

placental mosaicism (CPM) as a possible etiology for FGR. Although interesting, this diagnostic pathway needs to be evaluated further before being offered to patients. As demonstrated in our study, to increase diagnostic yield, CMA should be offered in addition to karyotype. CPM diagnosis will not modify the fetal prognosis in cases of normal fetal CMA nor will it affect the clinical management of the pregnancy.<sup>3</sup> However, it could result in patient anxiety and excess costs without any real benefit for the patient. ■

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## Accommodating vaccine preferences among women of childbearing age



**TO THE EDITORS:** After pregnant persons were excluded from the initial trials leading to emergency use authorizations for COVID-19 vaccines in the United States, Gray et al<sup>1</sup> demonstrated robust vaccine-induced immune responses among pregnant women following COVID-19 messenger RNA (mRNA) vaccination (Pfizer-BioNTech and Moderna), with placental and breastmilk immune transfer to neonates. Unfortunately, rare clotting events following Janssen and AstraZeneca COVID-19 vaccination, which have been disproportionately experienced by women of childbearing age, have dampened the enthusiasm for these vaccines. At present, tailored education and vaccine deployment efforts should prioritize pregnant persons to mitigate newly recognized maternal and neonatal health risks following SARS-CoV-2 infection.<sup>2</sup> Moreover, given the fundamental principles of self-determination, personhood, and patient autonomy that underlie informed consent, respecting patients' right to make voluntary and informed healthcare decisions requires that all individuals should be fully informed about the risks and benefits of each vaccine,

and—if feasible—provided a choice among the available COVID-19 vaccines.

Improving vaccine uptake among pregnant women is of heightened importance given recent evidence that pregnant women with SARS-CoV-2 infection have a considerably elevated risk of adverse maternal and neonatal health outcomes, including 22 times the risk of maternal mortality and twice the risk of both severe neonatal morbidity and perinatal morbidity and mortality than do pregnant women without SARS-CoV-2 infection.<sup>2</sup> Reassuringly, we found that 70% of surveyed pregnant women in the United States would definitely or most likely obtain a COVID-19 vaccine as soon as possible.<sup>3</sup> Understandably, the initial phase of the US vaccine rollout did not accommodate personal preferences among COVID-19 vaccines. However, in contrast to other countries with inadequate vaccine supplies or only 1 available vaccine, in the United States, 3 different COVID-19 vaccines are currently in supply that now exceeds demand because of vaccine hesitancy and apathy. With newfound evidence of maternal and neonatal protection

conferred by mRNA vaccines,<sup>1</sup> increased risk of adverse health outcomes associated with SARS-CoV-2 infection among pregnant women,<sup>2</sup> and disproportionate Janssen and AstraZeneca vaccine side effects among women of childbearing age, we strongly disagree with the recent suggestion that “health systems . . . should communicate to patients that they will receive, and only really need, one choice of vaccine.”<sup>4</sup> We believe that amid this public health crisis, these considerations necessitate that women of childbearing age be afforded a choice among COVID-19 vaccines to reduce elevated adverse vaccination side effects experienced by women of childbearing age, vaccine hesitancy, and the serious risks COVID-19 poses for pregnant women and their children.<sup>2</sup> ■

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## In vitro fertilization as an independent risk factor for placenta accreta spectrum



**TO THE EDITORS:** Salmanian et al<sup>1</sup> discussed the possible effects of less physiological levels of estradiol on the risk of placenta accreta spectrum (PAS) development in in vitro fertilization (IVF) cycles, especially in frozen embryo transfer (FET) cycles, through manipulating the process of normal implantation and placentation. To date, the exact effect of altered levels of estradiol on endometrial microenvironment around the time of implantation remains uncertain. In this letter, we will explain one mechanism by which altered levels of estradiol could modulate the process of normal placentation.

The mechanism by which altered levels of estradiol affect the decidua formation and placentation could include immune response modulation. PAS pathophysiology involves thin decidua formation and excessive trophoblast invasion, both of which could be mediated by altered levels of cytokines that are otherwise required in controlled and balanced concentrations for normal decidua formation and trophoblast invasion (eg, interleukin 6 [IL-6], IL-8, and IL-1 $\beta$ ).<sup>2</sup> Previously, we have explained the possible role of less physiological levels of estradiol in preeclampsia development in artificial FET cycles through, at least in part, the modulation of various cytokines required for normal trophoblast invasion, including IL-6, IL-8, and IL-1 $\beta$ .<sup>3</sup> Thus, it is reasonable to think that less physiological levels of estradiol, such as that associated with IVF pregnancies, could lead to either augmented or less than required concentrations of these cytokines that might ultimately contribute to shallow (with subsequent ischemia and preeclampsia development), excessive trophoblast invasion or thin decidua formation (with future development of PAS).

However, the exact dosage of estradiol that could impair normal placentation remains inconclusive. In the literature, Kaser et al<sup>4</sup> and Imudia et al<sup>5</sup> have identified the potential cutoff of estradiol that could affect placentation, 732 pg/mL to predict PAS in cryopreserved embryo transfer cycles and 3450 pg/mL to predict preeclampsia in fresh cycles, respectively. More research studies are needed to understand the exact mechanism by which less physiological levels of estradiol affect the microenvironment in the endometrium around

the time of implantation and the subsequent abnormal placentation in IVF pregnancies. ■

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