Reappearance of C-Peptide During the Third Trimester of Pregnancy in Type 1 Diabetes: Pancreatic Regeneration or Fetal Hyperinsulinism?

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OBJECTIVE

We assessed longitudinal patterns of maternal C-peptide concentration to examine the hypothesis of β-cell regeneration in pregnancy with type 1 diabetes.

RESEARCH DESIGN AND METHODS

C-peptide was measured on maternal serum samples from 127 participants (12, 24, and 34 weeks) and cord blood during the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT). C-peptide was measured using a highly sensitive direct and solid-phase competitive electrochemiluminescent immunoassay.

RESULTS

Three discrete patterns of maternal C-peptide trajectory were identified: pattern 1, undetectable throughout pregnancy, $n = 74$ (58%; maternal C-peptide <3 pmol/L); pattern 2, detectable at baseline, $n = 22$ (17%; maternal C-peptide 7–272 pmol/L at baseline); and pattern 3, undetectable maternal C-peptide at 12 and 24 weeks, which first became detectable at 34 weeks, $n = 31$ (24%; maternal C-peptide 4–26 pmol/L at 34 weeks). Baseline characteristics and third trimester glucose profiles of women with pattern 1 and pattern 3 C-peptide trajectories were similar, but women in pattern 3 had suboptimal glycemia (50% time above range) at 24 weeks' gestation. Offspring of women with pattern 3 C-peptide trajectories had elevated cord blood C-peptide (geometric mean 1,319 vs. 718 pmol/L; $P = 0.007$), increased rates of large for gestational age (90% vs. 60%; $P = 0.002$), neonatal hypoglycemia (42% vs. 14%; $P = 0.001$), and neonatal intensive care admission (45% vs. 23%; $P = 0.023$) compared with pattern 1 offspring.

CONCLUSIONS

First maternal C-peptide appearance at 34 weeks was associated with mid-trimester hyperglycemia, elevated cord blood C-peptide, and high rates of neonatal complications. This suggests transfer of C-peptide from fetal to maternal serum and is inconsistent with pregnancy-related β-cell regeneration.

Type 1 diabetes in pregnancy is associated with increased neonatal complications, including large for gestational age, neonatal hypoglycemia, and admission to the

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**A complete list of CONCEPTT Collaborative Group members can be found in APPENDIX 1.*

neonatal intensive care unit (NICU) (1). Despite recent advances in diabetes technology and improved maternal glycemia associated with the use of continuous glucose monitoring (CGM), neonatal outcomes remain suboptimal in this population (2–4). Fetal hyperinsulinism is a physiological response to maternal hyperglycemia and mediates many of these neonatal complications (5).

Pregnancy is considered to be a time when β-cell function and/or mass may increase in response to the rising gestational insulin resistance. Rodents expand β-cell numbers, and one pancreatic autopsy study of pregnant women suggested a 1.4 times rise in β-cell area with increased numbers of small islets (6). The small number of human studies of serum C-peptide concentration during pregnancy have yielded conflicting results (7–10). We previously showed no rise in maternal C-peptide concentration in 10 pregnant women studied under strict experimental conditions during early (12–16 weeks') and late (28–32 weeks') gestation (7). Another study, performed in routine clinical care, showed a rise in maternal C-peptide, including in women with previously undetectable C-peptide (8). Newer highly sensitive ELISAs and electrochemiluminescent assays have improved the ability to study small changes in serum C-peptide, even in established type 1 diabetes, and allow more detailed analysis of gestational changes in β-cell function across pregnancy.

The aim of this study was to assess longitudinal patterns of maternal C-peptide concentration using a highly sensitive electrochemiluminescent assay to examine the hypothesis of pregnancy-induced β-cell regeneration in women with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) was a multinational, randomized controlled trial to assess the effects of real-time CGM in comparison with standard care (capillary blood glucose monitoring) in pregnant women with type 1 diabetes (ClinicalTrials.gov NCT01788527; trial registered 11 February 2013). All women gave written informed consent. Further details on study design, eligibility criteria, end points, and results are given elsewhere (1). The CONCEPTT trial included 225 women recruited in early pregnancy or prepregnancy who completed the study with a liveborn singleton infant. A total of 127 out of 225 women gave a voluntary additional nonfasting serum sample for the biorepository at 12, 24, and 34 weeks for C-peptide analysis and have been included in this analysis. The sample was rapidly processed and stored frozen at −80°C prior to batch analysis at the end of the study. Outcome definitions used in the CONCEPTT study were adjudicated by the steering group and are provided in Appendix 2. Gestational age at delivery was based upon ultrasound measurements in early pregnancy (∼12 weeks).

Cord blood C-peptide was measured using a Dynacare test (Brampton, Ontario, Canada) on the Siemens IMMULITE 2000 platform (Siemens Healthineers, Cambridge, U.K.). This is a solid-phase, competitive chemiluminescent immunoassay. Both intra-assay and interassay coefficients of variation were <6% throughout the concentration range. Maternal serum C-peptide was measured using a highly sensitive direct electrochemiluminescence immunoassay with a mouse monoclonal anti–C-peptide antibody (Roche Diagnostics, Mannheim, Germany) on an E170 analyzer (Roche, Manheim, Germany) at the Academic Department of Blood Sciences, Royal Devon and Exeter NHS Foundation Trust. The limit of detection is 3.3 pmol/L with a coefficient of variation of <4% at across the reported range of picomoles per liter. This assay is capable of measuring extremely low levels of C-peptide with superior analytical performance compared with many other highly sensitive assays in common use. It is described more fully elsewhere (11).

Analysis

Our primary objective was to assess whether there was evidence for an increase in maternal C-peptide concentration during pregnancy. We also aimed to identify patterns of maternal C-peptide change during pregnancy by stratifying CONCEPTT participants into categories depending upon their baseline maternal serum C-peptide and the trajectory of gestational changes. We planned to use unadjusted logistic regression to compare maternal characteristics, antenatal glycemia, and pregnancy outcomes between women with and without detectable C-peptide in maternal serum and considered undetectable C-peptide in maternal serum (pattern 1) to be the reference category.

We described continuous data using mean ± SD and categorical data as *n* (%) as appropriate. Data regarding birth weight were analyzed as customized percentiles (adjusted for sex, gestational age, ethnicity, and maternal BMI) (12,13). C-peptide concentrations in maternal serum that were below the limit of detection (<3 pmol/L) were considered equal to the limit of detection for analysis and graphical representation. C-peptide concentrations in maternal and cord blood were converted logarithmically (base 10) prior to analysis. Although often cord C-peptide >90th centile is considered consistent with fetal hyperinsulinism in other populations (for example, obese pregnancy or in gestational diabetes), we considered this to be inappropriate for our population, as 61.8% of infants were large for gestational age at birth, and therefore, hyperinsulinism was likely to affect a higher proportion of infants. There was a natural inflection point at the 75th centile (1,415.5 pmol/L), which we took as our threshold. Student *t* tests were used to assess basic comparisons between groups classified according to maternal C-peptide patterns. Linear and logistic regression were used to assess the associations between maternal C-peptide pattern with continuous or categorical maternal and neonatal outcomes. Missing data were not imputed.

Data and Resource Availability

The data that support the findings of this study are available on request from the CONCEPTT trial steering committee via the senior author (H.R.M., helen.murphy@uea.ac.uk). The data are not publicly available as they contain information that could compromise research participant privacy/consent.

RESULTS

Women included in this study ($n = 127$) had type 1 diabetes with mean age of onset at 14.9 (SD 7.9) years and duration 16.9 (SD 7.7) years (Table 1). Included women were statistically similar to the whole CONCEPTT cohort (Supplementary Table 1). The mean age and BMI at enrolment were 31.8 years

Table 1—Characteristics of study participants

	CONCEPTT biorepository participants (n = 127)	Pattern 1, undetectable maternal C-peptide (n = 74) (58.3%)	Pattern 2, detectable maternal C-peptide (n = 22) (17.3%)	Pattern 3, maternal C-peptide first detected at 34 weeks (n = 31) (24.4%)
Baseline characteristics				
Maternal age, years	31.8 ± 4.4	31.8 ± 4.4	33.1 ± 3.8	30.8 ± 4.9
Prepregnancy BMI, kg/m^2	25.7 ± 4.6	26.6 ± 4.9	23.6 ± 2.5	24.9 ± 4.6
Duration of T1D, years	16.9 ± 7.7	18.6 ± 7.8	10.6 ± 5.7	17.3 ± 6.7
Age of onset of T1D, years	14.9 ± 7.9	13.2 ± 7.0	22.5 ± 7.4	13.5 ± 7.0
Insulin pump,#	60/127 (47.2)	36/74 (48.7)	9/22 (40.9)	15/31 (48.4)
Total daily insulin dose at 36 weeks, units/kg	84.4 ± 36.2	87.4 ± 41.8	77.3 ± 22.9	82.4 ± 28.5
Maternal serum C-peptide, pmol/L				
At 12 weeks	14.4 ± 41.8	<3.0 ± 0.0	68.8 ± 82.1	<3.0 ± 0.0
At 24 weeks	12.7 ± 37.1	<3.0 ± 0.0	59.0 ± 74.4	<3.0 ± 0.0
At 34 weeks	12.0 ± 22.8	<3.0 ± 0.0	47.0 ±38.8	8.8 ± 5.3
Glycemia at 12 weeks				
HbA_{1c}, %	6.9 ± 0.6	6.9 ± 0.6	6.8 ± 0.5	6.8 ± 0.7
HbA_{1c}, mmol/mol	51.5 ± 6.3	51.9 ± 6.3	50.7 ± 5.3	51.1 ± 7.1
Mean CGM glucose, mg/dL	135 ± 19.8	135 ± 21.6	133 ± 19.8	137 ± 21.6
Mean CGM glucose, mmol/L	7.5 ± 1.2	7.5 ± 1.2	7.4 ± 1.1	7.6 ± 1.2
CGM time in range, %	51.3 ± 13.0	51.1 ± 13.1	54.3 ± 13.8	49.6 ± 12.3
CGM time above range, %	39.9 ± 14.4	39.7 ± 14.2	38.2 ± 14.7	41.6 ± 15.0
CGM time below range, %	8.8 ± 6.5	9.3 ± 6.5	7.3 ± 7.0	8.8 ± 6.4
Glycemia at 24 weeks				
HbA_{1c}, %	6.3 ± 0.6	6.3 ± 0.6	6.2 ± 0.6	6.4 ± 0.7
HbA_{1c}, mmol/mol	45.2 ± 6.8	44.8 ± 6.5	44.1 ± 6.7	46.8 ± 7.2
Mean CGM glucose, mg/dL	130 ± 19.8	137 ± 19.8	132 ± 18.0	146 ± 25.2
Mean CGM glucose, mmol/L	7.7 ± 1.2	7.6 ± 1.1	7.3 ± 1.0	8.1 ± 1.4
CGM time in range, %	50.9 ± 15.1	51.9 ± 13.9	55.0 ± 14.8	45.3 ± 16.8
CGM time above range, %	43.5 ± 16.5	42.7 ± 15.3	38.0 ± 14.8	49.8 ± 18.9
CGM time below range, %	5.5 ± 5.5	5.3 ± 4.3	6.8 ± 9.0	5.0 ± 5.3
Glycemia at 34 weeks				
HbA_{1c}, %	6.4 ± 0.6	6.4 ± 0.6	6.3 ± 0.6	6.5 ± 0.6
HbA_{1c}, mmol/mol	46.4 ± 6.6	46.1 ± 6.6	45.7 ± 6.2	47.7 ± 7.1
Mean CGM glucose, mg/dL	131 ± 19.8	123 ± 14.4	121 ± 18.0	128 ± 19.8
Mean CGM glucose, mmol/L	6.9 ± 0.9	6.8 ± 0.8	6.7 ± 1.0	7.1 ± 1.1
CGM time in range, %	64.7 ± 14.1	65.2 ± 13.7	66.6 ± 15.9	62.3 ± 13.9
CGM time above range, %	30.4 ±14.0	29.1 ± 13.2	29.2 ± 15.6	34.0 ± 14.1
CGM time below range, %	4.9 ± 4.8	5.7 ± 5.2	4.2 ± 5.5	3.8 ± 3.1
Pregnancy outcomes				
Cesarean section	86/127 (67.7)	48/74 (64.9)	13/22 (59.1)	25/31 (80.6)
Vaginal delivery	31/127 (24.4)	19/74 (25.7)	8/22 (36.4)	4/31 (12.9)
Large for gestational age	83/127 (65.4)	44/74 (59.5)	11/22 (50.0)	28/31 (90.3)
Respiratory distress	6/127 (4.7)	2/74 (2.7)	No events	4/31 (12.9)
Neonatal hypoglycemia	27/127 (21.3)	10/74 (13.5)	4/22 (18.2)	13/31 (41.9)
NICU admission	37/127 (29.1)	17/74 (23.0)	6/22 (27.3)	14/31 (45.2)
Hyperbilirubinemia	31/127 (24.4)	16/74 (21.6)	3/22 (13.6)	12/31 (38.7)
Cord blood available	85/127 (66.9)	46/74 (62.2)	17/22 (78.9)	22/31 (71.0)
Cord blood C-peptide >75th centile	19/85 (22.4)	6/46 (13.0)	2/17 (11.8)	11/22 (50.0)
Cord blood C-peptide, pmol/L*	802 (55–4,965)	718 (172–4,551)	570 (160–4,518)	1,319 (55–4,965)

Data are shown as mean ± SD or n (%). Data are shown for all women who gave a biorepository sample for C-peptide analysis (n = 127) and subdivided into groups according to the pattern of maternal serum C-peptide. Pattern 1: undetectable maternal serum C-peptide throughout pregnancy. Pattern 2: detectable maternal serum C-peptide at 12 weeks' gestation. Pattern 3: undetectable maternal serum C-peptide at 12 and 24 weeks, which first became detectable at 34 weeks' gestation. #Among women on insulin pumps, we have detailed insulin regimen information available for 90 out of 110 women. A total of 41 out of 90 (45.6%) were taking lispro, and 49 out of 90 (54.4%) were taking aspart at 36 weeks. Among women who were using multiple daily injections (MDI), information is available for 108 out of 115 women. For women on MDI, long-acting insulin use included glargine (50 out of 108; 46.3%), detemir (48 out of 108; 44.4%), NPH insulin (4 out of 108; 3.7%), human insulin (2 out of 108; 1.9%), and degludec (2 out of 108; 1.9%). Short-acting insulin use for women on MDI included lispro (41 out of 108; 38.0%) and aspart (67 out of 108; 62.0%). *Geometric mean and range. The CGM time in range, time above range, and time below range were defined according to international recommendations as time in range 3.5–7.8 mmol/L (63–140 mg/dL) and time below range <3.5 mmol/L (<63 mg/dL) (17).

(SD 4.4) and 25.7 kg/m^2 (SD 4.6), respectively. At baseline, HbA_{1c} was 6.9% (SD 6.6) or 51.5 mmol/mol (SD 6.3), CGM time in range 51.3% (SD 13.0), time above range 39.9% (SD 14.4), time below range 8.8% (SD 6.5), and mean CGM glucose 129 mg/dL (SD 19.8). Most women had large-for-gestational-age infants (83 out of 127; 65.4%) and were delivered by cesarean section (86 out of 127; 67.7%). Common neonatal complications included neonatal hypoglycemia requiring intravenous dextrose (27 out of 127; 21.3%) and hyperbilirubinemia (31 out of 127; 24.4%), with almost one-third admitted for neonatal intensive care (37 out of 127; 29.1%). Cord blood was only available from a proportion of the cohort (85 out of 127; 66.9%).

Three longitudinal patterns of maternal C-peptide trajectory were identified (Table 1 and Fig. 1). Pattern 1, which included women with undetectable C-peptide in maternal serum at all time points, was the most common (74 out of 127; 58.3%; maternal C-peptide <3 pmol/L). Pattern 2 included women with detectable C-peptide at 12 weeks in maternal serum and was less common (22 out of 127; 17.3%; maternal C-peptide mean 68.8 ± 82.1 [range 7–272] pmol/L at 12 weeks, mean 59.0 ± 74.4 [range 3–308] pmol/L at 24 weeks, and 47.0 ± 38.8 [range 3–134] pmol/L at 34 weeks).

Pattern 3 included women with undetectable C-peptide in maternal serum at 12 and 24 weeks, with appearance of detectable maternal C-peptide for the first time at 34 weeks' gestation (31 out of 127; 24.4%; maternal C-peptide <3 pmol/L at 12 and 24 weeks and 4–26 pmol/L at 34 weeks). Their mean C-peptide concentrations were lower than women with detectable C-peptide throughout pregnancy (47.0 ± 38.8 vs. 8.8 ± 5.3 at 34 weeks). Women with pattern 2 had marked interindividual variability in C-peptide. No women with undetectable C-peptide in maternal serum at 12 weeks had detectable C-peptide in maternal serum at 24 weeks (Fig. 1).

We compared baseline maternal characteristics, antenatal glycemia, and pregnancy outcomes among the three groups (Table 1 and Supplementary Tables 2 and 3, and Figs. 1 and 2). Compared with women with undetectable C-peptide in maternal serum throughout pregnancy (pattern 1), women with detectable C-peptide in maternal serum (pattern 2) had a lower prepregnancy BMI (mean ± SD: 23.6 ± 2.5 vs. 26.6 ± 4.9 kg/m^2; $P = 0.006$), older age at diabetes diagnosis (22.5 ± 7.4 vs. 13.2 ± 7.0 years; $P < 0.001$), and a shorter duration of type 1 diabetes (10.6 ± 5.7 vs. 18.6 ± 7.8 years; $P < 0.001$). For women with detectable C-peptide in maternal serum during the first trimester, there was a trend for falling maternal C-peptide throughout pregnancy (mean ± SD: 68.8 ± 82.1 pmol/L at 12 weeks; 59.0 ± 74.3 pmol/L at 24 weeks; and 47.0 ± 38.9 pmol/L at 34 weeks; 12- vs. 34-week C-peptide, $P = 0.1$). Despite their favorable maternal characteristics and detectable C-peptide, glycemic control as assessed by HbA_{1c} and CGM metrics was comparable between women in pattern 1 and pattern 2 at all time points (Table 1 and Supplementary Tables 2). Their pregnancy outcomes were also similar, although obstetric and neonatal comparisons are limited by the small numbers of women ($n = 22$) in pattern 2 (Table 1 and Supplementary Tables 2 and 3). Total daily insulin doses were similar for women in patterns 1, 2, and 3 (Supplementary Fig. 1).

Women with undetectable maternal C-peptide throughout pregnancy (pattern 1) and detectable maternal C-peptide at 34 weeks only (pattern 3) had comparable baseline characteristics and first and third trimester glycemic profiles (Table 1). However, for CGM metrics, maternal time in range 63–140 mg/dL (3.5–7.8 mmol/L) at 24 weeks' gestation was significantly lower in women in pattern 3 (45.3 ± 16.8%) compared with women in pattern 1 (51.9 ± 13.9%; $P = 0.050$) and pattern 2 (55.0 ± 14.8%; $P = 0.037$). Women in pattern 3 also had a significantly higher time above range (49.8 ± 18.9 vs. 38.0 ± 14.8%; $P = 0.021$) and a higher mean CGM glucose (146 ± 25.2 vs. 132 ± 18.0 mg/dL [8.1 ± 1.4 vs. 7.3 ± 1.0 mmol/L]; $P = 0.027$) compared with

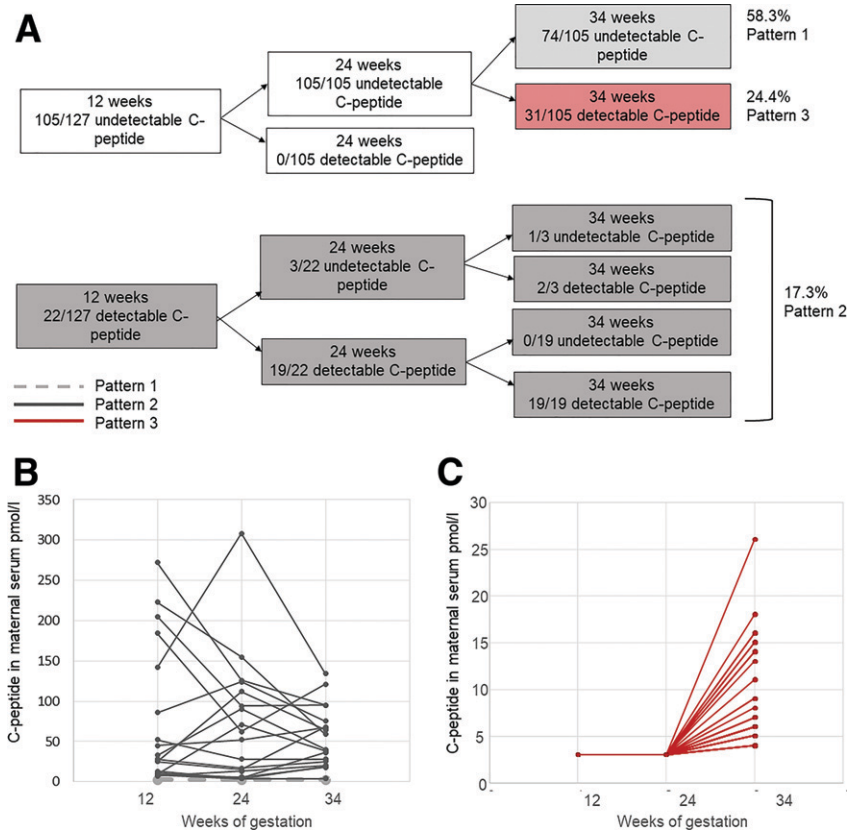

Figure 1—Longitudinal patterns of maternal serum C-peptide change in pregnancy (*A* and *B*) with more detail of women in pattern 3 (*C*). Pattern 1: undetectable maternal serum C-peptide throughout pregnancy. Pattern 2: detectable maternal serum C-peptide at 12 weeks' gestation. Pattern 3: undetectable maternal serum C-peptide at 12 and 24 weeks, which became detectable at 34 weeks' gestation.

women in pattern 2 at 24 weeks (Fig. 2).

Offspring of women with first appearance of C-peptide in maternal serum at 34 weeks had higher cord blood C-peptide concentration (available in a subset only; geometric mean 1,319 vs. 718 pmol/L; $P = 0.007$). Logistic regression results are given in Supplementary Table 3. Compared with pattern 1 offspring, infants of pattern 3 women had striking rates of large for gestational age (90.3% vs. 59.5%, pattern 1; $P = 0.002$), neonatal hypoglycemia (41.9% vs. 13.5%; $P = 0.001$), respiratory distress (12.9 vs. 2.7%; $P = 0.040$), and admission to NICU (45.2 vs. 23.0%; $P = 0.023$) (Table 1 and Supplementary Tables 2 and 3, and Fig. 2).

The new appearance of maternal serum C-peptide, when expressed as a categorical variable, was able to improve the prediction of suboptimal outcomes in women with type 1 diabetes in pregnancy compared with the use of HbA_{1c} at 24 weeks alone (Supplementary Fig. 2).

CONCLUSIONS

We found three discrete patterns of C-peptide trajectories in maternal serum in pregnant women with type 1 diabetes. Most women (58%) had undetectable maternal serum C-peptide levels throughout pregnancy. A smaller second group included 15% of women with detectable maternal serum C-peptide levels throughout pregnancy. They were characterized by favorable maternal characteristics lower BMI, later onset, and shorter duration of type 1 diabetes and improved glycemic control at 24 weeks, suggesting that they may still have had some functioning β-cells. However, their serum C-peptide levels tended to fall during pregnancy, possibly due to changes in maternal vascular volume, and their later gestation glycemic outcomes were comparable to women with and without detectable C-peptide. A third group of women had the unexpected first appearance of C-peptide in maternal serum at 34 weeks' gestation. This occurred in 25% of women and was associated with hyperglycemia at 24 weeks' gestation, higher cord C-peptide, and striking rates of neonatal complications attributed to excess fetal pancreatic insulin secretion, including 90% large-for-gestational-age neonates.

We previously found no longitudinal differences in fasting or meal-stimulated C-peptide production in maternal serum between early (12–16 weeks) and late pregnancy (28–32 weeks) in 10 women with type 1 diabetes using newer-generation C-peptide assay methodology under strictly standardized laboratory conditions (7). However, Nielsen et al. (8) measured C-peptide in a larger cohort of 90 Danish women with type 1 diabetes at six time points (8, 14, 21, 27, and 33 weeks and postpartum). They found detectable C-peptide in 43% of women during early pregnancy, rising to 97% by 33 weeks' gestation, with the median C-peptide concentration increasing from 6 to 11 pmol/L. The largest increase in the number of women with detectable C-peptide and in median C-peptide concentration occurred in late pregnancy (27 and 33 weeks' gestation). The proportion of women with detectable C-peptide and the median C-peptide concentration were similar between early pregnancy and postpartum periods. The authors did not address the disappearance and/or postpartum decline in C-peptide concentration but commented that C-peptide "did not cross the placenta in either direction." Another report in 10 pregnant women with type 1 diabetes also suggested an increase in insulin secretion before 10 weeks' gestation (9). However, the precision and sensitivity of C-peptide assays has improved in recent years, so earlier studies may not have consistently measured C-peptide at low concentrations. The assay used for maternal serum C-peptide quantification in this study allows maternal serum C-peptide to be measured at very low concentrations, with robust analytical performance and good reproducibility (11). Relatively few data exist regarding cord C-peptide in pregnancy with type 1 diabetes using modern assay technology.

Our study suggests that the first appearance of C-peptide in maternal serum at 34 weeks' gestation is likely of fetal origin, due to its associations with

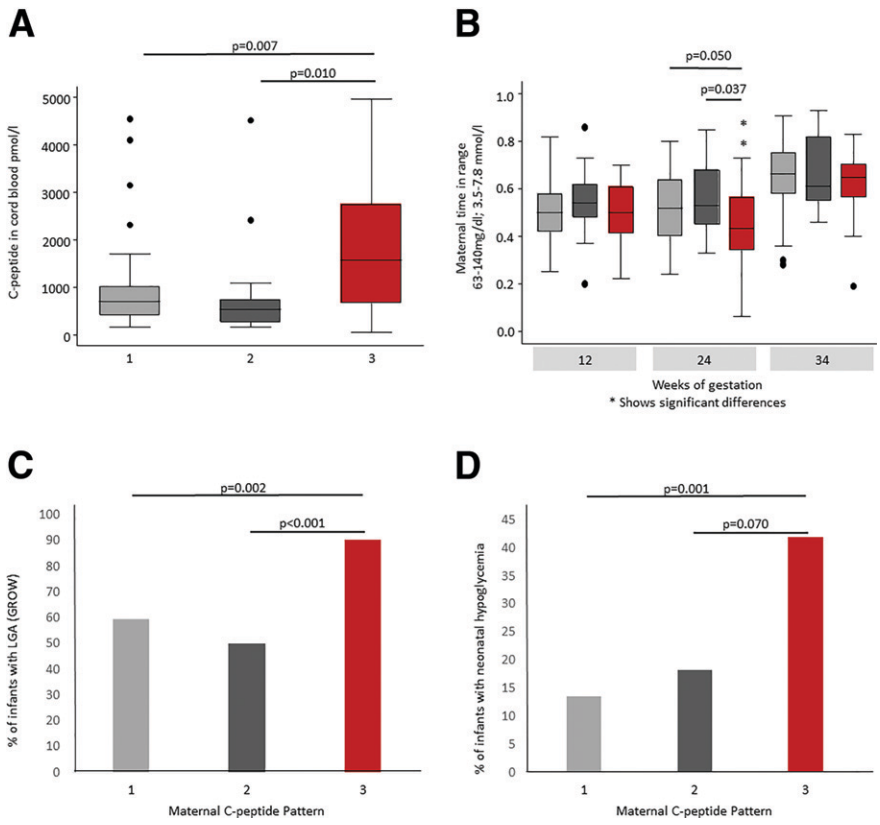

Figure 2—Associations between maternal serum C-peptide patterns 1–3 and cord blood C-peptide (*A*), maternal time-in-range (*B*; 3.5–7.8 mmol/L [63–140 mg/dL]), large for gestational age (LGA) (*C*), and neonatal hypoglycemia (*D*). Pattern 1: undetectable maternal C-peptide throughout pregnancy. Pattern 2: detectable maternal serum C-peptide at 12 weeks' gestation. Pattern 3: undetectable maternal serum C-peptide at 12 and 24 weeks, which first became detectable at 34 weeks' gestation.

higher cord blood C-peptide and striking rates of neonatal complications related to hyperinsulinism. This raises the possibility that previous reports of increased C-peptide in pregnancy with type 1 diabetes may have also been caused by fetal transfer to the maternal circulation rather than maternal β-cell hyperplasia. Further information is needed about the elimination of C-peptide from the fetus, distribution in fetal body fluids and amniotic fluid, renal clearance rates, and the proportion of peptide that might cross the placenta for accurate assessment of fetal to maternal transfer. However, preliminary mathematical modeling (Appendix 3) suggests that transfer of C-peptide from the fetus could feasibly result in measurable maternal plasma C-peptide concentrations in mothers with type 1 diabetes.

Our study also highlights the limitations in our understanding of fetal-to-maternal transport in the placenta. Although it is generally believed that intact insulin and C-peptide do not cross the placenta, these data are based upon early studies. The report by Gerö et al. in 1982 (14) used older C-peptide assays and does not exclude the possibility of fetal–maternal transfer of C-peptide or related fragments at low concentrations. A study in rhesus monkeys demonstrated that immunoreactive C-peptide fragments could cross the placenta from the maternal to fetal circulation (15). It is unclear if the first appearance of detectable C-peptide in maternal blood at 34 weeks' gestation represents intact C-peptide or immunoreactive fragments only. Previous work demonstrating that C-peptide may have biological roles influencing insulin action and degradation suggests this may be a fruitful avenue for further study (16).

This study raises a number of other questions. Pregnancies with fetal hyperinsulinism were generally similar to those without hyperinsulinism, having comparable duration of diabetes and glycemic status at 12 and 34 weeks, but with higher mean glucose, higher time above range, and a lower CGM time in range (but not HbA_{1c}) at 24 weeks. It is therefore possible that maternal hyperglycemia at 24 weeks, or increasing hyperglycemia between 12 and 24 weeks' gestation, might be important for the development of fetal hyperinsulinism. This limited improvement in maternal glycemia between 12 and 28–30 weeks is apparent from recent data showing that most women do not achieve the CGM time in range targets until the final weeks of pregnancy (17–19). Increased use of CGM continuously throughout pregnancy will facilitate more detailed longitudinal glycemic assessment. It is also possible that the fetal response to maternal hyperglycemia affects the degree of fetal hyperinsulinism (20,21).

Alternatively, unmeasured factors stimulating both maternal and fetal β-cell function, causing simultaneous maternal and fetal C-peptide release or other nonpancreatic cells producing insulin during pregnancy, cannot be excluded. Increased maternal β-cell function would be beneficial in pregnancy with type 1 diabetes, but there was no evidence of benefit in group 3. It is also possible that women in pattern 2 had enhanced β-cell function, but larger studies are required in women with detectable C-peptide to better understand the apparent decreasing maternal C-peptide concentration across gestation and its impacts on glycemic and pregnancy outcomes. Glucose is considered the most important insulin secretagogue, and very few nutrients are able to initiate insulin secretion in the absence of glucose. Several amino acids and fatty acids can amplify glucose-stimulated insulin secretion (reviewed in Rorsman and Ashcroft [22]). Situations in which β-cells are unable to demonstrate glucose-stimulated insulin secretion but demonstrate an insulin response to other nutrients have not, to our knowledge, been described in type 1 diabetes. The amino acid leucine can stimulate insulin release and could feasibly be responsible for this phenomenon. However, dietary information from a subset of CONCEPTT participants ($n = 94$) suggests that maternal antenatal protein intake was not higher than expected in the general population (mean protein intake 69 g or 17% of daily food energy; range 11–31%) (23). Furthermore, no consistent associations were found between leucine intake and maternal or cord C-peptide concentration (24). It is also possible that the new appearance of C-peptide in maternal serum is caused by problems in the placenta, which regulates crucial hormones. Further assessment of maternal C-peptide in pregnancy with type 1 diabetes, with placental histology and postpartum C-peptide trajectory (25) for comparison, would be useful. We cannot exclude the possibility that the C-peptide measured in this study is coming from an ectopic source, but this seems an unlikely explanation for one in four pregnant women.

We consider the first appearance of C-peptide in maternal serum at 34 weeks to be most likely due to fetal-to-maternal C-peptide transfer. It is also possible that this process occurred in some women with detectable C-peptide throughout pregnancy (e.g., those in group 2). These women have higher C-peptide concentrations in maternal serum, possibly reflecting some residual β-cell function as well as fetal-to-maternal C-peptide transfer. In embryonic development, pancreatic β-cells form at 7–8 weeks and begin to secrete insulin at 12–14 weeks' gestation (26). It is possible that the fetus of a mother with type 1 diabetes might have altered β-cell development, with capacity for insulin secretion in advance of this, but we consider it unlikely that fetal β-cell mass would be sufficiently large or functional at 12 weeks to provide measurable C-peptide in the maternal circulation.

Our study benefited from longitudinal measurements of maternal serum C-peptide in 127 pregnant women with type 1 diabetes with detailed CGM glycemic profiles and paired cord blood C-peptide for the majority of the cohort. Maternal C-peptide concentration was measured using an established and highly-sensitive assay with robust performance (11). There were some limitations; we did not have cord blood samples from all pregnancies, and detailed glycemic assessments using CGM were only available at 12, 24, and 34 weeks' gestation with no postpartum C-peptide measurement and no data about longer-term consequences of offspring hyperinsulinism. There were no intrapartum maternal samples taken around the time of delivery (~37 weeks) for direct comparison with cord blood C-peptide. We also did not have prepregnancy samples for the majority of women and cannot exclude an early first trimester rise in maternal β-cell function, as has been reported elsewhere (9,27). We also lacked simultaneous plasma or serum glucose data and details regarding the time of day for maternal

samples and timing in relation to the last meal, but did previously report substantial diurnal variability in maternal C-peptide concentration across the 24-h day (7).

Although the Pedersen hypothesis explains the pathology of diabetes in pregnancy, it has not been possible to measure fetal hyperinsulinism at a time point that could still influence clinical management. Previous attempts by Weiss et al. (28) and Carpenter et al. (29) using amniotic fluid sampling were effective but challenging to implement clinically on a large scale. Our findings suggest that increases in maternal C-peptide at 34 weeks could provide an opportunity for more precise monitoring of the hyperinsulinemic fetus. If confirmed by others, third trimester maternal serum C-peptide could be used to assess fetal metabolic function and predict neonatal complications in mothers with undetectable C-peptide in early pregnancy, especially those with midgestation hyperglycemia. As highly sensitive C-peptide assays become more widely available, this biomarker has potential for clinical use. Further improvements to C-peptide assay performance may also allow better characterization of women with detectable and undetectable C-peptide.

Future work is needed to assess if maternal C-peptide has potential as a biomarker above and beyond CGM time-in-range metrics to facilitate early identification of fetal hyperinsulinism. The detection of fetal hyperinsulinism could facilitate targeted interventions; for example, more stringent glycemic targets (17), automated insulin delivery, improved delivery planning (30), or specific perinatal protocols such as neonatal CGM (31) or prophylaxis with buccal mucosal glucogel to prevent neonatal hypoglycemia (32). It is also plausible that a maternal C-peptide–related biomarker could be used to identify hyperinsulinism in pregnancies affected by gestational diabetes or type 2 diabetes or in pregnancies with evidence of accelerated fetal growth.

In conclusion, we found that C-peptide first detected in maternal serum at 34 weeks was associated with higher cord-blood C-peptide and clinical complications of fetal hyperinsulinism, including large for gestational age and neonatal hypoglycemia. We suggest that increasing maternal C-peptide in late gestation represents detectable fetal hyperinsulinism rather than enhanced maternal β-cell function. Increasing focus on early biochemical identification of hyperinsulinemic offspring could provide new opportunities for personalized fetal monitoring in pregnancies with type 1 diabetes.

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Author Contributions. C.L.M. designed the study, analyzed and interpreted the data, and wrote and revised the manuscript. R.A.O. designed the study, contributed to data analysis and interpretation, and contributed to manuscript writing and revisions. T.J.M. measured C-peptide, contributed to data interpretation, reviewed and revised the manuscript, and contributed to the discussion. D.S.F. and A.T.H. all contributed to data interpretation and discussion and reviewed and revised the manuscript. H.R.M. contributed to study design, data analysis, data interpretation, and discussion and reviewed and revised the manuscript. All authors gave approval of the final version of the manuscript prior to publication. C.L.M. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX 1

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APPENDIX 2

Definitions of outcomes used in the CONCEPTT trial. Large for gestational age (LGA): birth weight >90th centile using customized GROW centiles, calculated using version 8 (2017) of the GROW calculator using data about maternal self-reported ethnicity, parity, height, weight, gestational age at birth, and neonatal sex (8). Respiratory distress: respiratory difficulties requiring any positive pressure ventilation ≥24 h beyond resuscitation period (10 min) and/or given surfactant within 72 h after birth. Neonatal hypoglycemia: a plasma glucose <2.6 mmol/L on one or more occasions, starting at 30–60 min after birth, and necessitating intravenous dextrose within the first 48 h of life. Admission to the NICU: admission to NICU for at least 24 h. Hyperbilirubinemia: significant jaundice based on bilirubin levels requiring treatment with phototherapy >6 continuous h, an exchange transfusion, or receiving intravenous γ-globulin or requiring readmission into hospital during the first 7 days of life.

APPENDIX 3

Calculations related to possible C-peptide transfer across the placenta. In order to ascertain if the volume of fetal C-peptide synthesis would be likely to result in measurable C-peptide concentrations in maternal serum, we aimed to provide an assessment of this mathematically. Unfortunately, as there are so many unknown variables, it is difficult to do an accurate volume of distribution calculation. However, we have done some provisional modeling suggesting that this is physiologically possible. While lots of important information is missing, the available information we have available suggests the transfer of C-peptide from the fetus could realistically result in measurable maternal plasma C-peptide concentrations in a mother with type 1 diabetes. Calculations are as follows: as pregnant women at term have a circulating volume of around 5 L, this gives a clearance of 6.93 L/h: 0.5 h = 0.693 × 5 L/clearance (equation: t1/2 = 0.693 × Vd/CL). As the fetus has a much smaller circulating volume, clearance would be lower at 0.44 L/h: 0.5 h = 0.693 × 0.32 L/clearance (equation: t1/2 = 0.693 × Vd/CL). For the fetus, the rate of production of C-peptide in order to provide a steady state within the blood (k0) is below (ignoring first pass hepatic metabolism). We have used a cord blood concentration of 1300 pmol/L as an example as this is around the median for pattern 3. Infusion rate K0 = concentration in plasma/clearance. K0 = 1,300 pmol/L/0.44 = 2954 pmol/h. As rate in must equal rate out in order to maintain a steady state, we assume that 2,954 pmol/h could be theoretically available to enter the maternal circulation. Plasma concentration in mothers (for a steady state infusion) C = k0/CL = 2,954 pmol/h/6.93 L = 426 pmol/L. In practice, it is likely that transfer between fetus and mother may be 5–50% rather than 100% of available C-peptide in cord blood, resulting in feasible concentrations of 21–213 pmol/L in the maternal circulation. We have based our modelling on several assumptions:

- Adult C-peptide is cleared by the kidney and metabolized in the liver. For the fetus, we assumed that there are three potential routes to eliminate C-peptide—renal excretion into the amniotic fluid, hepatic metabolism, and transfer to the maternal circulation.
- Previous work in adults suggests the half-life of C-peptide is around 30 min. It is unclear how this might change in pregnancy. It is also unclear how this might be different in a fetus. We assumed consistent half-lives of 30 min in both mother and fetus, but this is unlikely to be accurate.
- In terms of calculations, the situation is similar to receiving an intravenous infusion. The fetus receives a regular supply of C-peptide from β-cells into the circulation, and potentially, the mother receives a regular supply of C-peptide from the fetus. Unlike a drug that is injected into the intravenous compartment, C-peptide will undergo first pass metabolism by the liver, removing a proportion. We have no way of estimating the proportion of secreted C-peptide that might be removed by a fetal liver and have therefore omitted this step, resulting in an unavoidable underestimation of fetal C-peptide production.
- In order to do a much more accurate assessment, further information is needed about the elimination of C-peptide from the fetus, distribution in fetal body fluids and amniotic fluid, clearance rates, and the proportion of peptide which might cross the placenta for accurate assessment of fetal to maternal transfer.

We conclude that while lots of important information is missing, the information we have available suggests the transfer of C-peptide from the fetus could realistically result in measurable maternal plasma C-peptide concentrations in a mother with type 1 diabetes.

References

1. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347-2359
2. Feig DS, Corcoy R, Donovan LE, et al.; CONCEPTT Collaborative Group. Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial. Diabetes Care 2018;41:2471–2479
3. Mackin ST, Nelson SM, Kerssens JJ, et al.; SDRN Epidemiology Group. Diabetes and pregnancy: national trends over a 15 year period. Diabetologia 2018;61:1081–1088
4. Murphy HR, Bell R, Cartwright C, et al. Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study. Diabetologia 2017;60:1668–1677
5. Metzger BE, Persson B, Lowe LP, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. Pediatrics 2010;126:e1545–e1552
6. Butler AE, Cao-Minh L, Galasso R, et al. Adaptive changes in pancreatic beta cell fractional area and beta cell turnover in human pregnancy. Diabetologia 2010;53:2167–2176
7. 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
8. Nielsen LR, Rehfeld JF, Pedersen-Bjergaard U, Damm P, Mathiesen ER. Pregnancy-induced rise in serum C-peptide concentrations in women with type 1 diabetes. Diabetes Care 2009;32:1052–1057
9. Ilic S, Jovanovic L, Wollitzer AO. Is the paradoxical first trimester drop in insulin requirement due to an increase in C-peptide concentration in pregnant Type I diabetic women? Diabetologia 2000;43:1329–1330
10. Markoska A, Mendoza LC, Valaiyapathi R, Thorn C, Dornhorst A. Insulin sensitivity assessed using urine C peptide creatinine ratio (UCPCR) in pregnancy: cross-sectional analysis of an English multiethnic cohort. BMJ Open 2018;8:e020029
11. Oram RA, Jones AG, Besser RE, et al. The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. Diabetologia 2014;57:187–191
12. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992;339:283–287
13. Gardosi J. Gestation Network. Customised weight centile calculator. GROW v8.1 UK. Accessed 26 May 2021. Available from https://www.gestation.net/index.htm

14. Gerö L, Baranyi E, Békefi D, Dimény E, Szalay J, Tamăs G Jr. Investigation on serum C-peptide concentrations in pregnant diabetic women and in newborns of diabetic mothers. Horm Metab Res 1982;14:516–520
15. Gruppuso PA, Susa JB, Sehgal P, Frank B, Schwartz R. Metabolism and placental transfer of ^{125}I-proinsulin and ^{125}I-tyrosylated C-peptide in the pregnant rhesus monkey. J Clin Invest 1987;80:1132–1137
16. Jörnvall H, Lindahl E, Astorga-Wells J, et al. Oligomerization and insulin interactions of proinsulin C-peptide: Threefold relationships to properties of insulin. Biochem Biophys Res Commun 2010;391:1561–1566
17. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603
18. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia 2019;62:1143–1153
19. Murphy HR. Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. Diabetologia 2019;62:1123–1128
20. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with iabetes and vascular disease. Lancet 1999;353:1789–1792
21. Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S. Mutations in the glucokinase gene of the fetus result in reduced birth weight. Nat Genet 1998;19:268–270
22. Rorsman P, Ashcroft FM. Pancreatic β-cell electrical activity and insulin secretion: of mice and men. Physiol Rev 2018;98:117–214
23. Neoh SL, Grisoni JA, Feig DS; CONCEPTT Collaborative Group. Dietary intakes of women with type 1 diabetes before and during pregnancy: a pre-specified secondary subgroup analysis among CONCEPTT participants. Diabet Med 2020;37:1841–1848
24. Stewart ZA, Yamamoto JM, Meek CL, Sanchez J, Feig D, Murphy HR. Associations between maternal metabolomic and lipidomic profiles across gestation with neonatal birthweight in type 1 diabetes pregnancy. Presented at the 79th Scientific Sessions of the American Diabetes Association, 7–11 June 2019, San Francisco, CA. Abstract 1385P
25. Achong N, McIntyre HD, Callaway L, Duncan EL. Glycaemic behaviour during breastfeeding in women with Type 1 diabetes. Diabet Med 2016;33:947–955
26. Jennings RE, Berry AA, Strutt JP, Gerrard DT, Hanley NA. Human pancreas development. Development 2015;142:3126–3137
27. Powe CE, Huston Presley LP, Locascio JJ, Catalano PM. Augmented insulin secretory response in early pregnancy. Diabetologia 2019;62:1445–1452
28. Weiss PAM, Hofmann HM, Winter RR, Lichtenegger W, Pürstner P, Haas J. Diagnosis and treatment of gestational diabetes according to amniotic fluid insulin levels. Arch Gynecol 1986;239:81–91
29. Carpenter MW, Canick JA, Hogan JW, Shellum C, Somers M, Star JA. Amniotic fluid insulin at 14-20 weeks' gestation: association with later maternal glucose intolerance and birth macrosomia. Diabetes Care 2001;24:1259–1263
30. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. N Engl J Med 2016;375:644–654
31. Beardsall K, Thomson L, Guy C, et al.; REACT Investigators. Protocol of a randomised controlled trial of real-time continuous glucose monitoring in neonatal intensive care 'REACT'. BMJ Open 2018;8:e020816
32. Hegarty JE, Harding JE, Gamble GD, Crowther CA, Edlin R, Alsweiler JM. Prophylactic oral dextrose gel for newborn babies at risk of neonatal hypoglycaemia: a randomised controlled dose-finding trial (the PrehPOD Study). PLoS Med 2016;13:e1002155