Effective Health Care Program

Pregnancy
**Preterm Birth**

# Progestogens for Prevention of Preterm Birth

## Focus of Research for Clinicians

A systematic review of 63 clinical studies published from 1966 to October 2011 examined the comparative effectiveness, benefits, and adverse effects of progestogens used to prevent preterm birth in several categories of at-risk women. The full report listing all studies and the results of the analysis is available at www.effectivehealthcare.ahrq.gov/pretermbirth.cfm. This summary, based on the full report of research evidence, is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

## Background Information

Preterm births, which occur before completion of 37 weeks of pregnancy, are associated with more than 85 percent of perinatal morbidity and mortality, both maternal and infant. In the United States, 12.5 percent of live births each year are preterm, but efforts to reduce the rate have been unsuccessful.

The current clinical focus is on early intervention based on risks. In the United States, about 133,000 pregnant women per year have a history of spontaneous preterm birth and are candidates for intervention. A natural role of progesterone is to help maintain pregnancy. As evidence accrues from controlled trials, the use of progestogens (natural and synthetic progestin forms of progesterone) for women with prior preterm birth is increasingly regarded as beneficial.

Still, progestogen use for these women is limited by lack of synthesized evidence about effectiveness, optimal formulations, administration routes, doses and timing of drug delivery, modifiers of treatment effect, and a need for more data on short- and long-term risks. Also unresolved is whether other at-risk groups can benefit from progestogens.

## Conclusions

Progestogens reduce the risk of preterm birth for women with prior spontaneous preterm births and current singleton pregnancies. Women with a short cervix may also benefit, but the evidence is limited. For women with multiple gestations, there is no benefit. For all other indications, the evidence is insufficient to guide care. The incidence of rare adverse events and the effects of modifiers are unknown, and direct comparisons of progestogen formulations, doses, timing, and durations of use have not been made. The evidence is insufficient to know whether progestogen use prevents morbidity or promotes normal childhood development.

## Clinical Bottom Line

### Benefits

**By Indication (Risk Group)**

- For women with current singleton pregnancies and a history of spontaneous preterm birth who are treated with progestogens:
  - The risk of preterm birth (prior to 37 weeks) is reduced by one-third (absolute risk reduction = 9.4%; NNT* = 11). ●●○
  - Neonatal mortality risk is reduced by half (absolute risk reduction = 1.7%; NNT = 59). ●○○
  - Birth weights may increase, but the estimated effect is not statistically significant. ●●○
- In women with a short cervix, progestogen treatment reduces the risk of preterm birth, but the size of the effect is not clearly established (an absolute risk reduction of 9% and 15% in two trials). ●○○
- In women with multiple gestations (twin or triplet), there is no benefit of progestogen use:
  - Birth is not delayed. ●●○
  - Birth weights are not improved. ●●○
  - The evidence is insufficient to estimate effects on neonatal mortality rates. ○○○
- The evidence is insufficient for all other indications, including women with symptoms of preterm labor, and for populations with varied risk factors. ○○○
- The evidence about benefits of progestogens for other maternal, fetal, neonatal, and perinatal outcomes (e.g., conditions of prematurity, NICU† admissions) is insufficient to guide clinical decisionmaking. ○○○

**By Formulation/Route of Administration**

- When assessed by routes of administration alone (injected, oral, and vaginal), all formulations reduce the risk of preterm birth, but none reduce neonatal mortality rates. (Strength of evidence not rated)
- Without head-to-head trials, the evidence is insufficient to determine if formulation and administration route are associated with different maternal or fetal outcomes or adverse effects. ○○○

*NNT = number needed to treat: the number of patients to be treated to find the effect in one patient more than in the control group
†NICU = neonatal intensive care unit
*(Continued on back)*

**Strength of Evidence Scale**

| | | |
|---|---|---|
| High: | ●●● | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate: | ●●○ | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. |
| Low: | ●○○ | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. |
| Insufficient: | ○○○ | Evidence is either unavailable or does not permit a conclusion. |

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## Clinical Bottom Line *(Continued)*

### Adverse Effects

**Safety of Progestogens**

- Study withdrawal rates (a measure of tolerability) were similar for treated and control groups.
- The most common adverse effects were related to route of administration (injection site discomfort, vaginal irritation).
- The evidence is insufficient to understand the short- and long-term maternal and fetal adverse effects. ○○○

## Gaps in Knowledge

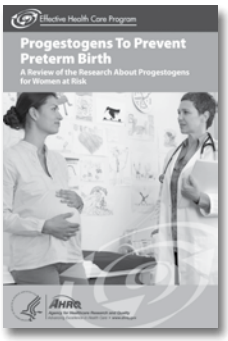
- In the research to date, the variety of outcome measurements, drugs, doses, and administration routes used limit the usefulness of the data for meta-analysis and lower the applicability of the studies for clinical decisionmaking.
- Direct evidence is limited about the health benefits expected from preventing preterm birth (e.g., effects on NICU admissions, conditions of prematurity, neonatal survival, and childhood development). Reporting of adverse effects in both women and children is inadequate.
- The few available studies are too small to determine benefits or risk of adverse effects for many subpopulations (e.g., women with symptoms of preterm labor or populations with mixed risk factors).
- Effects on neonatal mortality are not clear, due to imprecise classification (e.g., perinatal vs. neonatal or fetal) and inconsistent reporting of this outcome.
- The evidence about the influence of potential modifiers of effectiveness and safety is insufficient to guide care. Examples include the dose, timing, and duration of treatment; maternal characteristics (e.g., number and severity of prior preterm births, cervical length, body mass index, socioeconomic status, race and ethnicity, assisted reproduction); and cointerventions (e.g., cervical cerclage, bed rest, tocolytics, cortisol, nursing surveillance).
- Large-scale comparative effectiveness and surveillance research is needed that is powered to differentiate effects in both treatment and control groups and can evaluate both immediate and long-term benefits and adverse effects for each category of at-risk women and their infants.

## What To Discuss With Your Patients

- Progestogens reduce the risk of preterm birth for women who previously had a spontaneous preterm birth and who currently have a singleton pregnancy. Women with a short cervix may also benefit. Progestogens do not prevent preterm birth for twin or triplet gestations.
- There is little evidence about using progestogens for women with preterm labor or other risk factors for preterm birth.
- The evidence about differences between the oral, injection, or vaginal methods for treatment is limited.
- It is not known if progestogens will provide short- or long-term benefits to the infant or pregnant woman, other than delaying birth, and there is little evidence about short- and long-term adverse effects.

## Resource for Patients

*Progestogens To Prevent Preterm Birth, A Review of the Research About Progestogens for Women at Risk* is a free companion to this clinician research summary. It covers:




- The ability of progestogens to reduce the risk of preterm birth for some at-risk women
- The types of progestogens that are used
- The limited evidence about short- and long-term benefits and adverse effects

## Ordering Information

For electronic copies of *Progestogens To Prevent Preterm Birth, A Review of the Research About Progestogens for Women at Risk*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/pretermbirth.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

## Source

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