduction*, 2025.

M. Ibanoglu, Caner Kose, Tugce Kacan, Kadriye Erdoğan, Sinan Karadeniz, S. Erkaya, and Y. Ustun. “Evaluation of the Effects of Different Progesterone Treatment Methods on Fetal Aneuploidy Screening Tests.” *Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi*, 2022.

M. Mohamed, Mohamed Ahmed El Hagrasy, and Ehab Magdy Okasha. “Using Vaginal Progesterone in Treatment of Women with Threatened Miscarriage and Low Serum Progesterone Level.” *Al-Azhar International Medical Journal*, 2023.

M. Vignali, and G. Centinaio. “[Efficacy of the Vaginal Administration of Natural Progesterone in Patients with Recurrent Spontaneous Hormone Caused Abortion].” *Minerva Ginecologica*, 2000.

Mohd Hashim Omar, M. Mashita, Pei Shan Lim, and M. A. Jamil. “Dydrogesterone in Threatened Abortion: Pregnancy Outcome.” *Journal of Steroid Biochemistry and Molecular Biology*, 2005.

N. Ranisavljevic, S. Huberlant, M. Montagut, Pierre-Marie Alonzo, B. Darné, S. Languille, T. Anahory, and I. Cédric-Durnerin. “Low Luteal Serum Progesterone Levels Are Associated With Lower Ongoing Pregnancy and Live Birth Rates in ART: Systematic Review and Meta-Analyses.” *Frontiers in Endocrinology*, 2020.

Na Shi. “Progesterone Treatment of Threatened Abortion, Maternal Serum Levels of Progesterone-Induced Blocking Fac-Tor and Its Clinical Significance,” 2015.

Nazia Kanwal, and Hamza Sarwar. “EFFICACY AND ROLE OF DYDROGESTERONE IN PREVENTING MISCARRIAGE: A SYSTEMATIC REVIEW AND META-ANALYSIS.” *Journal of Medical & Health Sciences Review*, 2025.

O. Sefrioui, A. Madkour, N. Bouamoud, I. Kaarouch, B. Saadani, S. Amzazi, H. Copin, M. Benkhalifa, and N. Louanjli. “Luteal Progesterone Level Correlated with Immunotherapy Success of Patients with Repeated Implantation Failures.” *bioRxiv*, 2019.

O. Taha. “Assessment of the Immunomodulatory Role of Dydrogesterone in Preventing Pregnancy Loss in Threatened Abortion.” *World Journal of Gynecology & Womens Health*, 2020.

Pinar Kırıcı, and E. Tanrıverdi. “Effects of Different Progesterone Doses on the Concentrations of Proinflammatory and Anti-Inflammatory Cytokines in Pregnant Women With Threatened Abortion.” *Cureus*, 2021.

Priti Singh, and K. Sinha. “COMPARATIVE STUDY OF DYDROGESTERONE AND NATURAL MICRONISED PROGESTERONE (NMP) IN THREATENED ABORTION.” *International Journal of Scientific Research*, 2021.

R. D., and Archana Reddy. “Use of Progestogens in Pregnancy and Its Maternal and Fetal Outcome.” *International Journal of Reproduction Contraception Obstetrics and Gynecology*, 2025.

R. Pillai, J. Konje, D. Tincello, and N. Potdar. "Role of Serum Biomarkers in the Prediction of Outcome in Women with Threatened Miscarriage: A Systematic Review and Diagnostic Accuracy Meta-Analysis." *Human Reproduction Update*, 2015.

Rahmatunnesa, K. Fatema, Mohammad Abdur Rahman, Khaleda Parvin, Mazriha Naeem Mishi, and Umme Johora. "Single Serum Progesterone Measurement: A Key Diagnostic and Prognostic Tool in Threatened Abortion." *International Journal of Reproduction Contraception Obstetrics and Gynecology*, 2025.

Ramachandhiran Udayar Pandian. "Dydrogesterone in Threatened Miscarriage: A Malaysian Experience." *Maturitas*, 2009.

S. Alimohamadi, P. Javadian, M. Gharedaghi, Nima Javadian, H. Alinia, Soghra Khazardoust, S. Borna, and S. Hantoushzadeh. "Progesterone and Threatened Abortion: A Randomized Clinical Trial on Endocervical Cytokine Concentrations." *Journal of Reproductive Immunology*, 2013.

S. Khanum, and J. Ahmed. "Role of Human Chorionic Gonadotrophin Compared to 17-Alpha-Hydroxyprogesterone in the Management of Threatened Abortion: Experience in a Military Hospital in Dhaka, Bangladesh." *BIRDEM Medical Journal*, 2019.

S. Xie. "Comparison of Clinical Effects of Dydrogestrone and Progesterone in the Treatment of Threatened Abortion," 2020.

Shasha Ying, and Man-man Zhang. "Comparison of Clinical Efficacy of Dydrogesterone and Progesterone in the Treatment of Threatened Abortion," 2020.

Shayna Siew, Celene Yan Yan Hui, T. Tan, J. Allen, R. Malhotra, and Truls Østbye. "Micronized Progesterone Compared With Dydrogesterone for Threatened Miscarriage: A Randomized Controlled Trial [328]," 2015.

Umar Dhani, Ova Emilia, and R. Siswosudarmo. “PERBANDINGAN ANTARA PEMBERIAN PROGESTERON VAGINAL DAN ALLYLESTRENOL ORAL PADA PENANGANAN ABORTUS IMINENS,” 2015.

Uzma Gull, Mona Zafar, and Adiba Akhtar. “EFFICACY OF DYDROGESTERONE IN THE MANAGEMENT OF THREATENED MISCARRIAGE IN THE FIRST TRIMESTER.” *Pakistan Armed Forces Medical Journal*, 2012.

Xia Xu. “Effect of Serum Progesterone Level on Treatment Outcomes of Threatened Abortion of Luteal Phase Dysfunction,” 2017.

Yi Gong, Tong Jiang, Yang Sun, Guo-Lin Wu, Bu-Wei Han, Ying Shi, Shan Guan, and Jian Li. “Can Single Progesterone Concentration Predict Miscarriage in Early Pregnant Women with Threatened Miscarriage: A Systematic Review and Meta-Analysis.” *BMC Pregnancy and Childbirth*, 2024.

C. O. Шурпьяк, and B. I. Пирогова. “The Importance of Progesteron for the Safety of Pregnancy at Early and Late Terms.” *Reproduktivnaâ Èndokrinologiâ*, 2019.