

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 lies³ 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. ■

Professor Moshe Hod
Rabin Medical Center
Tel Aviv University
Tel Aviv-Yafo, Israel

Doctor Anil Kapur
World Diabetes Federation
Copenhagen, Denmark

Professor H. David McIntyre, MD
Mater Health and Mater Research
University of Queensland
Queensland, Australia

For the FIGO Working Group on Hyperglycemia in Pregnancy and the FIGO Pregnancy and Prevention of early NCD Committee

REFERENCES

1. Hod M, Kapur A, McIntyre HD. Evidence in support of the international association of diabetes in pregnancy study groups' criteria for diagnosing gestational diabetes worldwide in 2019. *Am J Obstet Gynecol* 2019 Jan, <https://doi.org/10.1016/j.ajog.2019.01.206>.
2. Agarwal MM, Dhath GS, Othman Y. Gestational diabetes mellitus prevalence: effect of the laboratory analytical variation. *Diabetes Res Clin Pract* 2015;109:493–9.
3. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. *Diabetes Res Clin Pract* 2014;103:176–85.

© 2019 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2019.02.042>

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. ■

Panagiotis Rigopoulos, BPharm, MSc
Ioannis Dardalas, BPharm, MSc
Chryssa Pourzitaki, MD, MSc, MHA, PhD
Department of Clinical Pharmacology
Faculty of Medicine, School of Health Sciences
Aristotle University of Thessaloniki
Thessaloniki, Greece
chpour@gmail.com

REFERENCES

1. Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. *Am J Obstet Gynecol* 2019 Jan 7. pii: S0002-9378(19)30004-3.
2. Food And Drug Administration. Methotrexate Injection, USP. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/011719s1171bl.pdf. Accessed April 9, 2019.
3. European Medicines Agency. EMA reviewing risk of dosing errors with methotrexate. EMA/215649/2018. Available at: https://www.ema.europa.eu/en/documents/referral/methotrexate-article-31-referral-review-started_en.pdf. Accessed April 9, 2019.

europa.eu/en/documents/referral/methotrexate-article-31-referral-review-started_en.pdf. Accessed April 9, 2019.

4. Marret H, Fauconnier A, Dubernard G, et al. Evidence-based evaluation and expertise of methotrexate off label use in gynecology and obstetrics: work of the CNGOF. *J Gynecol Obstet Biol Reprod (Paris)* 2015;44:230–6. [in French].

© 2019 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2019.02.043>

Can in utero fetal pacing cause cardiac complications?



TO THE EDITORS: I read with interest what seems to be the first-ever report of successful in utero transesophageal pacing.¹ The authors had successfully adopted a technique known to treat newborns with tachyarrhythmia to the fetus. Fetal transesophageal pacing was reasonably undertaken as a last resort to prevent the demise of the hydropic fetus after the failure of medical treatment. In 1995, we reported 3 cases of endoscopic delivery of surfactant to preterm fetuses in labor.²

The flexible fiberscope was inserted under constant endoscopic visual control to avoid possible trauma to the fetus and the mother. Surfactant was injected into the mouths of 3 preterm fetuses through a catheter placed through the biopsy channel of the fiberscope. Fetal heart rate tracings as well as neonatal and maternal outcome are reported for each case.

Clinical thinking at that time was that surfactant are to be delivered as early as possible.

Although the first 3 fetuses showed no major fetal heart rate irregularities during the procedure, we did note deep spontaneous decelerations in a fetus when the endoscope was located between the pharynx and esophagus, forcing us to

terminate the procedure. As more experience in the transesophageal approach to the fetus is being gained, these complications may be encountered. ■

Boris M. Petrikovsky, MD, PhD
Sunny Isles Medical Center
Miami, FL
bpetriko@gmail.com

The author reports no conflict of interest.

REFERENCES

1. Stinemann J, Maltret A, Haydar A, Stos B, Bonnet D. Successful in utero trans esophageal pacing for severe drug-resistant tachyarrhythmia. *Am J Obstet Gynecol* 2018;219(4):320–5.
2. Petrikovsky B, Lysikiewicz A, Markin LB, Slomko Z. In utero surfactant administration to preterm human fetuses using endoscopy. *Fetal Diagn Ther* 1995;10(2):127–30.

© 2019 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2019.03.006>