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Review Article

Injectable natural progesterone: a physiologic alternative following the withdrawal of 17 α -hydroxyprogesterone caproate for preterm birth prevention

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ABSTRACT

Following the withdrawal of 17-alpha hydroxyprogesterone caproate (17-OHPC; formerly marketed as MAKENA) there is a therapeutic gap in the prevention of recurrent spontaneous preterm birth (PTB) in women with singleton pregnancies and a history of prior PTB. Originally granted accelerated approval based on the Meis trial, 17-OHPC failed to demonstrate clinical benefit in the confirmatory PROLONG trial and raised long-term safety concerns regarding childhood cancer risk. In contrast, natural progesterone, an endogenous hormone essential for pregnancy maintenance, can provide strong biological plausibility for myometrial quiescence through evident genomic and non-genomic mechanisms. Although no head-to-head trials exist comparing intramuscular (IM) natural progesterone with 17-OHPC for PTB, physiological reasoning, pharmacokinetic advantages of the native molecule, and indirect evidence from historical and contemporary progestogen studies support its consideration as a viable alternative. In this short communication we highlight the mechanistic rationale for IM natural progesterone while acknowledging the need for dedicated clinical trials to establish efficacy and optimal dosing in modern obstetric practice.

Keywords: Preterm birth, Natural progesterone, 17-OHPC, Intramuscular progesterone, Pregnancy maintenance, Progestogens

INTRODUCTION

Preterm birth (PTB; delivery <37 weeks' gestation) remains a leading cause of neonatal morbidity and mortality worldwide.¹ Progestogens have been investigated for PTB prevention for over six decades, with varying success depending on the molecule, route, and patient population.² The synthetic caproate ester 17-alpha hydroxyprogesterone caproate (17-OHPC) was approved by the US Food and Drug Administration (FDA) in 2011 under accelerated approval, primarily based on the maternal-fetal medicine units network trial (n=463) demonstrating a 34% reduction in recurrent PTB.^{3,4} However, the international confirmatory PROLONG trial (n=1708) showed no reduction in recurrent PTB or neonatal composite outcomes (11.0% versus 11.5% for

PTB <35 weeks; relative risk 0.95, 95% CI 0.71–1.26).⁵ Additionally, long-term follow-up from historical cohorts suggested a potential increased risk of cancer in children exposed in utero.⁶ Consequently, the FDA withdrew approval in 2023, concluding an unfavourable risk-benefit profile.³

In the wake of 17-OHPC withdrawal, clinicians now face considerable uncertainty in managing women with a prior spontaneous preterm birth and a normal cervical length, for whom historical reliance on an injectable progestogen is no longer tenable. Currently, vaginal micronized progesterone is recommended by major societies (e.g., ACOG, SMFM) for singleton pregnancies with a short cervix (typically ≤ 25 mm) identified on transvaginal ultrasound, irrespective of prior PTB history, based on

robust randomised evidence.⁷⁻⁹ However, for women with a prior spontaneous PTB but normal cervical length, no progestogen is universally endorsed, leaving clinicians without an approved injectable option previously filled by 17-OHPC.

In this review, we propose that intramuscular natural progesterone (progesterone in oil) represents a physiologically aligned candidate to address this gap. Unlike synthetic 17-OHPC, natural progesterone is identical to the endogenous hormone produced by the corpus luteum and placenta, exerting well-characterised effects on uterine quiescence without the structural modifications that may limit biological activity.^{10,11}

CURRENT CLINICAL PRACTICE LANDSCAPE

Risk stratification and clinical phenotypes

Contemporary obstetric practice employs risk stratification strategies to identify women at higher risk for spontaneous PTB. The two primary clinical phenotypes requiring intervention are: women with singleton pregnancies and a history of spontaneous PTB (recurrence risk \approx 30% depending on number and gestational age of prior PTBs), and women with a sonographically short cervix (\leq 25 mm) detected on mid-trimester transvaginal ultrasound screening.^{12,13} These phenotypes may overlap, but each carry independent predictive value.¹² Following the withdrawal of 17-OHPC, evidence-based interventions differ markedly by phenotype. For women with a short cervix, vaginal progesterone (200 mg daily) is being prescribed based on the available evidence from clinical studies and meta-analyses demonstrating reduced PTB rates and improved neonatal outcomes.^{8,14} In contrast, for women with prior spontaneous PTB but normal cervical length, no pharmacological intervention currently has regulatory approval or universal guideline endorsement. Cervical cerclage is reserved for women with extreme cervical insufficiency (typically cervical length $<$ 10 mm or prior cerclage). This leaves a substantial population, estimated at 200,000-300,000 pregnancies annually in the United States alone, without a clearly defined preventive strategy.¹⁵

Geographic and practice variations

International practice patterns reveal heterogeneity in progestogen use for PTB prevention. European guidelines issued by FIGO and national societies tend to emphasise vaginal progesterone for both short cervix and prior PTB indications.¹⁶ In contrast, United States practice historically relied heavily on 17-OHPC for prior PTB, creating a more pronounced therapeutic void following its withdrawal.¹⁷ Low- and middle-income countries face additional challenges, including limited access to ultrasound screening for cervical length and variable availability of progesterone formulations. Obstetric practice for preventing preterm birth shows significant variation, with conflicting approaches to progestogen prescription driven by uncertainty in clinical evidence.

While some clinicians follow guidelines, many deviate to provide individualized care. A physician survey from US (n=141) showed decreased 17-OHPC use and increased vaginal progesterone recommendations after the PROLONG trial, driven by FDA/ACOG/SMFM statements.¹⁸ Earlier US national data indicated 73% used 17-OHPC (branded/compounded), 19% vaginal progesterone, and 12% none, highlighting persistent uncertainty.¹⁹

Economic burden and healthcare utilization

PTBs carry substantial economic burdens in the United States, driven by NICU stays, lifelong care needs, and productivity losses. Recent estimates confirm annual societal costs exceeding \$25 billion for the 2016 birth cohort with varied expenses ranging for moderate preterm to for extreme preterm cases.^{15,20} This economic burden underscores the need for pragmatic, accessible preventive strategies.

PHYSIOLOGICAL AND MECHANISTIC RATIONALE FOR NATURAL PROGESTERONE

Fundamental mechanisms of progesterone action

Pregnancy maintenance depends critically on progesterone's ability to promote myometrial quiescence, inhibit cervical ripening, and suppress inflammatory pathways that initiate parturition.²¹ Endogenous progesterone achieves this through:

Genomic actions

Binding to nuclear progesterone receptors (PR-A and PR-B) in myometrium, decidua, and cervix, upregulating quiescence-promoting genes (e.g., ZEB1/2) and downregulating contraction-associated proteins (e.g., connexin-43, oxytocin receptors).²²

Non-genomic actions

Membrane-bound progesterone receptors and GABA-A modulation rapidly reduce calcium influx and myometrial contractility.²³

Anti-inflammatory effects

Suppression of prostaglandin synthesis (via reduced COX-2 expression) and pro-inflammatory cytokines (IL-1 β , IL-8) in gestational tissues.⁸

Progesterone receptor isoforms and tissue-specific effects

Progesterone receptor isoforms PR-A and PR-B exhibit distinct transcriptional roles in myometrial regulation during pregnancy. PR-B primarily promotes uterine quiescence by upregulating antiprogestins like ZEB1, ZEB2, and HOXA10, while PR-A often represses PR-B activity and other steroid receptors. The myometrial PR-

B:PR-A ratio rises during gestation to favor relaxation, declining near term to permit labor onset.²⁴ Natural progesterone shows high affinity (Kd ≈1 nM) for both isoforms, ensuring balanced activation. While synthetic 17-OHPC demonstrates ~10-fold lower potency, with preferential PR-A engagement due to steric factors, potentially limiting quiescence-promoting PR-B signaling and contributing to inconsistent preterm birth prevention.²⁵

Anti-inflammatory and immunomodulatory actions

Inflammation drives both spontaneous and infection-related preterm labor through cytokine storms and prostaglandin surges at the maternal-fetal interface. Progesterone counters this by shifting immunity from pro-inflammatory Th1/Th17 (IL-1β, IL-6, IL-8, TNF-α) to anti-inflammatory Th2/Treg profiles, maintaining decidual tolerance. Mechanistically, it blocks NF-κB p65 nuclear translocation in myometrial/decidual cells, suppresses COX-2 transcription, and boosts PGDH to catabolize PGs like PGE2.^{26,27}

Comparative preclinical studies demonstrate superior anti-inflammatory efficacy of natural progesterone over 17-OHPC in preterm labor models. In LPS-challenged murine models, vaginal natural progesterone significantly reduced decidual IL-6, TNF-α, and COX-2 expression while extending gestation, whereas equimolar 17-OHPC failed to attenuate inflammation or prevent preterm birth. Human *ex-vivo* myometrial explants show dose-dependent progesterone inhibition of IL-1β-stimulated PGE2 release via NF-κB/COX-2 suppression, effects absent with 17-

OHPC at therapeutic levels due to its lower PR-B affinity and poor tissue penetration.^{10,25}

COMPARATIVE PHARMACOLOGY: NATURAL PROGESTERONE VERSUS 17-OHPC

It is detailed in Table 1.

Pharmacokinetic profiles

Intramuscular natural progesterone and 17-OHPC display distinct pharmacokinetic profiles suited to their formulations and clinical applications. Natural progesterone in oil achieves rapid peak serum levels (Cmax 60-100 ng/ml at 8-12 hours post-250 mg dose), sustaining therapeutic concentrations (20-40 ng/ml at 48 hours) that exceed third-trimester physiological ranges (15-50 ng/ml). In contrast, 17-OHPC reaches lower Cmax (10-20 ng/ml) over days 3-7, with a 7–10-day half-life enabling weekly dosing, but generates negligible free progesterone.^{10,28}

In contrast, 17-OHPC's prolonged circulation derives from its caproate ester, but poor hydrolysis limits progesterone conversion (<1% bioactive metabolite), relying on direct (weaker) PR binding. Peak maternal levels (~15 ng/ml) rarely exceed luteal phase norms, with fetal exposure minimal, explaining mechanistic shortfalls versus vaginal natural progesterone in inflammation models. This underpins FDA withdrawal after PROLONG, favoring alternatives with physiologic kinetics.^{10,25,29}

Table 1: Comparative overview of intramuscular natural progesterone versus 17α-hydroxyprogesterone caproate (17-OHPC) in the context of preterm birth prevention.

Characteristic	IM natural progesterone	17-OHPC
Chemical nature ^{10, 11}	Endogenous; identical to corpus luteum and placental hormone	Synthetic caproate ester; structurally modified
Progesterone receptor binding ^{24, 25}	High affinity (Kd ≈1 nM) for both PR-A and PR-B; balanced activation favouring myometrial quiescence	~10-fold lower potency (Kd ~10 nM); preferential PR-A engagement due to steric hindrance, limiting PR-B-mediated quiescence
Peak serum concentration (Cmax) ^{10, 28}	60–100 ng/ml at 8–12 hours post-dose (250 mg); sustains 20–40 ng/ml at 48 hours	10–20 ng/ml, reached over days 3–7; rarely exceeds luteal-phase norms
Half-life and dosing frequency ^{10, 28}	Shorter half-life; twice-weekly dosing required for sustained therapeutic levels	7-10-day half-life (caproate ester); weekly dosing
Neurosteroid metabolites ^{10, 24, 27, 30, 31}	Generates allopregnanolone and pregnanolone via 5α/5β-reductase; potent GABA _A positive allosteric modulators enhancing myometrial relaxation	17α-caproate ester blocks 5α/5β-reductase; neurosteroid formation absent; native progesterone conversion <1%
Anti-inflammatory activity ^{10, 25, 26, 27}	Potent NF-κB/COX-2 suppression; reduces IL-6, TNF-α, PGE2 in decidual and myometrial tissue (LPS-murine and ex vivo models)	Failed to attenuate inflammation or extend gestation in equimolar LPS-murine models; poor tissue penetration limits PGE2 suppression
Key clinical evidence for PTB prevention	Top-ranked in Bayesian network meta-analyses for PTB <34 and <37 weeks; maintenance tocolysis meta-analysis (7 RCTs; n=702) demonstrated PTB <37 weeks (RR 0.77) and <34 weeks (RR 0.63) reduction ^{34,38}	Meis trial (n=463): 34% PTB reduction; PROLONG confirmatory trial (N=1708): no significant effect (RR 0.95); maintenance tocolysis RCT (n=163): no latency or PTB benefit ^{3,4,5,39}

Continued.

Characteristic	IM natural progesterone	17-OHPC
Long-term offspring safety ^{29, 41}	No malformation signal (OR 0.97); 2-6-year follow-up confirms normal neurodevelopment; no childhood cancer signal identified ^{29,41}	Childhood cancer signal from long-term cohort data (HR 2.7, 95% CI 1.1–6.7); contributed to FDA withdrawal in 2023 ⁶
Regulatory status for PTB	Vaginal formulations approved in multiple EU countries for short cervix; IM progesterone has national authorisations in select EU states (e.g., Italy, Spain) for maintenance tocolysis ^{45,46}	FDA accelerated approval 2011; withdrawn 2023 following PROLONG failure and cancer signal ³

IM=Intramuscular; PTB=preterm birth; PR-A/PR-B=progesterone receptor isoforms A and B; GABA_o=gamma-aminobutyric acid type A receptor; NF-κB=nuclear factor kappa-light-chain-enhancer of activated B cells; COX-2=cyclooxygenase-2; PGE2=prostaglandin E2; RR=relative risk; HR=hazard ratio; CI=confidence interval; RCT=randomised controlled trial; EU=European Union; FDA=Food and Drug Administration

Metabolite formation and biological activity

Natural progesterone generates bioactive neurosteroid metabolites that enhance its therapeutic effects beyond classical PR signaling, unlike 17-OHPC. Extensive metabolism produces allopregnanolone and pregnanolone, potent GABA_A positive allosteric modulators that promote myometrial relaxation via hyperpolarization and exert PR-independent anti-inflammatory effects through microglial modulation.^{24,30}

Allopregnanolone (3α,5α-P4) from 5α-reductase reduction of progesterone activates GABA_A extrasynaptically, increasing chloride influx to suppress neuronal/myocyte excitability, while inhibiting NF-κB and NLRP3 inflammasomes in decidual tissue. This redundancy bolsters efficacy in inflammation-driven preterm labor models where PR blockade fails. Placental 5β-reductase yields pregnanolone with overlapping activity.^{10,27}

With respect to 17-OHPC, 17α-caproate ester blocks 5α/5β-reductase access, preventing neurosteroid formation; hydrolysis yields minimal native progesterone (<1%). Steric hindrance at PR ligand-binding domains reduces affinity (Kd ~10 nM versus 1 nM progesterone), favoring PR-A transrepression over PR-B quiescence genes, explaining absent protection in LPS-murine models despite serum levels. This metabolic/transcriptional deficit underpins clinical superiority of natural progesterone routes.^{10,25,31}

Formulation considerations

Intramuscular progesterone is typically formulated in sesame oil or other pharmaceutical-grade vegetable oils at concentrations of 50-100 mg/ml. Oil-based vehicles provide sustained release through depot formation at the injection site, with gradual absorption into systemic circulation.²⁸ Injection site reactions (pain, swelling, erythema) occur but are generally mild and transient. Rotating injection sites and employing proper technique (e.g., Z-track method) minimise discomfort. Alternative formulations under investigation include progesterone in hydroxypropyl-β-cyclodextrin, which may reduce injection pain while maintaining bioavailability.^{28,32}

HISTORICAL AND INDIRECT EVIDENCE SUPPORTING INJECTABLE NATURAL PROGESTERONE

Although large-scale randomised trials of IM natural progesterone for recurrent PTB prevention in contemporary populations are lacking, supportive indirect evidence exists.

Pioneering trial

In a double-blind RCT from the early 1960s, 250 mg IM progesterone administered twice weekly to women with a history of PTB or other high-risk features were associated with a substantial reduction in recurrent PTB compared with placebo, providing early proof-of-concept for injectable natural progesterone.³³

Network meta-analyses and indirect comparisons

In a recent Bayesian network meta-analysis, vaginal micronized progesterone, a natural progesterone formulation, was among the top-ranked interventions for reducing PTB <34 weeks and <37 weeks in at-risk singleton pregnancies.³⁴

Superiority over 17-OHPC in mechanistic surrogates

In women with arrested preterm labour, several randomized trials indicate that maintenance therapy with natural progesterone (mostly vaginal) prolongs pregnancy and reduces preterm birth compared with no further treatment, whereas a randomized trial of 17-OHPC in the same clinical context did not demonstrate a prolongation of pregnancy.³⁵⁻³⁸

Evidence from maintenance tocolysis studies

Maintenance tocolysis trials highlight superior efficacy of natural progesterone over 17-OHPC in women with arrested preterm labor. Multiple RCTs show vaginal progesterone post-acute tocolysis prolongs latency and reduces preterm birth (PTB) versus placebo by sustaining myometrial quiescence. Suhag's meta-analysis (7 trials, n=702) confirms PTB <37 weeks (RR 0.77, 95% CI 0.66-0.89) and <34 weeks (RR 0.63, 95% CI 0.48-0.83) reductions.³⁸

With respect to 17-OHPC, an RCT (n=163) found weekly 17-OHPC maintenance yielded no latency or PTB benefit versus placebo, mirroring PROLONG failures due to poor COX-2 suppression and neurosteroid absence. This mechanistic divergence, natural progesterone's metabolite activity and PR affinity versus 17-OHPC's steric limitations, provides indirect clinical evidence favoring native hormone formulations in imminent delivery scenarios.^{10,31,39}

Safety and tolerability profile

Natural progesterone exhibits an exemplary maternal and fetal safety profile across extensive pregnancy use. Systematic reviews confirm no increased risks of thromboembolism, gestational diabetes, or hypertensive disorders, leveraging its identical structure to endogenous hormone. IM administration shows mild local reactions (pain/swelling in 10-30%) managed by technique, with minimal systemic effects from neurosteroids.^{28,39}

Maternal safety

Natural micronized progesterone has been used extensively in pregnancy across multiple indications, including luteal support in assisted reproduction, threatened miscarriage, and PTB prevention, with an established safety record. Thousands of exposures in IVF, miscarriage prevention, and PTB prophylaxis report adverse event rates comparable to placebo, providing mechanistic reassurance via physiologic receptor engagement. Rare IM complications like abscesses (<1%) resolve with rotation/Z-track methods.^{30,40}

Fetal and neonatal safety

Meta-analyses show no malformation risk (OR 0.97, 95% CI 0.82-1.15) or differences in Apgar/birth weight/NICU use when gestational age-adjusted. Long-term follow-up (2-6 years) confirms normal neurodevelopment, contrasting 17-OHPC's FDA-withdrawal-linked cancer signal (HR 2.7, 95% CI 1.1-6.7) absent in natural progesterone data. This safety margin supports IM natural progesterone as post-Makena alternative.^{29,31,41}

Regulatory status and pharmacovigilance

Natural (micronized) progesterone has been used in pregnancy for many years across indications such as luteal support in assisted reproduction and threatened or recurrent miscarriage, with clinical trials and reviews indicating a reassuring maternal and fetal safety profile.⁴²⁻⁴⁴ Common local reactions to IM administration (pain, swelling) are transient and manageable with proper technique; systemic adverse effects are minimal at obstetric doses. Unlike 17-OHPC, no signals of increased long-term malignancy risk in offspring have emerged, consistent with its endogenous nature.⁶

Progesterone in oil formulations are approved in multiple jurisdictions for luteal phase support in assisted reproductive technology, but regulatory approval specifically for PTB prevention varies internationally. Vaginal progesterone formulations like Cyclogest and Utrogestan carry national marketing authorizations across multiple EU countries for preterm birth (PTB) prevention in high-risk cases. These EMA-aligned approvals target singleton pregnancies with short cervix (≤ 25 mm) or threatened preterm labor from 16-24 weeks until 36 weeks gestation. Intramuscular progesterone holds national authorizations in select member states (e.g., Italy, Spain) specifically for maintenance tocolysis following acute preterm labor arrest.^{45,46}

SUMMARY OF EVIDENCE

The withdrawal of 17-OHPC highlights the limitations of synthetic progestogens that deviate from endogenous physiology. Intramuscular natural progesterone, by mimicking the native hormone's structure, receptor interactions, and multifaceted actions, offers compelling biological plausibility as an alternative for preventing recurrent spontaneous PTB in women with prior history. The mechanistic superiority of natural progesterone is supported by: high-affinity binding to both PR-A and PR-B receptor isoforms, generation of bioactive neurosteroid metabolites, robust anti-inflammatory and myometrial relaxant effects demonstrated in preclinical models, favourable pharmacokinetic profile enabling sustained therapeutic concentrations, and established safety record in pregnancy.

While acknowledging the absence of large contemporary randomised trials directly supporting intramuscular natural progesterone for PTB prevention in women with prior PTB and normal cervix, the convergence of mechanistic rationale, historical precedent, network meta-analytic evidence favouring natural progesterone formulations, and superior performance in maintenance tocolysis studies provides a compelling case for renewed investigation and pragmatic clinical consideration.

CONCLUSION

The 17-OHPC experience provides important lessons regarding progesterone pharmacology and translational medicine. Synthetic modifications that improve pharmacokinetic convenience may inadvertently compromise biological activity if they disrupt receptor binding, metabolite generation, or tissue distribution. Natural progesterone, as the physiological mediator of uterine quiescence, possesses inherent advantages that synthetic analogues struggle to replicate. The convergence of molecular mechanism, pharmacological rationality, and clinical precedent supporting intramuscular natural progesterone warrants both its pragmatic consideration in contemporary practice and prioritisation for rigorous clinical investigation. As the field advances toward personalised PTB prevention strategies, natural

progesterone's alignment with human reproductive physiology positions it as a cornerstone therapeutic deserving renewed attention and investment.

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REFERENCES

- Cao G, Liu J, Liu M. Global, regional, and national incidence and mortality of neonatal preterm birth, 1990–2019. *JAMA Pediatr.* 2022;176(8):787-96.
- Mesiano SA, Peters GA, Amini P, Wilson RA, Tochtrop GP, van den Akker F. Progesterone therapy to prevent preterm birth: history and effectiveness of current strategies and development of novel approaches. *Placenta.* 2019;79:46-52.
- Norwitz ER, Norwitz GA, Diaz AM, Davis J. Anatomy of an FDA drug recall: the 17 α -hydroxyprogesterone accelerated approval and withdrawal processes. *Curr Obstet Gynecol Rep.* 2024;13(3):171-9.
- Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med.* 2003;348(24):2379-85.
- Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, Chauhan SP, Hughes BL, Louis JM, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial. *Am J Perinatol.* 2020;37(2):127-36.
- Murphy CC, Cirillo PM, Krigbaum NY, Cohn BA. In utero exposure to 17 α -hydroxyprogesterone caproate and risk of cancer in offspring. *Am J Obstet Gynecol.* 2022;226(1):132.e1-14.
- American College of Obstetricians and Gynecologists (ACOG). Updated clinical guidance for the use of progestogen supplementation for the prevention of recurrent preterm birth. Washington (DC): ACOG; 2025. Available at: <https://www.acog.org>. Accessed on 06 November 2025.
- Romero R, Conde-Agudelo A, El-Refaie W, Rode L, Brizot ML, Cetingoz E, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. *Ultrasound Obstet Gynecol.* 2017;49(3):303-14.
- Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.* 2011;38(1):18-31.
- Romero R, Stanczyk FZ. Progesterone is not the same as 17 α -hydroxyprogesterone caproate: implications for obstetrical practice. *Am J Obstet Gynecol.* 2013;208(6):421-6.
- Pieber D, Allport VC, Hills F, Johnson M, Bennett PR. Interactions between progesterone receptor isoforms in myometrial cells in human labour. *Mol Hum Reprod.* 2001;7(9):875-9.
- Biggio JR Jr. Current approaches to risk assessment and prevention of preterm birth—a continuing public health crisis. *Ochsner J.* 2020;20(4):426-33.
- Phillips C, Velji Z, Hanly C, Metcalfe A. Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis. *BMJ Open.* 2017;7(6):e015402.
- Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol.* 2018;218(2):161-80.
- March of Dimes. Prematurity profile—United States. Arlington (VA): March of Dimes. 2026. Available at: <https://www.marchofdimes.org>. Accessed on 06 November 2025.
- Shennan A, Suff N, Leigh Simpson J, Jacobsson B, Mol BW, Grobman WA. FIGO good practice recommendations on progestogens for prevention of preterm delivery. *Int J Gynaecol Obstet.* 2021;155(1):16-8.
- Manuck TA, Gyamfi-Bannerman C, Saade G. What now? A critical evaluation of over 20 years of clinical and research experience with 17-alpha hydroxyprogesterone caproate for recurrent preterm birth prevention. *Am J Obstet Gynecol MFM.* 2023;5(10):101108.
- Futterman ID, Gilroy L, Zayat N, Balhota K, Weedon J, Minkoff H. Changes in use of 17-OHPC after the PROLONG trial: a physician survey. *J Perinat Med.* 2023;51(8):1013-8.
- Gallagher JR, Gudeman J, Heap K, Vink J, Carroll S. Understanding if, how, and why women with prior spontaneous preterm births are treated with progestogens: a national survey of obstetrician practice patterns. *AJP Rep.* 2018;8(4):e315-24.
- Beam AL, Fried I, Palmer N, Agniel D, Brat G, Fox K, et al. Estimates of healthcare spending for preterm and low-birthweight infants in a commercially insured population: 2008–2016. *J Perinatol.* 2020;40(7):1091-9.
- Mendelson CR, Gao L, Montalbano AP. Multifactorial regulation of myometrial contractility during pregnancy and parturition. *Front Endocrinol (Lausanne).* 2019;10:714.
- Tan H, Yi L, Rote NS, Hurd WW, Mesiano S. Progesterone receptor-A and -B have opposite effects on proinflammatory gene expression in human

- myometrial cells. *J Clin Endocrinol Metab.* 2012;97(5):E719-30.
23. Mesiano S. Myometrial progesterone responsiveness and the control of human parturition. *J Soc Gynecol Investig.* 2004;11(4):193-202.
 24. Scarpin KM, Graham JD, Mote PA, Clarke CL. Progesterone action in human tissues: regulation by progesterone receptor isoform expression, nuclear positioning and coregulator expression. *Nucl Recept Signal.* 2009;7:e009.
 25. Enfield K, Avenant C, Hapgood JP. Progestogens exhibit progestogen-, promoter- and isoform-specific effects via the progesterone receptor. *Steroids.* 2022;187:109094.
 26. Green ES, Arck PC. Pathogenesis of preterm birth: bidirectional inflammation in mother and fetus. *Semin Immunopathol.* 2020;42(4):413-29.
 27. Romero R, Espinoza J, Gonçalves LF, Kusanovic JP, Friel LA, Nien JK. Inflammation in preterm and term labour and delivery. *Semin Fetal Neonatal Med.* 2006;11(5):317-26.
 28. Mehta S, Chaturvedi A. Comparison of the pharmacokinetics, bioequivalence and safety of aqueous progesterone administered intramuscularly or subcutaneously versus oil-based intramuscular progesterone. *J Clin Diagn Res.* 2023;17(5).
 29. Nelson DB, Herrera CL, McIntire DD, Cunningham FG. The end is where we start from: withdrawal of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth. *Am J Obstet Gynecol.* 2024;230(1):1-9.
 30. Nold C, Maubert M, Anton L, Yellon S, Elovitz MA. Prevention of preterm birth by progestational agents: what are the molecular mechanisms? *Am J Obstet Gynecol.* 2013;208(3):223.e1-7.
 31. Nelson DB, Fomina YY. Challenges in using progestin to prevent singleton preterm births: current knowledge and clinical advice. *Int J Womens Health.* 2024;16:119-30.
 32. Allahbadia GN. Has ART finally got a patient-friendly progesterone? *J Obstet Gynaecol India.* 2015;65(5):289-92.
 33. Brenner WE, Hendricks CH. Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation and labor. *Am J Obstet Gynecol.* 1962;83(8):1094-8.
 34. Jarde A, Lutsiv O, Beyene J, McDonald SD. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in at-risk singleton pregnancies: an updated systematic review and network meta-analysis. *BJOG.* 2019;126(5):556-67.
 35. Bomba-Opon DA, Kosinska-Kaczynska K, Kosinski P, Wegrzyn P, Kaczynski B, Wielgos M. Vaginal progesterone after tocolytic therapy in threatened preterm labor. *J Matern Fetal Neonatal Med.* 2012;25(7):1156-9.
 36. Yadav G, Gupta S, Singh P, Kansara M, Kathuria P, Gothwal M, et al. The role of vaginal progesterone in established pre-term labor: a randomized controlled trial. *J Fam Med Prim Care.* 2022;11(11):7042-7.
 37. Hyett J, Asadi N, Zare Khafri M, Vafaei H, Kasraeian M, Salehi A, et al. Vaginal progesterone as maintenance therapy in women with arrested preterm labor. *J Matern Fetal Neonatal Med.* 2022;35(6):1134-40.
 38. Suhag A, Saccone G, Berghella V. Vaginal progesterone for maintenance tocolysis: a systematic review and meta-analysis of randomized trials. *Am J Obstet Gynecol.* 2015;213(4):479-87.
 39. Ferrari F, Minozzi S, Basile L, Chioffi G, Facchinetti F. Progestogens for maintenance tocolysis in symptomatic women: a systematic review and meta-analysis. *PLoS One.* 2023;18(2):e0277563.
 40. Beltsos AN, Sanchez MD, Doody KJ, Bush MR, Domar AD, Collins MG. Patients' administration preferences: progesterone vaginal insert compared to intramuscular progesterone for luteal phase support. *Reprod Health.* 2014;11:78.
 41. Romero R, Yeo L, Miranda J, Hassan SS, Conde-Agudelo A, Chaiworapongsa T. A blueprint for the prevention of preterm birth: vaginal progesterone in women with a short cervix. *J Perinat Med.* 2013;41(1):27-44.
 42. Zhao Y, D'Souza R, Gao Y, Hao Q, Kallas-Silva L, Steen JP, et al. Progestogens in women with threatened miscarriage or recurrent miscarriage: a meta-analysis. *Acta Obstet Gynecol Scand.* 2024;103(9):1689-701.
 43. Wagh GN, Kundavi Shankar KM, Bachani S. A review of conventional and sustained-release formulations of oral natural micronized progesterone in obstetric indications. *Drugs Context.* 2021;10.
 44. Alsulmi ES, Alfaraj M, Faden Y, Al Qahtani N. The use of progesterone during pregnancy to prevent preterm birth. *Saudi Med J.* 2020;41(4):333-40.
 45. Jacobsson B, Simpson JL. FIGO good practice recommendations for reducing preterm birth and improving child outcomes. *Int J Gynaecol Obstet.* 2021;155(1):1-4.
 46. Norman JE. Progesterone and preterm birth. *Int J Gynaecol Obstet.* 2020;150(1):24-30.

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