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SPECIAL ARTICLE

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FIGO good practice recommendations on progestogens for prevention of preterm delivery

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Abstract

Women at high risk of preterm birth (either a previous spontaneous preterm birth and/or sonographic short cervix) with a singleton gestation should be offered daily vaginal progesterone or weekly 17-OHPC treatment to prevent preterm birth. Benefit is most significant in those with prior history of preterm birth and a short cervix. For women with a previous spontaneous preterm birth and a cervix ≥30 mm the effectiveness of progesterone is uncertain. In asymptomatic women with no prior history of previous preterm birth, no mid-trimester loss, or no short cervical length, progesterone therapy is not recommended for the prevention of preterm birth. For those with unselected multiple pregnancies, progesterone therapy is not recommended for the prevention of preterm birth. Daily vaginal progesterone or weekly 17-OHPC treatment can be used for the prevention of preterm birth. The preparation used should be decided by the woman and her clinician. There is no evidence of neurological or developmental benefit or harm in babies whose mothers use progestogens for preterm birth prevention antenatally.

KEYWORDS
antenatal, child outcome, preterm delivery, prevention, progesterone

* The Members of the FIGO Working Group for Preterm Birth, 2018–2021 are listed at the end of the article.

1 | INTRODUCTION

Endogenous progesterone is essential for the maintenance of pregnancy, and local decline in progesterone activity is thought to have a role in labor induction. Therefore, progestogens have been increasingly used in women at high risk of preterm birth as they are believed to counter this functional decline and provide anti-inflammatory effects. Several randomized controlled trials (RCTs) and meta-analyses have been undertaken to help provide an evidence-based approach to prevent preterm birth and determine the optimal regimes and populations to target.

Types of progestogens:

1. Natural progesterone, similar to that produced by the body and commonly administered as a vaginal gel or pessary
2. Semisynthetic progestogens, which have a different chemical structure and include 17-hydroxyprogesterone caproate (17-OHPC), given as a weekly intramuscular injection.

2 | ASYMPTOMATIC WOMEN WITH A SINGLETON GESTATION AT HIGH RISK OF PRETERM BIRTH

The EPPPIC meta-analysis included individual patient data from randomized trials of progestogens to prevent preterm birth, including 31 trials and 11 644 participants.[1] It demonstrated that both vaginal progesterone and 17-OHPC reduced the risk of preterm birth before 34 weeks for a high-risk population with singleton gestations. In addition, a benefit was seen among included participants who were only eligible for the original trials due to short cervical length (defined by different thresholds in different trials) or history of preterm birth (vaginal progesterone: 9 trials, 3769 women; relative risk [RR] 0.78, 95% CI 0.68–0.90; 17-OHPC: 5 trials, 3053 women; RR 0.83, 95% CI 0.68–1.01).

Recommendation: Women at high risk of preterm birth (either a previous spontaneous preterm birth and/or sonographic short cervix) with a singleton gestation should be offered daily vaginal progesterone or weekly 17-OHPC treatment to prevent preterm birth. Whether progesterone is effective in women with previous spontaneous preterm birth and a normal length cervix (>30 mm at midtrimester ultrasound) is uncertain.

3 | ASYMPTOMATIC WOMEN WITH A SINGLETON GESTATION WITHOUT A PRIOR HISTORY OF PRETERM BIRTH OR SHORT CERVICAL LENGTH

In the EPPPIC meta-analysis, the effect of progestogens on preterm birth reduction did not statistically differ based on the history of preterm birth or the presence of a short cervix. However, few women enrolled in any of the included trials that did not have either of these risk factors. As such, it remains uncertain whether and to what extent progestogens will or will not benefit this population.

Recommendation: In asymptomatic women with no prior history of previous preterm birth, no mid-trimester loss, or no short cervical length, progesterone therapy is not recommended for the prevention of preterm birth.

4 | ASYMPTOMATIC WOMEN WITH A MULTIPLE PREGNANCY

The EPPPIC meta-analysis shows that progestogen administration does not reduce preterm birth before 34 weeks in women with unselected multiple pregnancies (16 trials; vaginal progesterone: RR 1.01, 95% CI 0.84–1.20; 17-OHPC: RR 1.04, 95% CI 0.92–1.18).[1] The majority of women included in the meta-analysis had no other risk factors for preterm birth. This is consistent with the 2019 Cochrane review, which included 16 trials and 4548 women.[2] A recent additional study came to the same conclusion for unselected multiple pregnancies.[3]

Recommendation: For women with unselected multiple pregnancies, progesterone therapy is not recommended for the prevention of preterm birth. For women with multiple pregnancies and a risk factor such as previous preterm birth, it is unknown whether progesterone therapy is effective.

5 | OTHER ISSUES

5.1 | Type of progestogen

In the EPPPIC meta-analysis, there were only two trials that provided direct data comparing vaginal progesterone and 17-OHPC, and these showed no statistical difference between the two types of progestogen (preterm birth <34 weeks RR 1.18, 95% CI 0.69–2.03).[1]

Recommendation: Daily vaginal progesterone or weekly 17-OHPC treatment can be used for the prevention of preterm birth. The preparation used should be decided by the woman and her clinician.

5.2 | Long-term effects of progestogens

Only two studies have examined the long-term effects of progestogens in those with singleton gestations.[4,5] The follow-up study to the Meis et al. 2003 trial of 17-OHPC showed no difference between 17-OHPC and placebo groups in any of the developmental domains of children assessed at approximately two years.[4] A childhood developmental assessment was one of the three primary outcomes in the OPPTIMUM study, which showed no difference in cognitive composite score between the active and the placebo groups.[5] A recent systematic review comprising a

multitude of developmental measurements with a broad age range at assessment did not find evidence of benefit or harm in offspring prenatally exposed to progesterone treatment for the prevention of preterm birth (5 trials, 4222 measurements of children between 6 months and 8 years).[6]

Recommendation: There is no evidence of neurological or developmental benefit or harm in babies whose mothers use progestogens for preterm birth prevention antenatally.

CONFLICTS OF INTEREST

Andrew Shennan reports payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Manipal India; support for attending meetings and/or travel from Hologic; leadership or fiduciary roles in the HTA Commissioning Board UK and Action on Pre-eclampsia charity. Natalie Suff reports no conflicts of interest. Jo Leigh Simpson reports royalties from Springer and Elsevier; consulting fees from the Illumina Clinical Expert Panel 2020; payment or honoraria for lectures, presentations, speakers bureaus, or educational events from the 1st and 2nd International Congresses on the Future of Women's Health, and a speaker's bureau at ASRM 2019; participation on a data safety monitoring board or advisory board for the FDA DSMB; and leadership or fiduciary roles in IFFS and PGDIS. Bo Jacobbson reports research grants from Swedish Research Council, Norwegian Research Council, March of Dimes, Burroughs Wellcome Fund and the US National Institute of Health; clinical diagnostic trials on NIPT with Ariosa (completed), Natera (ongoing), Vanadis (completed) and Hologic (ongoing) with expendidures reimbused per patient; clinical probiotic studies with product provided by FukoPharma (ongoing, no funding) and BioGaia (ongoing; also provided a research grant for the specific study); collaboration in IMPACT study where Roche, Perkin Elmer and Thermo Fisher provided reagents to PLGF analyses; coordination of scientific conferences and meetings with commercial partners as such as NNFM 2015, ESPBC 2016 and a Nordic educational meeting about NIPT and preeclampsia screening. Bo Jacobbson is also Chair of the FIGO Working Group for Preterm Birth and the European Association of Perinatal Medicine's special interest group of preterm delivery; steering group member of Genomic Medicine Sweden; chairs the Genomic Medicine Sweden complex diseases group; and is Swedish representative in the Nordic Society of Precision Medicine. Ben W. Mol reports an investigator grant from NHMRC; consultancy for ObsEva; and research funding from Guerbet, Ferring, and Merck KGaA. William A. Grobman reports no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors and the FIGO Working Group for Preterm Birth drafted the concept and idea of the paper. AS wrote the first version of the manuscript. JLS, BJ, BM, and WAG revised various versions of the manuscript. All authors and working group members commented on the manuscript and approved the final version.

MEMBERS OF THE FIGO WORKING GROUP FOR PRETERM BIRTH, 2018–2021

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