cause. Although some data supporting this hypothesis are available, relatively few studies have addressed this question.

In this abstracted article, the authors performed a systematic review and meta-analysis, and evaluated the risk of stillbirth, PTB, and small-for-gestational age birth in a subsequent pregnancy after occurrence of one or more of these disorders in a previous birth. They found that although many studies have investigated recurrence of these disorders (ie, recurrent PTB after PTB in a first pregnancy), fewer have studied the occurrence of a different adverse outcome (ie, stillbirth after PTB in a first pregnancy). They found that the risk for another adverse outcome was increased, with OR of 1.7 to 2.0, after a single adverse outcome in the index pregnancy. The OR was significantly higher for women who had multiple adverse outcomes, such as PTB of an SGA infant. More adverse outcomes, and more severe adverse outcomes, resulted in increasingly high OR for adverse outcomes in the next pregnancy.

These results are not terribly surprising, but they are important. Although the recurrence risk of PTB, SGA birth, and stillbirth are well recognized, the increased risk of occurrence of a different adverse outcome is not as well appreciated. The authors point out that the risks are equivalent to many accepted risk factors for poor outcomes, such as smoking, advanced maternal age, or obesity. It seems reasonable that increased monitoring of these pregnancies is warranted, although what type of monitoring and what intervention to use are far less clear. Low-dose aspirin is a low-risk, low-cost intervention that should probably be recommended to any woman with a prior adverse pregnancy outcome. However, whether progesterone or cervical length monitoring is indicated is much less clear. In considering specifically the PTB risk, the limitation of this type of meta-analysis is the limited information that is provided about these pregnancies, including importantly the lack of distinction of spontaneous versus indicated PTBs. Are women with a well-grown fetus at risk of stillbirth? Are women with a prior indicated PTB due to preeclampsia at risk of FGR, or stillbirth, if the preeclampsia does not recur? The answers to these questions remain unclear.

What to do with these results in practice? It may be reasonable to use a generalizable high-risk protocol, in which women who have had a prior pregnancy complication likely due to poor placentation are followed closely with a combination of cervical length and PTB monitoring, ultrasound for fetal growth, and potentially antenatal surveillance due to risk of stillbirth. In addition, although low-dose aspirin is currently recommended only for women with risk factors specifically for preeclampsia, again the risk is low and a lack of studies to demonstrate benefit do not mean there is no benefit.—MEN

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**Effect of Maternal Age on the Risk of Preterm Birth: A Large Cohort Study**

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**ABSTRACT**

As maternal age at pregnancy continues to increase worldwide, researchers have become more interested in outcomes of pregnancy in women of advanced age. Although complications such as placenta previa, fetal growth restriction or fetal demise, gestational diabetes, hypertensive disorders of pregnancy, and cesarean delivery are
known to be more common in older pregnant women, the relationship between maternal age and preterm birth (PTB) is uncertain.

The aim of this retrospective cohort study was to evaluate the relationship between advanced maternal age and the risk of both spontaneous and iatrogenic PTB. Data were obtained from the QUARISMA randomized controlled trial, a cluster intervention trial that collected data on 184,000 pregnancies across 32 hospitals in Quebec, Canada, from 2008 to 2011. Inclusion criteria were birth at or after 24 gestational weeks of a fetus weighing more than 500 g; maternal age greater than 20 years; singleton pregnancies; and absence of fetal malformations and intrauterine fetal demise. Pregnancies were sequestered into 5 maternal age categories, and these were compared based on maternal medical history, pregnancy characteristics, and maternal/obstetrical complications. Odds ratios for preterm (<37 weeks) and very PTB (<32 weeks) were calculated for each age group using adjustment by multivariate logistic regression for risk factors, maternal characteristics, and gestational complications.

A total of 165,195 pregnancies were included in the study. Rates of preterm and very PTB were lowest in the 30 to 34 years old group (5.7% and 0.6%, respectively) and highest in the older than 40 years maternal age group (7.8% and 1.0%, respectively). The adjusted odds ratio of prematurity stratified by age subgroup presented a U-shaped distribution with an adjusted odds ratio of 1.08 (95% confidence interval [CI], 1.01–1.15) for the 20 to 24 years old group and 1.20 (95% CI, 1.06–1.36) for the older than 40 years old group. Compared with the 30 to 34 years old group, odds ratios for PTB, very PTB, spontaneous PTB, and iatrogenic PTB for the older than 40 years maternal age group were, respectively, 1.39 (95% CI, 1.24–1.57), 1.68 (95% CI, 1.21–1.31), 1.20 (95% CI, 1.04–1.39), and 1.91 (95% CI, 1.56–1.34). Rates of chronic hypertension, pregestational diabetes, gestational diabetes, assisted reproductive techniques, invasive procedure, placenta previa, and obesity all increased linearly with maternal age.

The results of this study found that advanced maternal age is associated directly with an increased risk of PTB. Multivariate analysis showed a U-shaped relationship between maternal age and risk of PTB, with the lowest risk occurring in mothers aged 30 to 34 years.

**EDITORIAL COMMENT**

(One cultural change of note in the past several decades has been a substantial increase in the average maternal age at delivery. In developed countries, including the United States, the average maternal age at delivery is now approximately 30 years, and the percentage of women delivering at age 35 years or older has increased almost 8 times (NCHS Data Brief. 2009; (21):1–8). Many adverse pregnancy outcomes are known to increase with maternal age, and many maternal comorbidities are associated with increased age. Many of these adverse outcomes can lead to PTB; however, it is not known whether maternal age is associated with PTB in the absence of such comorbidities. That is, is a healthy, fit woman older than 35 years or even 40 years at increased risk of PTB?

In this abstracted article, the authors were interested in the risk of PTB in older women, including both spontaneous and indicated. The study was a secondary analysis of a large trial focused on decreasing rates of cesarean delivery; this secondary analysis included 165,195 births with 21,416 to women aged 35 ± 39 years and 4138 in women aged 40 years or more. Older women had higher rates of hypertension, diabetes, obesity, assisted reproduction, diagnostic procedures, and placenta previa. Gestational hypertension was highest at both extremes of maternal age. Rates of PTB were lowest at 30 to 34 years, and highest in women older than 40 years. After adjustment for confounders, age 40 years was associated with an increased risk of PTB, although the odds ratio was less than 2. Spontaneous PTB was associated with younger maternal age, while older age was associated with higher rates of iatrogenic PTB. Most OR were relatively low (<2), except for placenta previa, which had an OR of 7 for PTB at less than 32 weeks and at less than 37 weeks.

There are a number of interesting findings in this study. Although maternal age was associated with a higher risk of PTB, even when adjusting for a large number of confounders (primiparity, medical history [chronic hypertension, pregestational and gestational diabetes, renal disease, cardiac disease, thrombophilia, systemic erythematosus lupus and Crohn disease], smoking, drug use [past or current], use of assisted reproductive technologies, occurrence of an invasive procedure, hypertensive complications, and placenta previa), the OR for PTB was relatively low. It has been noted that an OR in this range is often later found to be spurious—this small increase certainly might represent unmeasured confounders or risk factors. It is also interesting that 30 to 34 years of age was the group with the lowest risk of PTB, at lower risk than women in their 20s.
Conversely, it is not surprising that hypertension and comorbidities were the greatest risk factors for PTB. Chronic hypertension is highly associated with maternal age and is highly associated with adverse pregnancy outcomes (Am J Obstet Gynecol. 2016;215(6):787.e1–787.e8). Hypertension is one of the leading causes of mortality; clearly the association with adverse pregnancy outcomes is also an indication of the significance of this condition.

What does this mean for patient counseling? Women who are older but healthy should certainly not be dissuaded from pursuing pregnancy and should be reassured that their risk is minimally increased, if at all (other than for aneuploidy). Women who are older and who do have comorbidities should be encouraged to optimize those before pregnancy, particularly hypertension.—MEN

Prevention of Malaria in Pregnancy

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ABSTRACT

Although the World Health Organization (WHO) has established recommendations for prevention of malaria, it remains one of the most preventable causes of adverse birth outcomes. The WHO recommends intermittent preventive treatment in pregnancy (IPTp) with for women who are HIV-negative, or co-trimoxazole prophylaxis for women who are HIV-positive. However, parasite resistance to sulfadoxine pyrimethamine in sub-Saharan Africa has led researchers to pursue other screen-and-treat approaches.

This analysis reviews the effect of sulfadoxine-pyrimethamine on IPTp efficacy and summarizes trials focused on the prevention of malaria in pregnancy in areas where malaria is endemic. A total of 65 efficacy-related articles were included.

Sulfadoxine-pyrimethamine as IPTp in pregnant women reduces the risk of comorbidities including anemia, antenatal and placental parasitemia, spontaneous abortions, and low birthweight. Reviews of this regimen have found it to be highly cost-effective when combined with existing antenatal services. A meta-analysis conducted in Africa found that 3-course or monthly IPTp with sulfadoxine-pyrimethamine was much more effective in reducing adverse birth outcomes than the standard 2-course regimen, leading the WHO to update its guidelines in 2012. Observational studies have shown that resistance to sulfadoxine-pyrimethamine reduces the parasitological efficacy of IPTp and duration of prophylaxis. High resistance is found in regions where prevalence of parasites with quintuple Plasmodium falciparum dihydrofolate reductase (Pfdhfr) and dihydropteroate synthetase (Pfdhps) mutations is greater than 90%. Even in such locations, sulfadoxine-pyrimethamine regimens continue to have beneficial effects on low birthweight. Research into alternative IPTp therapies are ongoing, yet many proposed alternatives thus far have found that they are tolerated poorly by patients. Two trials of IPTp using dihydroartemisinin-piperaquine show that it was well tolerated compared with sulfadoxine-pyrimethamine and associated with greater reductions in malaria and fetal loss.

Four studies examined intermittent screening and treatment in pregnancy (ISTp) as an alternative to IPTp in areas of high resistance and high sensitivity to sulfadoxine-pyrimethamine. Meta-analysis of these trials, which involve rapid diagnostic testing and artemisinin-based combination therapy, revealed ISTp was associated with a 25-g decrease in mean birthweight (95% confidence interval, 7–44; \( P = 0.0088, n = 8659 \)). There is a gap in the research on pharmacokinetic and dynamic drug interactions between antiretroviral and antimalarial drugs in pregnancy. Research in sub-Saharan Africa revealed lack of education targeting women on care of malaria in pregnancy. Studies related to operational feasibility revealed confusion over