



RESPONSE TO COMMENT ON MEEK ET AL.

Reappearance of C-Peptide During the Third Trimester in Type 1 Diabetes Pregnancy: Pancreatic Regeneration or Fetal Hyperinsulinism? Diabetes Care 2021;44:1826–1834

Claire L. Meek,^{1,2,3} Richard A. Oram,⁴
 Timothy J. McDonald,^{4,5}
 Denice S. Feig,^{6,7}
 Andrew T. Hattersley,⁴ and
 Helen R. Murphy,^{2,8,9} on behalf of the
 CONCEPTT Collaborative Group*

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We read with interest the letter and study synopsis from Ivanisevic and Djelmis (1) and published descriptions ($n = \sim 30$) of their cohort of pregnant women with type 1 diabetes (T1D) (2). It is unclear how many of their participants had detectable C-peptide at baseline. Typically, <50% of women with T1D have detectable C-peptide in early pregnancy, suggesting residual β -cell function (3).

Among Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) participants, we identified three patterns in C-peptide trajectory (3). Group 1 (58%; $n = 74$) had undetectable C-peptide throughout pregnancy. Group 2 (17%; $n = 22$) had detectable C-peptide initially, 25–200 pmol/L, which remained detectable throughout pregnancy. They had lower BMI as well as later onset and shorter duration of T1D and favorable glycemia. Our novel and unexpected finding identified a subgroup of women with undetectable C-peptide at baseline and 24 weeks that became

detectable at low concentration, 4–26 pmol/L, at 34 weeks of gestation (group 3; 24%; $n = 31$). There was no evidence of fetal C-peptide crossing the placenta in group 1. The relatively higher concentrations of maternal C-peptide would have masked any effect in group 2. Group 3 women had suboptimal glycemia and higher cord C-peptide, consistent with fetal hyperinsulinemia, and striking rates of neonatal morbidity. We therefore concluded that fetal C-peptide may have crossed the placenta into maternal circulation in late pregnancy. As this pattern was only evident in 24% of pregnant women, we are unsurprised that maternal and cord C-peptide were not correlated in the cohort described by Ivanisevic and Djelmis (1) as a whole.

Ivanisevic and Djelmis (1) identified that residual β -cell function was associated with improved glycemia, reduced macrosomia, and increased maternal C-peptide during pregnancy. We found that among group 2 women, maternal serum C-peptide levels tended to fall, possibly due to vascular changes during

pregnancy. Previous work demonstrated that C-peptide concentrations are highly variable both within and between women during pregnancy (3,4). Larger samples are needed to comment on pregnancy outcomes, but it is well established that women with shorter duration of T1D, who are most likely to have endogenous insulin secretion, have favorable antenatal glycemia and fewer neonatal complications (5).

Ivanisevic and Djelmis (1) suggested immunological tolerance augments β -cell function in pregnancy. We considered this and measured GAD, islet cell, IA2, and ZnT8 autoantibodies at 12, 24, and 34 weeks. Participants with detectable C-peptide (group 2) were more likely to still have detectable GAD or islet cell antibodies than women in groups 1 and 3. However, diabetes-related autoantibody positivity was stable for all groups throughout pregnancy, with no evidence of new immune phenomena, which might occur if quiescent β -cells became functional again.

¹The Wellcome Trust-MRC Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Addenbrooke's Hospital, Cambridge, U.K.

²Wolfson Diabetes and Endocrinology Clinic, Cambridge University Hospitals, Addenbrooke's Hospital, Cambridge, U.K.

³Department of Clinical Biochemistry, Cambridge University Hospitals, Addenbrooke's Hospital, Cambridge, U.K.

⁴Department of Diabetes Research, University of Exeter, Royal Devon and Exeter Hospital, Exeter, U.K.

⁵Academic Department of Blood Sciences, Royal Devon and Exeter NHS Foundation Trust, Exeter, U.K.

⁶Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, Canada

⁷Lunenfeld-Tanenbaum Research Institute, Toronto, Canada

⁸Department of Women and Children's Health, King's College London, St. Thomas' Hospital, London, U.K.

⁹Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, U.K.

Corresponding author: Claire Meek, clm70@cam.ac.uk

*A complete list of CONCEPTT Collaborative Group members can be found in the APPENDIX of the original article by Meek et al. (<https://doi.org/10.2337/dci21-0028>).

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In conclusion, transplacental movement of small quantities of C-peptide during late gestation is the most plausible explanation for the novel appearance of C-peptide in maternal serum in late pregnancy. However, other unmeasured factors stimulating maternal and/or fetal β -cell function, or nonpancreatic cells producing insulin or related fragments during pregnancy, cannot be excluded. Larger studies with longitudinal C-peptide assessment before, during, and after pregnancy are warranted to further investigate these unexpected findings among a subset of women with T1D.

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