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New considerations on which patients might benefit from progesterone therapy to prevent preterm birth, management strategies for IVF pregnancies, and tips for assessing and treating pregnant and postpartum patients with acute or secondary headache

IN THIS ARTICLE

In the musical *Hamilton,* there is a line from the song "The Election of 1800" in which, after a tumultuous time, Thomas Jefferson pleads for a sense of normalcy with, "Can we get back to politics?"

Trying to get back to "normal," whatever that is, characterized the year 2022. Peeking out from under the constant shadow of the COVID-19 pandemic (not really gone, definitely not forgotten) were some blockbuster obstetrical headlines, including those on the CHAP (Chronic Hypertension and Pregnancy) trial and the impact of the *Dobbs v Jackson* Supreme Court decision. As these have been extensively covered in both OBG MANAGEMENT and other publications, in this Update we simply ask, "Can we get back to obstetrics?" as we focus on some straightforward patient care guidelines.

Thus, we offer updated information on the use of progesterone for preterm birth prevention, management of pregnancies that result from in vitro fertilization (IVF), and headache management in pregnant and postpartum patients.

Society guidance and FDA advisement on the use of progesterone for the prevention of spontaneous preterm birth

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics. Prediction and prevention of spontaneous preterm birth. ACOG practice bulletin no. 234. Obstet Gynecol. 2021;138:e65-e90.

EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. Lancet. 2021;397:1183-1194.

This is not déjà vu! Progesterone and spontaneous preterm birth (sPTB) is a hot topic again. If you wonder what to tell your patients, you are not alone. Preterm birth (PTB) continues to pose a challenge in obstetrics, with a most recently reported overall rate of 10.49%[1] in the United States—a 4% increase from 2019. Preterm birth accounts for approximately 75% of perinatal mortality and more than half of neonatal morbidity.[2]

What has *not* changed

A recent practice bulletin from the American College of Obstetricians and Gynecologists (ACOG) notes that some risk factors and screening assessments for PTB remain unchanged, including[2]:

- A history of PTB increases the risk for subsequent PTB. Risk increases with the number of prior preterm deliveries.
- A short cervix (<25 mm between 16 and 24 weeks' gestation) is a risk factor for sPTB.
- The cervix should be visualized during the anatomy ultrasound exam (18 0/7 to 22 6/7 weeks' gestation) in all pregnant patients regardless of prior birth history. If the cervix length (CL) appears shortened on transabdominal imaging, transvaginal (TV) imaging should be performed.
- Patients with a current singleton pregnancy and history of sPTB should have serial TV cervical measurements between 16 0/7 and 24 0/7 weeks' gestation.[2]

EPPPIC changes and key takeaway points

In a meta-analysis of data from 31 randomized controlled trials, the EPPPIC (Evaluating Progestogens for Preventing Preterm birth International Collaborative) investigators compared vaginal progesterone, intramuscular 17-hydroxyprogesterone caproate (17-OHPC), or oral progesterone with control or with each other in women at risk for PTB.[3] Outcomes included PTB and the associated adverse neonatal and maternal outcomes.

The EPPPIC study's main findings were:

- Singleton pregnancies at high risk for PTB due to prior sPTB or short cervix who received 17-OHPC or vaginal progesterone were less likely to deliver before 34 weeks' gestation compared with those who received no treatment.
- There is a benefit to both 17-OHPC and vaginal progesterone in reducing the risk of PTB, with no clear evidence to support one intervention's effectiveness over the other.
- There is benefit to either 17-OHPC or vaginal progesterone for CL less than 25 mm. The shorter the CL, the greater the absolute risk reduction on PTB.
- In multifetal pregnancies, use of 17-OHPC, when compared with placebo, was shown to increase the risk of preterm premature rupture of membranes. Neither 17-OHPC nor vaginal progesterone was found to reduce the risk of sPTB in multifetal pregnancies.[3]

What continues to change

While the March 30, 2021, statement from the Society for Maternal-Fetal Medicine (SMFM), "Response to EPPPIC and consideration for the use of progestogens for the prevention of preterm birth" (https://www.smfm.org/publications/383-smfm-statement-response-to-epppic-and-considerations-of-the-use-of-progestogens-for-the-prevention-of-preterm-birth), stands, ACOG has withdrawn its accompanying Practice Advisory on guidance for integrating the EPPPIC findings.

In August 2022, the US Food and Drug Administration (FDA) granted a hearing on the Center for Drug Evaluation and Research's proposal to withdraw approval for Makena (hydroxyprogesterone caproate injection, 250 mg/mL, once weekly) on the basis that available evidence does not demonstrate that it is effective for its approved indication to reduce the risk of PTB in women with a singleton pregnancy with a history of singleton sPTB.[4]

FAST TRACK

According to the EPPPIC data, there is a benefit to both 17-OHPC and vaginal progesterone in reducing the risk of PTB, with no clear evidence to support one intervention's effectiveness over the other

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The key takeaway points from the FDA hearing (October 17–19, 2022) were:

- A better designed randomized controlled confirmatory trial is needed in the most at-risk patients to determine if Makena is effective for its approved indication.
- Makena and its approved generic equivalents remain on the market until the FDA makes its final decision regarding approval.[4]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

For now, the decision to use intramuscular progesterone in women with a prior sPTB should be based on shared decision-making between the health care provider and patient, with discussion of its benefits, risks, and uncertainties. SMFM currently recommends that women with a singleton pregnancy and a short CL (<25 mm) without a history of prior sPTB be offered treatment with a progesterone. While 17-OHPC and vaginal progesterone appear to offer benefit to women with a singleton pregnancy and either a short CL or a history of sPTB, the greatest benefit and least risk is seen with use of vaginal progesterone. In multifetal pregnancies, there is not enough evidence to recommend the use of progesterone outside of clinical trials.

Although in our practice we still offer 17-OHPC to patients with the counseling noted above, we have focused more on the use of vaginal progesterone in women with singleton pregnancies and a history of sPTB or short CL

Managing pregnancies that result from IVF

Society for Maternal-Fetal Medicine (SMFM); Ghidini A, Gandhi M, McCoy J, et al; Publications Committee. Society for Maternal-Fetal Medicine consult series #60: management of pregnancies resulting from in vitro fertilization. Am J Obstet Gynecol. 2022;226:B2-B12.

Assisted reproductive technology contributes to 1.6% of all infant births, and although most pregnancies are uncomplicated, some specific risks alter management.[5–7] For example, IVF is associated with increased rates of prematurity and its complications, fetal growth restriction, low birth weight, congenital anomalies, genetic abnormalities, and placental abnormalities. In addition, there is doubling of the risk of morbidities to the pregnant IVF patient, including but not limited to hypertensive disorders and diabetes. These complications are thought to be related to both the process of IVF itself as well as to conditions that contribute to subfertility and infertility in the first place.

Genetic screening and diagnostic testing options

IVF pregnancies have a documented increase in chromosomal abnormalities compared with spontaneously conceived pregnancies due to the following factors:

- karyotypic abnormalities in couples with infertility
- microdeletions on the Y chromosome in patients with oligospermia or azoospermia
- de novo chromosomal abnormalities in IVF pregnancies that utilize intracytoplasmic sperm injection (ICSI)
- fragile X mutations in patients with reduced ovarian reserve
- imprinting disorders in patients with fertility issues.

A common misconception is that preimplantation genetic testing renders prenatal genetic screening or testing unnecessary. However, preimplantation testing can be anywhere from 43% to 84% concordant with prenatal diagnostic testing due to biologic and technical factors. Therefore, all pregnancies should be offered the same options of aneuploidy screening as well as diagnostic testing. Pretest counseling should include an increased risk in IVF pregnancies of false-positives for the first-trimester screen and "no-call" results for cell-free fetal DNA. Additionally, diagnostic testing is recommended specifically in cases where mosaic embryos are transferred when euploid embryos are not available.

Counseling on fetal reduction for multifetal pregnancies

The risks of multifetal pregnancies (particularly higher order multiples) are significant and well documented for both the patient and the fetuses. It is therefore recommended that the option of multifetal pregnancy reduction be discussed, including the risks and benefits of reduction versus pregnancy continuation, timing, procedural considerations, and genetic testing options.[5,8]

Detailed anatomic survey and fetal echocardiogram are indicated

Fetal anomalies, including congenital cardiac defects, occur at a higher rate in IVF pregnancies compared with spontaneously conceived pregnancies (475/10,000 live births vs 317/10,000 live births). Placental anomalies (such as placenta previa, vasa previa, and velamentous cord insertion) are also more common in this population. A detailed anatomic survey is therefore recommended for all IVF pregnancies and it is suggested that a fetal echocardiogram is offered these patients as well.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

While the expected outcome is good for most pregnancies conceived via IVF, there is an increased risk of adverse perinatal outcomes that varies based on individual patient characteristics and IVF technical aspects. Individualized care plans for these patients should include counseling regarding genetic screening and testing options, multifetal reduction in multiple gestations, imaging for fetal anomalies, and fetal surveillance in the third trimester.

Pregnancy management and delivery considerations

Despite an increased risk of preterm birth, preeclampsia, and fetal growth restriction in IVF pregnancies (odds ratios range, 1.4–2), serial cervical lengths, serial growth ultrasound exams, and low-dose aspirin are not recommended for the sole indication of IVF. Due to lack of data on the utility of serial exams, a single screening cervical length at the time of anatomic survey and a third-trimester growth assessment are recommended. For aspirin, IVF qualifies as a "moderate" risk factor for preeclampsia; it is therefore recommended if another moderate risk factor is present (for example, nulliparity, obesity, or family history of preeclampsia).[9]

There is a 2- to 3-fold increased risk of stillbirth in IVF pregnancies; therefore, antenatal surveillance in the third trimester is recommended (weekly starting at 36 weeks for the sole indication of IVF).[10] As no specific studies have evaluated the timing of delivery in IVF pregnancies, delivery recommendations include the option of 39-week delivery with shared decision-making with the patient.

FAST TRACK

There is a 2- to 3-fold increased risk of stillbirth in IVF pregnancies; therefore, antenatal surveillance in the third trimester is recommended

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Evaluating and treating headaches in pregnancy and postpartum

American College of Obstetricians and Gynecologists. Clinical practice guideline no. 3: headaches in pregnancy and postpartum. Obstet Gynecol. 2022;139:944-972.

For obstetricians, headaches are a common and often frustrating condition to treat, as many of the available diagnostic tools and medications are either not recommended or have no data on use in pregnancy and lactation. Additionally, a headache is not always just a headache but could be a sign of a time-sensitive serious complication. An updated guideline from the American College of Obstetricians and Gynecologists approaches the topic of headaches in a stepwise algorithm that promotes efficiency and efficacy in diagnosis and treatment.[11]

FAST TRACK

Reassuringly, headache frequency decreases by 30% to 80% during pregnancy, which allows for the option to decrease, change, or stop current medications, ideally prior to pregnancy

Types of headaches

The primary headache types—migraine, cluster, and tension—are distinguished from each other by patient characteristics, quality, duration, location, and related symptoms. Reassuringly, headache frequency decreases by 30% to 80% during pregnancy, which allows for the option to decrease, change, or stop current medications, ideally prior to pregnancy. Prevention via use of calcium channel blockers, antihistamines, or β-blockers is recommended, as requiring acute treatments more than 2 days per week increases the risk of medication overuse headaches.

Treating acute headache

For patients who present with an acute headache consistent with their usual type, treatment starts with known medications that are compatible with pregnancy and proceeds in a stepwise fashion:

1. Acetaminophen 1,000 mg orally with or without caffeine 130 mg orally (maximum dose, acetaminophen < 3.25–4 g per day, caffeine 200 mg per day)
2. Metoclopramide 10 mg intravenously with or without diphenhydramine 25 mg intravenously (for nausea and to counteract restlessness and offer sedation)
3. If headache continues after steps 1 and 2, consider the following secondary treatment options: magnesium sulfate 1–2 g intravenously, sumatriptan 6 mg subcutaneously or 20-mg nasal spray, ibuprofen 600 mg orally once, or ketorolac 30 mg intravenously once (second trimester only)
4. If continued treatment and/or hospitalization is required after step 3, steroids can be used: prednisone 20 mg 4 times a day for 2 days or methylprednisolone 4-mg dose pack over 6 days
5. Do not use butalbital, opioids, or ergotamines due to lack of efficacy in providing additional pain relief, potential for addiction, risk of medication overuse headaches, and association with fetal/pregnancy abnormalities.

Consider secondary headache

An acute headache discordant from the patient's usual type or with concerning symptoms ("red flags") requires consideration of secondary headaches as well as a comprehensive symptom evaluation, imaging, and consultation as needed. While secondary headaches postpartum are most likely musculoskeletal in nature, the following symptoms need to be evaluated immediately:

- rapid onset/change from baseline
- "thunderclap" nature
- hypertension
- fever
- focal neurologic deficits (blurry vision or blindness, confusion, seizures)
- altered consciousness
- laboratory abnormalities.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Calcium channel blockers and antihistamines are recommended for primary headache prevention.

Acetaminophen, caffeine, diphenhydramine, and metoclopramide administered in a stepwise manner are recommended for acute treatment of primary headache in pregnancy. Nonsteroidal anti-inflammatory agents and triptans may be added during lactation and postpartum.

Butalbital and opioids are not recommended for acute treatment of headaches in pregnancy and postpartum due to risk of medication overuse headaches, dependence, and neonatal abstinence syndrome.

"Red flag" headache symptoms warrant imaging, prompt treatment of severe hypertension, and timely treatment of potentially life-threatening intracranial conditions.

The differential diagnosis includes preeclampsia, reversible cerebral vasoconstriction syndrome (RCVS), posterior reversible encephalopathy syndrome (PRES), infection, cerebral venous sinus thrombosis (CVST), post–dural puncture (PDP) headache, idiopathic intracranial hypertension (IIH), and less likely, carotid dissection, subarachnoid hemorrhage, intracranial hemorrhage, pituitary apoplexy, or neoplasm.

Treatment. Individualized treatment depends on the diagnosis. Preeclampsia with severe features is treated with antihypertensive medication, magnesium sulfate, and delivery planning. PDP headache is treated with epidural blood patch, sphenopalatine block, or occipital block with an anesthesiology consultation. If preeclampsia and PDP are ruled out, or if there are more concerning neurologic features, imaging is essential, as 25% of pregnant patients with acute headaches will have a secondary etiology. Magnetic resonance imaging without contrast is preferred due to concerns about gadolinium crossing the placenta and the lack of data on long-term accumulation in fetal tissues. Once diagnosed on imaging, PRES and RCVS are treated with antihypertensives and delivery. CVST is treated with anticoagulation and a thrombophilia workup. IIH may be treated with acetazolamide after 20 weeks or serial lumbar punctures. Intracranial vascular abnormalities may be treated with endoscopic resection and steroids. ●

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