

# Prescribing aspirin to improve pregnancy outcomes: Expand the indications? Increase the dose?

Low-dose aspirin is effective in reducing the risk of developing preeclampsia. Questions remain about who should be treated and the optimal aspirin dose.



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Authors of a recent Cochrane review concluded that low-dose aspirin treatment of 1,000 pregnant women at risk of developing preeclampsia resulted in 16 fewer cases of preeclampsia, 16 fewer preterm births, 7 fewer cases of small-for-gestational age newborns, and 5 fewer fetal or neonatal deaths.<sup>1</sup>

The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force (USPSTF) recommend treatment with 81 mg of aspirin daily, initiated before 16 weeks of pregnancy to prevent preeclampsia in women with one major risk factor (personal history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal or autoimmune disease) or at least two moderate risk factors (nulliparity; obesity; mother or sister with preeclampsia; a sociodemographic characteristic such as African American race or low socioeconomic status; age  $\geq 35$  years; personal history factors such as prior low birth weight infant, previous adverse pregnancy

outcome, or >10-year interpregnancy interval).<sup>2,3</sup> Healthy pregnant women with a previous uncomplicated full-term delivery do not need treatment with low-dose aspirin.<sup>2,3</sup>

However, evolving data and expert opinion suggest that expanding the indications for aspirin treatment and increasing the recommended dose of aspirin may be warranted.

## Nulliparity

**Nulliparity is the single clinical characteristic that is associated with the greatest number of cases of preeclampsia.**<sup>4</sup> Hence, from a public health perspective, reducing the rate of preeclampsia among nulliparous women is a top priority.

ACOG and USPSTF do not recommend aspirin treatment for all nulliparous women because risk factors help to identify those nulliparous women who benefit from aspirin treatment.

However, a recent cost-effectiveness analysis compared the health

care costs and rates of preeclampsia for 4 prevention strategies among all pregnant women in the United States (nulliparous and parous)<sup>5</sup>:

1. no aspirin use
2. use of aspirin based on biomarker and ultrasound measurements
3. use of aspirin based on USPSTF guidelines for identifying women at risk
4. prescription of aspirin to all pregnant women.

Health care costs and rates of preeclampsia were lowest with the universal prescription of aspirin to all pregnant women in the United States. Compared with universal prescription of aspirin, the USPSTF approach, the biomarker-ultrasound approach, and the no aspirin approach were associated with 346, 308, and 762 additional cases of preeclampsia per 100,000 women. In sensitivity analyses, universal aspirin was the optimal strategy under most assumptions.

Another cost effectiveness analysis concluded that among *nulliparous* pregnant women, universal

aspirin treatment was superior to aspirin treatment based on biomarker-ultrasound identification of women at high risk.<sup>6</sup>

In a recent clinical trial performed in India, Guatemala, Pakistan, Democratic Republic of Congo, Kenya, and Zambia, 14,361 nulliparous women were randomly assigned to placebo or 81 mg of aspirin daily between 6 and 14 weeks of gestation.<sup>7</sup> Preterm birth (<37 weeks' gestation) occurred in 13.1% and 11.6% of women treated with placebo or aspirin (relative risk [RR], 0.89; 95% confidence interval [CI], 0.81 to 0.98,  $P = .012$ ). Most of the decrease in preterm birth appeared to be due to a decrease in the rate of preeclampsia in the aspirin-treated nulliparous women. The investigators also noted that aspirin treatment of nulliparous women resulted in a statistically significant decrease in perinatal mortality (RR, 0.86) and early preterm delivery, <34 weeks' gestation (RR, 0.75).

Universal prescription of low-dose aspirin to nulliparous women in order to prevent preeclampsia and preterm birth may become recognized as an optimal public health strategy. As a step toward universal prescription of aspirin to nulliparous women,



an opt-out rather than a screen-in strategy might be considered.<sup>8</sup>

### Booking systolic blood pressure, 120 to 134 mm Hg

All obstetricians recognize that women with chronic hypertension should be treated with low-dose aspirin because they are at high risk for preeclampsia. However, there is evidence that nulliparous women with a booking systolic pressure  $\geq 120$  mm Hg might also benefit from low-dose aspirin treatment. In one US trial, 3,135 nulliparous normotensive women (booking blood

pressure [BP] <135/85 mm Hg) were randomly assigned to treatment with aspirin (60 mg daily) or placebo initiated between 13 and 26 weeks' gestation. Preeclampsia occurred in 6.3% and 4.6% of the women treated with placebo or aspirin, respectively (RR, 0.7; 95% CI, 0.6–1.0;  $P = .05$ ).<sup>9</sup> A secondary analysis showed that, among 519 nulliparous women with a booking systolic BP from 120 to 134 mm Hg, compared with placebo, low-dose aspirin treatment reduced the rate of preeclampsia from 11.9% to 5.6%.<sup>9</sup> Aspirin did not reduce the rate of preeclampsia among nulliparous women with a

**TABLE Risks of aspirin treatment<sup>16,a</sup>**

| Adverse effect  | Aspirin group<br>(150 mg daily; n = 798) | Placebo group<br>(n = 822) |
|---|--|----------------------------|
| Headache and/or dizziness                                     | 9.6%                                     | 8.8%                       |
| Nausea and/or vomiting  | 5.0%                                     | 4.4%                       |
| Abdominal and/or pelvic pain                                  | 3.3%                                     | 4.0%                       |
| Vaginal bleeding  | 3.6%                                     | 2.6%                       |
| Nasal bleeding  | 2.0%                                     | 3.3%                       |
| Gingival, hemorrhoidal, or scleral bleeding and skin bruising | 0.9%                                     | 0.6%                       |
| Anemia  | 0.5%                                     | 0.9%                       |

<sup>a</sup>Reported adverse effects in a clinical trial of 1,776 women treated with aspirin 150 mg or placebo daily, initiated at 11 to 14 weeks' gestation and discontinued at 36 weeks' gestation.

booking systolic BP <120 mm Hg.<sup>9</sup> A systematic review of risk factors for developing preeclampsia reported that a booking diastolic BP of ≥80 mm Hg was associated with an increased risk of developing preeclampsia (RR, 1.38).<sup>10</sup>

The American Heart Association (AHA) and the American College of Cardiology (ACC) recently updated the definition of hypertension.<sup>11</sup> Normal BP is now defined as a systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Elevated BP is a systolic pressure of 120 to 129 mm Hg and diastolic pressure of <80 mm Hg. Stage I hypertension is a systolic BP from 130 to 139 mm Hg or diastolic blood pressure from 80 to 89 mm Hg. Stage II hypertension is a systolic BP of ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.<sup>11</sup>

A recent study reported that 90% of women at 12 weeks' gestation have a BP of ≤130 mm Hg systolic and ≤80 mm Hg diastolic, suggesting that the AHA-ACC criteria for stage I hypertension are reasonable.<sup>12</sup> Obstetricians have not yet fully adopted the AHA-ACC criteria for defining stage I hypertension in pregnant women. Future research may demonstrate that a booking systolic BP ≥130 mm Hg or a diastolic BP ≥80 mm Hg are major risk factors for developing preeclampsia and warrant treatment with low-dose aspirin.

### **Pregnancy resulting from fertility therapy**

Current ACOG and USPSTF guidelines do not specifically identify pregnancies resulting from assisted reproductive technology as a major or moderate risk factor for preeclampsia.<sup>2,3</sup> In a study comparing 83,582 births resulting from in vitro fertilization (IVF) and 1,382,311 births to fertile women, treatment with autologous cryopreserved

embryos (adjusted odds ratio [aOR], 1.30), fresh donor embryos (aOR, 1.92), and cryopreserved donor embryos (aOR, 1.70) significantly increased the risk of preeclampsia.<sup>13</sup> However, use of fresh autologous embryos did not increase the risk of preeclampsia (aOR, 1.04). These associations persisted after controlling for diabetes, hypertension, body mass index, and cause of infertility.<sup>13</sup>

Other studies also have reported that use of cryopreserved embryos is associated with a higher rate of preeclampsia than use of fresh autologous embryos. In a study of 825 infertile women undergoing IVF and randomly assigned to single embryo cryopreserved or fresh cycles, the rate of preeclampsia was 3.1% and 1.0% in the pregnancies that resulted from cryopreserved versus fresh cycles.<sup>14</sup>

### **What is the optimal dose of aspirin?**

ACOG and the USPSTF recommend aspirin 81 mg daily for the prevention of preeclampsia.<sup>2,3</sup> The International Federation of Gynecology and Obstetrics (FIGO) recommends aspirin 150 mg daily for the prevention of preeclampsia.<sup>15</sup> The FIGO recommendation is based, in part, on the results of a large international clinical trial that randomly assigned 1,776 women at high risk for preeclampsia as determined by clinical factors plus biomarker and ultrasound screening to receive aspirin 150 mg daily or placebo daily initiated at 11 to 14 weeks' gestation and continued until 36 weeks' gestation.<sup>16</sup> Preeclampsia before 37 weeks' gestation occurred in 4.3% and 1.6% of women in the placebo and aspirin groups (OR, 0.38; 95% CI, 0.20–0.74; *P* = .004).<sup>16</sup> FIGO recommends that women at risk for preeclampsia with a body

mass <40 kg take aspirin 100 mg daily and women with a body mass ≥40 kg take aspirin at a dose of 150 mg daily. For women who live in a country where aspirin is not available in a pill containing 150 mg, FIGO recommends taking two 81 mg tablets.<sup>15</sup> FIGO recommends initiating aspirin between 11 and 14 weeks and 6 days of gestation and continuing aspirin therapy until 36 weeks of gestation.<sup>15</sup>

### **Aspirin is an inexpensive intervention with many possible benefits**

For many nulliparous women and some parous women aspirin treatment initiated early in pregnancy will improve maternal and newborn outcomes, including reducing the risk of preeclampsia, preterm birth, and intrauterine growth restriction.<sup>1</sup> Obstetricians may want to begin to expand the indications for offering aspirin to prevent preeclampsia from those recommended by ACOG and the USPSTF to include nulliparous women with a booking systolic pressure of 120 to 134 mm Hg and women whose pregnancy was the result of an assisted reproduction treatment that used cryopreserved embryos. In addition, obstetricians who currently prescribe 81 mg of aspirin daily might want to consider increasing the prescribed dose to 162 mg of aspirin daily (two 81 mg tablets daily or one-half of a 325 mg tablet). Aspirin costs about less than 5 cents per 81 mg tablet (according to GoodRx website). It is an inexpensive intervention that could benefit many mothers and newborns. ●



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## Do ObGyns think hormonal contraception should be offered over the counter?

In their advocacy column, “OTC hormonal contraception: An important goal in the fight for reproductive justice” (January 2020), Abby L. Schultz, MD, and Megan L. Evans, MD, MPH, discussed a recent committee opinion from the American College of Obstetricians and Gynecologists (ACOG) focused on improving contraception access by offering oral contraceptive pills, progesterone-only pills, the patch, vaginal rings, and depot medroxyprogesterone acetate over the counter (OTC). The authors agreed with ACOG’s stance and offered several reasons why.

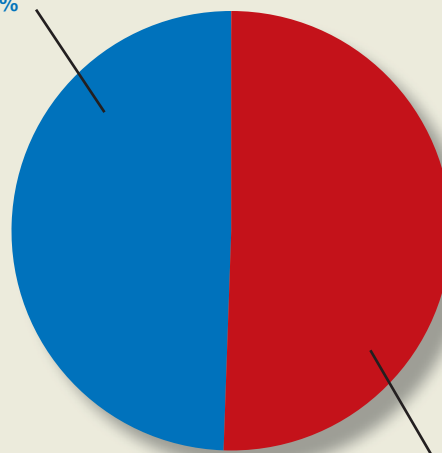
OBG MANAGEMENT polled readers to see their thoughts on the question of whether or not hormonal contraception should be offered OTC.

### Poll results

A total of 166 readers cast their vote:

- 50.6% (84 readers) said no
- 49.4% (82 readers) said yes

Agree that hormonal contraception should be offered OTC  
49.4%



Do not agree that hormonal contraception should be offered OTC  
50.6%