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

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We read with interest the letter and study synopsis from Ivanisevic and Djelmis (1) and published descriptions (n = ~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.

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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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References

1. Ivanisevic M, Djelmis J. Comment on Meek et al. Reappearance of C-peptide during the third trimester of pregnancy in type 1 diabetes: pancreatic regeneration or fetal hyperinsulinism? Diabetes Care 2021;44:1826–1834 (Letter). Diabetes Care 2022;45:e41–e42. DOI: 10.2337/dc21-2072

2. Ivanisevic M, Delmis K, Herman M, Horvaticek M, Berberovic E, Djelmis J. Concentrations of fatty acids among macrosomic neonates delivered by healthy women and women with type 1 diabetes mellitus. Int J Gynaecol Obstet 2020;149:309–317

3. Meek CL, Oram RA, McDonald TJ, Feig DS, Hattersley AT, Murphy HR; CONCEPTT Collaborative Group. Reappearance of C-peptide during the third trimester of pregnancy in type 1 diabetes: pancreatic regeneration or fetal hyperinsulinism? Diabetes Care 2021;44:1826–1834

4. Murphy HR, Elleri D, Allen JM, Simmons D, Nodale M, Hovorka R. Plasma C-peptide concentration in women with type 1 diabetes during early and late pregnancy. Diabet Med 2012;29:e361–e364

5. Murphy HR, Howgate C, O'Keefe J, et al.; National Pregnancy in Diabetes (NPID) advisory group. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. Lancet Diabetes Endocrinol 2021;9:153–164