

Progesterone Use Associated with 18% Reduction in Miscarriage Risk Among Women with History of Miscarriages

Team A: Kersten Bartelt, RN; Eric Barkley

Team B: Christopher Alban, MD; Jacob Gasser

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Key Findings

- Women with a history of miscarriages who received progesterone in the year before their pregnancy were 18% less likely to experience a miscarriage than those who did not receive progesterone before their pregnancy.

Miscarriage is a common and often emotionally devastating outcome of pregnancy. Women with prior pregnancy losses often seek interventions that might improve their chances of a healthy birth. Because progesterone plays a critical role in maintaining early pregnancy, progesterone supplementation has been considered a treatment for women with recurrent miscarriages. However, evidence from clinical trials and reviews has been mixed, leaving uncertainty for both patients and clinicians.^{1,2}

To further understand the relationship between progesterone supplementation and miscarriages, we studied 84,009 pregnancies among women who had at least one prior miscarriage or fetal demise. We accounted for maternal age, BMI, race and ethnicity, social vulnerability, comorbidities, fertility treatments, and count of prior pregnancies. Women who were started on progesterone after the pregnancy began were excluded to avoid confounding by indication, since clinicians are more likely to prescribe progesterone to pregnancies already perceived as threatened.

We found that women who received progesterone prior to pregnancy were 18% less likely to experience a miscarriage compared to those who did not receive progesterone.

Miscarriage Likelihood by Progesterone Use

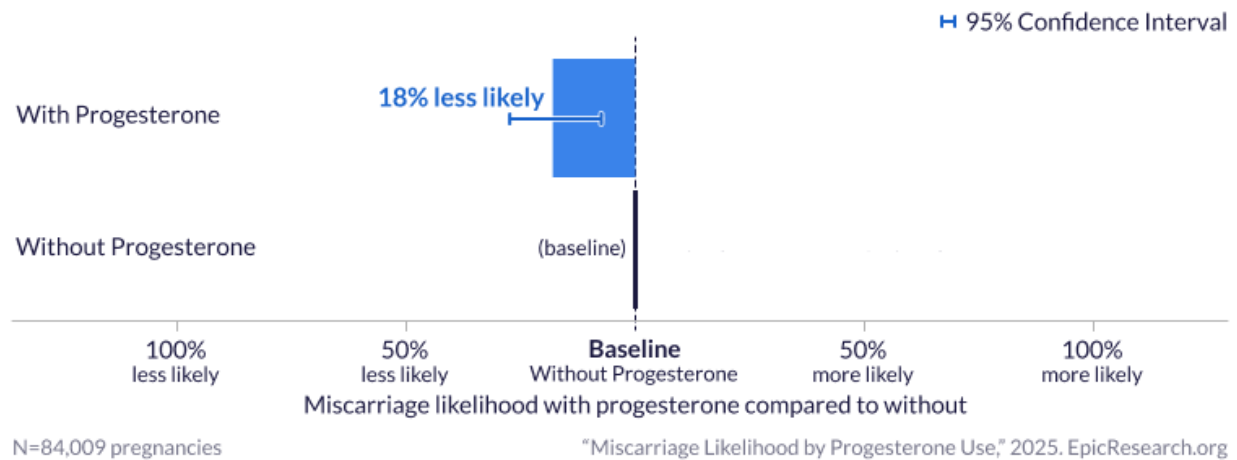


Figure 1. The likelihood of an expectant mother experiencing a miscarriage by whether she was prescribed progesterone.

A sensitivity analysis analyzing the type of progesterone used, based on the pharmaceutical class, found similar results.

These data come from *Cosmos*, a dataset created in collaboration with a community of Epic health systems representing more than 300 million patient records from 1,700 hospitals and more than 40,000 clinics from all 50 U.S. states, Canada, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

References

1. Coomarasamy A, Devall AJ, Cheed V, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med*. 2019;380(19):1815-1824. doi:10.1056/NEJMoa1813730
2. Devall AJ, Papadopoulou A, Podeseck M, et al. Progestogens for preventing miscarriage: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;4(4):CD013792. doi:10.1002/14651858.CD013792.pub2

Data Definitions

Term	Definition
Study period	Pregnancies ending between 2/14/2017 and 7/2/2025
Study population: inclusion	Pregnancies with: • A documented pregnancy start date or a gestational age at delivery • Mothers aged 18 to 45 at the start of the pregnancy • At least one previous miscarriage or fetal demise • At least one outpatient face-to-face encounter prior to the pregnancy start date

Study population: exclusion	Pregnancy with multiples Pregnancy with no active progesterone order in the year prior to the start of the pregnancy, but an order for progesterone initiated during the pregnancy.
Exposures	Progesterone order active in the year prior to the start of the pregnancy
Outcomes	Fetal demise
Confounders	Maternal age at conception: 18-29, 30-39, 40-45 Maternal pre-pregnancy BMI: <18.5, 18.5-<25, 25-<30, 30-<35, 35+ SVI quintile Race and ethnicity: Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic, Asian, non-Hispanic other Gravity count Para count Prior C-section: Y/N History of smoking Diagnoses any time before pregnancy end, including problem list: • Gestational diabetes: O24.4* • Preeclampsia / pregnancy hypertension: ICD-10-CM code O18, O1[3-6]* • Diabetes: ICD-10-CM code E11*, E10*, E08*, E09*, O24.1* • Hypertension: ICD-10-CM code I10*, I1A.0, O11*, O10* • CKD: N18* or SNOMED 709044004 • Thrombophilia: ICD-10-CM code D68.5* or D68.6* • Thyroid disease: ICD-10-CM code E0[0-7]* • Anxiety: ICD-10-CM code F4[0-1]*, F06.4*, F93.0*, F94.0* • Asthma: SNOMED code 195967001 • Auto-immune: SNOMED code 85828009 • Depression: ICD-10-CM code F32* • Epilepsy: SNOMED code 84757009 • Hypothyroid: SNOMED code 40930008 IUI fertility treatment: CPT code 58321 or 58322 IVF fertility treatment: CPT 58974, 89280 HCPCS S4011, S4015 Fertility medication: clomid (RxNorm code 2596), letrozole (RxNorm code 72965), or metformin (RxNorm code 6809)
Outpatient face-to-face encounter	Encounters of type "Emergency," "Office Visit," "Well Child," "Follow-up," "Telemedicine," "Urgent Care," "Walk-In," "Routine Prenatal," "Postpartum Visit," "Fetal Care Consult," or "Hospital Outpatient Visit"
Progesterone	A medication with ATC code G03D[AB]*, RxNorm code 8727 or 7514, pharmaceutical class of "PROGESTATIONAL AGENTS" or "ESTROGEN-PROGESTIN WITH ANTIMINERALOCORTICOID COMB," pharmaceutical subclass of "Progestins," or a simple generic name of "MEDROXYPROGESTERONE ACETATE," "HYDROXYPROGESTERONE CAPROATE," or "HYDROXYPROGESTERONE CAPROATE/PF"
Model specifications	Cox PH regression model
Limitations	Different indications and strengths of progesterone were explored as a sensitivity analysis but not in the primary analysis. We do not have documentation of any suspected causes of the prior miscarriages or fetal demises.

Table 1: Miscarriage Likelihood by Progesterone Use

	Odds Ratio	Lower 95% CI	Upper 95% CI
Exposed to Progesterone	0.82	0.73	0.93
Gravidity 3	0.80	0.67	0.96
Gravidity 4	0.84	0.70	1.00
Gravidity 5	0.90	0.74	1.08
Gravidity 6+	0.85	0.71	1.03
Prior Cesarean	1.12	1.03	1.23
Prior Fetal Demise 2	1.41	1.23	1.62
Prior Fetal Demise 3+	2.24	1.65	3.04
Prior Abortion Single	1.14	1.02	1.28
Prior Abortion Multiple	1.51	1.33	1.71
Maternal Age 30-39	1.01	0.92	1.11
Maternal Age 40-45	1.13	0.95	1.35
Asian	0.49	0.33	0.72
Black	1.37	1.24	1.53
Hispanic	0.85	0.74	0.98
Other Race	1.19	1.04	1.36
SVI 20-39%	1.03	0.84	1.26
SVI 40-59%	1.13	0.93	1.36
SVI 60-79%	1.23	1.02	1.47
SVI 80-100%	1.21	1.01	1.44
Unknown SVI	1.13	0.78	1.64
Gestational Diabetes	0.81	0.69	0.95
Preeclampsia	1.19	1.07	1.33
Diabetes	1.33	1.15	1.55
Hypertension	1.47	1.31	1.65
CKD	1.58	1.23	2.03
Thrombophilia	0.97	0.79	1.18
Thyroid Disease	0.83	0.66	1.03
Anxiety	0.83	0.75	0.92
Asthma	0.84	0.75	0.94
Autoimmune	1.07	0.89	1.28
Depression	0.98	0.88	1.10
Epilepsy	0.89	0.67	1.17
Hypothyroid	1.18	0.91	1.53
Ever Smoker	1.09	0.99	1.19
Had Fertility Treatment Meds	0.99	0.79	1.25
IUI	0.48	0.07	3.46
IVF	0.54	0.17	1.69

Underweight BMI	1.12	0.73	1.73
Overweight BMI	1.02	0.89	1.18
Obese BMI	1.02	0.88	1.18
Morbidly Obese BMI	0.99	0.85	1.14
Unknown BMI	0.99	0.87	1.13
High Risk Progesterone Response	1.11	0.36	3.43