Letter to the editor in response to: Evidence in support of the international association of diabetes in pregnancy study groups' criteria for diagnosing gestational diabetes worldwide in 2019

TO THE EDITORS: We read with interest the data on the long-term risks of untreated mild hyperglycemia from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.[1] Any national or international debate on the diagnostic criteria for gestational diabetes mellitus (GDM) also should be informed by the changes in preanalytical laboratory standards for measuring maternal plasma glucose since HAPO. For the HAPO study, glycolysis was inhibited by placing samples in a sodium fluoride additive on an ice water slurry and cell separation within 60 minutes.[2] Since 2011, it is recommended that cell separation takes place within 30 minutes and if this is not possible that sample tubes contain citrate buffer, not sodium fluoride.[3] In 121 women selectively screened for GDM with a 1-step 75-g oral glucose tolerance test in our hospital, the stricter guidelines increased the rate of GDM from 14.2% (n = 22) under customary conditions to 38.1% (n = 59) applying the 2011 standards ($P < .01$).[4] Failure to implement contemporary laboratory standards may lead to the diagnosis of GDM being missed and to underestimation of the prevalence.

Epidemiologically, if following inadequate inhibition of glycolysis, cases of more severe hyperglycemia continue to be classified as GDM but milder cases of hyperglycemia are erroneously included in the non-GDM group (see Table 1),[1] then the long-term risk of GDM may be statistically exaggerated. It also means that in obstetric practice women with mild GDM potentially undiagnosed may miss the window of opportunity for positive interventions highlighted.[1]

As part of the diagnostic debate, we also suggest that long-term risks of GDM be calculated based on an adjusted odds ratio of 2.0 for delivery and neonatal outcomes favored by some professional bodies in North America, rather than 1.75 favored by others.[1] The frequency of primary outcomes were categorized by equal ranges of mg/dL into 7 plasma glucose categories for fasting plasma glucose, and continuous relationships were evident with no obvious cut-off point for risk (see Figure 1).[1] However, the numbers of women in each category is unstated. As the clinical outcomes were based on centiles, we also suggest categorizing the glucose measurements by population centiles, which might identify a cut-off centile that optimizes diagnostic sensitivity and specificity. Although we appreciate the expert call to immediate action on broadening consensus, we believe there may be merit in further contemplation of the data already collected by HAPO. ■

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REPLY

We thank O'Malley et al for their interest in our clinical opinion.[1] They correctly highlight the importance of sampling technique, specimen transport, and laboratory methodology in the diagnosis of gestational diabetes mellitus (GDM). Although their arguments relate primarily to preanalytic variation, we note that, as clearly reported by Agarwal et al,[2] analytic variations also have a major potential impact, with the frequency of GDM diagnoses potentially halving or doubling depending on analytic variations within the acceptable (approximately 5%) range for well standardized glucose measurements.

However, we do not consider that these issues are relevant to interpretation of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) and HAPO follow-up studies as reported in Table 1 of our paper.[1] Pregnancy glucose

samples in HAPO were collected using a standard protocol, and all assays were conducted at a single central laboratory in Belfast. Only these standardized results were used for classification of participants as "GDM" or "non-GDM." Thus, although there is a valid argument for calibration of other glucose methodologies (both preanalytic and analytic) to the HAPO assay, sampling and laboratory variations are not relevant to the short- or long-term outcomes as reported in our paper.

On a global level, it is even more challenging to implement standardized glucose measurements in low-resource settings, where approximately 90% of the global burden of hyperglycemia in pregnancy lies[3] and where, in the absence of formal laboratories, handheld capillary glucose meters are the only practical means of testing available. Laboratory standardization is clearly an important issue, but global availability of affordable, precise, and accurate point-of-care glucose testing should arguably also receive a high priority. ■

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Emphasis on the off-label use of methotrexate for ectopic pregnancy

TO THE EDITORS: The article by Alur-Gupta et al presents a high level of research evidence on the use of methotrexate (MTX) in the treatment of ectopic pregnancy, with a 2-dose vs a single-dose protocol.[1] Many other studies have demonstrated similar effectiveness between MTX and surgical management in the treatment of stable ectopic pregnancies. However, the fact that the use of MTX in the treatment of ectopic pregnancy is officially "off label" should be emphasized, along with characterizing its administration as "mainstay of medical management" and "first-line therapy."

To date, MTX has no official license for the treatment of ectopic pregnancy from Food and Drug Administration, while since April 2018 the European Medicines Agency has started a review about MTX dosing errors, initiated at the request of Spain, under Article 31 of Directive 2001/83/EC.[2,3]

MTX's side effects derive by its irreversible inhibition action on the dihydrofolate reductase enzyme, which has a primary role in purine synthesis. Rapidly proliferating cells like bone marrow cells or gastrointestinal epithelial cells are the most vulnerable to MTX's effects, resulting in hemorrhage and a decrease in blood cell production. The short-term dosage schemes of MTX administration are associated with infrequent side effects in comparison with chronic treatment, but these may include hepatotoxicity, nephrotoxicity, and myelosuppression. Despite the low prevalence of these side effects, they can lead to severe and even fatal outcomes. In the literature, there are several case reports indicating severe toxicity and mortality following MTX administration in ectopic pregnancies. These have occurred in either single, double, or multi-dosage schemes, and most refer to patients with no preexisting medical problems.

In 2016 the French College of Gynecology and Obstetrics published an overview about the use of MTX in ectopic pregnancy, stating that it is an "off-label" use and concluding that the presented guidelines refer to a temporary recommendation for 3 years.[4] Similar warnings should always accompany the off-label use of MTX to help promote the drug's safe use, and raising awareness about every off-label use of a drug is critical, especially when it has been correlated with fatal toxicities. ■

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