Untreated Mild Hyperglycemia During Pregnancy and Anthropometric Measures of Obesity in Offspring at Age 5–7 Years

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OBJECTIVE

Obesity in the offspring of women with hyperglycemia during pregnancy has been reported, but the results are conflicting. This study examined the association of hyperglycemia during pregnancy and anthropometry in 5- to 7-year-old offspring whose mothers participated in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study at the Belfast Centre.

RESEARCH DESIGN AND METHODS

Women in the HAPO study underwent a 75-g oral glucose tolerance test (OGTT) at approximately 28 weeks of gestation. Mothers and caregivers remained blinded to the results unless the fasting plasma glucose (FPG) concentration was >5.8 mmol/L or the 2-h plasma glucose (2hPG) concentration was >11.1 mmol/L. Offspring weight, height, and skinfold thicknesses (triceps, subscapular, and suprailiac) were measured at age 5–7 years. Overweight, obesity, and extreme obesity were defined as a BMI z score ≥85th, ≥95th, and ≥99th percentile, respectively, based on the 1990 British Growth Standard.

RESULTS

Belfast HAPO offspring (n = 1,320, 82%) aged 5–7 years attended for follow-up. With use of multiple regression, maternal FPG, 1h PG, and 2hPG did not show any relation to offspring BMI z score or offspring skinfold sum independent of maternal BMI at OGTT and offspring birth weight z score. This lack of association with maternal glycemia persisted with the offspring BMI z score expressed as ≥85th, ≥95th, or 99th percentile and the sum of skinfolds expressed as ≥90th percentile specific for sex. The initially significant relation between FPG and all offspring adiposity measures was explained by maternal BMI at the OGTT.

CONCLUSIONS

After adjustment for maternal BMI at the OGTT, higher maternal FPG concentration during pregnancy (short of diabetes) is no longer a risk factor for obesity, as reflected by BMI and the sum of skinfolds in offspring aged 5–7 years.

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A number of studies have now shown that the offspring of women with gestational diabetes mellitus (GDM) are at increased risk of obesity (1,2), particularly from adolescence into young adulthood (3–7), although the evidence is conflicting (8,9). Furthermore, the findings before adolescence are even more discordant (10–14). One explanation for those studies failing to show an association is the possible attenuation of risk due to the treatment of maternal GDM during pregnancy. On the other hand, reports (1,2) showing evidence of a positive relation often pertain to populations with high rates of both diabetes and obesity, raising questions as to their general relevance. Additional criticisms include the inclusion of both GDM subjects and those whose diabetes preceded pregnancy and the frequent failure to adjust for important confounding variables, particularly maternal BMI (10,15). Furthermore, interstudy comparisons are difficult because of differing diagnostic methodologies and criteria, both geographically and over time.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was a multicenter observational study that was designed to examine the associations between hyperglycemia during pregnancy (short of diabetes) and adverse pregnancy outcomes. Participating women underwent a 75-g oral glucose tolerance test (OGTT) at an average of 28 weeks of gestation with detailed examination of the offspring at birth (16). Of particular note is the fact that caregivers were blinded to the OGTT results during the parent study unless these fell outside predefined thresholds, thus minimizing confounding of later offspring outcome results from any glucose-directed therapeutic intervention during pregnancy. The Belfast HAPO Follow-Up Study is an ancillary study that is following up the offspring at the Belfast center and represents a relatively unique cohort of carefully characterized subjects drawn from a homogenous population. In our preliminary study of offspring at the age of 2–3 years, no association between maternal hyperglycemia and offspring adiposity was identified (17). The aim of the current study was to extend these findings by further follow-up of the complete cohort at age 5–7 years.

RESEARCH DESIGN AND METHODS

The Belfast HAPO Family Study was a cohort observational study wherein

women participating in the Belfast (U.K.) center of the HAPO study along with their offspring were invited for further follow-up examinations. This article describes a study of the offspring at age 5–7 years of women who had remained blinded to their HAPO study pregnancy OGTT results. Measurements in the offspring included weight (to the nearest 0.1 kg; scale model 708; Seca, Birmingham, U.K.); height (to the nearest 0.1 cm using a calibrated stadiometer); and skinfold thicknesses at triceps, subscapular, and suprailiac sites (performed in duplicate and measured to the nearest 0.1 mm using skinfold calipers; Holtain, Crymych, U.K.). Offspring BMI was converted to an SD (z score) using the 1990 British Growth Standard, which takes into account the child's age and sex (18). Overweight, obesity, and extreme obesity were defined as BMI z scores of ≥85th, ≥95th, and ≥99th percentile, respectively. A summary skinfold thickness measure was derived by addition of the mean thickness of skinfolds from each of the measured sites, and a sex-specific 90th percentile cutoff value was derived to define excess adiposity. Maternal pregnancy OGTT glucose results (at 0, 60, and 120 min), BMI at OGTT, offspring birth weight, cord C-peptide concentration (in micrograms per liter), and the sum of neonatal skinfolds from flank, triceps, and subscapular sites were available from the HAPO study data. Offspring were deemed to be large for gestational age (LGA) if their birth weight was greater than the 90th percentile for gestational age at birth as per the 1990 British Growth Standard. Based on the new 2013 World Health Organization (WHO) criteria for GDM (19), the presence of GDM (excluding unblinded participants) was related to offspring adiposity. Area under the curve (AUC) for plasma glucose (PG) concentration obtained on the maternal OGTT results was also calculated (19). Mothers were classified by the BMI at the OGTT as obese (≥33 kg/m^2), overweight (28.5–32.9 kg/m^2), and normal weight (<28.5 kg/m^2), as previously reported for the classification of BMI categories at 28 weeks of gestation (20). The follow-up study was restricted to women of white European ethnicity and their offspring, as only 28 of the 1,677 women enrolled at the Belfast center were of other ethnicities.

Statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY). Baseline characteristics are presented as the mean (± SD) or proportions, and were compared between those who did and those who did not attend follow-up sessions with the independent samples t test or χ^2 test. The distribution of the sum of skinfolds (at birth and at age 5–7 years) and the cord C-peptide concentration showed positive skew and were logarithmically transformed. In separate simple linear regression analyses, offspring BMI z score and sum of skinfolds were used as the dependent variables, and maternal OGTT glucose measures and cord C-peptide concentrations were used as the predictors. Significant associations were further examined using multiple regression analyses with adjustment for potential confounders. Logistic regression was used to calculate the odds ratio (OR) for excess offspring adiposity associated with each of the OGTT glucose values and also for determining excess risk associated with maternal OGTT results within the GDM range, as defined by WHO 2013 criteria. Significant associations were adjusted for maternal BMI at OGTT and offspring birth weight z score, as these had displayed independent association with offspring adiposity in multiple regression analysis. Finally, logistic regression models were also used to examine the relation between excess offspring adiposity and maternal fasting PG (FPG) levels at OGTT, pregnancy BMI, and offspring birth weight. Nonlinear relationships were investigated by including a quadratic term for the predictor variable in the equation for linear and logistic regression, and also by fitting restricted cubic splines. In light of the multiplicity of statistical tests performed, statistical significance for all analyses was set at $P < 0.01$.

RESULTS

Of the participating 1,677 women from the Belfast (U.K.) center, 1,649 (98%) were of white European ethnicity, and of these, 1,612 (98%) had remained blinded to glucose status throughout pregnancy. Of these, six women experienced antepartum fetal deaths and two experienced neonatal deaths. Of the remaining 1,604 women, 1,320 (82.3%) attended for follow-up with their 5- to 7-year-old offspring (age range 5.6–7.7 years). Data on

offspring BMI and skinfold thickness were unavailable in three and nine participants, respectively, due to parental refusal for measurements, and maternal 1-h glucose measurements during the pregnancy OGTT were unavailable in one mother. Of the 284 mothers who did not attend follow-up for the study, 86 did not respond to an invitation, 2 had died since completion of the original HAPO study, 1 child was terminally ill, 36 others had left the area, 136 refused participation for other reasons, and 23 were unable to keep their scheduled appointments. Women who did not participate were slightly but not significantly heavier and more likely to be obese compared with those who participated (Table 1). They were also younger, had fewer years of education, were more often smokers, and were less likely to be married or cohabiting during pregnancy. However, the mean OGTT glucose measures were similar between the two groups. In addition, offspring who did not participate had a similar sex distribution, birth weight z score, and frequency of LGA status compared with those who took part. The overall prevalence of overweight and obesity in the offspring at ages 5–7 years, based on the 1990 British Growth Standard, was 24.1%, with 10.9% being obese and 4.7% extremely obese (≥99th percentile).

To make the most efficient use of the data, the relation between offspring adiposity at 5–7 years of age and maternal glycemia was examined using continuous variables via regression analysis (Table 2). In the unadjusted analysis, only maternal FPG concentration showed a significant association with offspring BMI z score (regression coefficient 0.31 per mmol/L [95% CI 0.14–0.48], $P <$ 0.001) and $\log_{10}$-transformed sum of skinfolds (regression coefficient 0.040 [95% CI 0.016–0.064], $P = 0.005$, equivalent to a 9.6% [95% CI 3.8–15.9%] greater sum of skinfolds per millimole per liter). However, neither relationship remained significant when adjusted for maternal BMI at the OGTT, offspring birth weight z score, age at follow-up, and sex. Independent of maternal FPG level, maternal BMI at the OGTT (regression coefficient 0.06 per kg/m^2 [95% CI 0.05–0.07], $P <$ 0.001) and offspring birth weight z score (regression coefficient 0.14 [95% CI 0.08–0.20], $P <$ 0.001) were independently related to

offspring BMI z score. None of the offspring adiposity measures were significantly associated with cord C-peptide concentration. In the logistic regression analysis (Table 3), maternal FPG was associated with offspring overweight and obesity (OR 2.01 [95% CI 1.37–2.96], $P <$ 0.001), obesity (OR 2.37 [95% CI 1.41–3.98], $P = 0.001$), extreme obesity (OR 4.32 [95% CI 2.07–9.04], $P <$ 0.001), and the sum of skinfolds ≥90th percentile (OR 2.48 [95% CI 1.44–4.26], $P = 0.001$). However, after adjusting for maternal BMI and offspring birth weight z score, FPG concentration no longer showed a significant association with any of these outcomes. The adjusted relation of FPG concentration with extreme offspring obesity was significant at the conventional 5% significance level (OR 2.32 [95% CI 1.05–5.13], $P = 0.04$), but not

at the 1% level used in this study. Women with GDM, as determined by WHO 2013 criteria, had an increased risk for offspring BMI z score ≥85th percentile at 5–7 years, but the relation did not persist after further adjustment. Table 4 shows the results of logistic regression to examine the contribution of maternal BMI and birth weight toward explaining the relation between maternal FPG concentration and excess offspring adiposity. On adjusting for maternal BMI, FPG concentration failed to show a significant relation with any of the examined offspring outcomes. Adjustment for birth weight z score had little effect on the statistical significance, suggesting that maternal BMI, and not offspring birth weight, explains the relationship between FPG concentration and later offspring adiposity.

Table 1—Characteristics of participant mothers at pregnancy OGTT and of their offspring at birth and at 5–7 years of age at follow-up

	Follow-up status		
	Yes (n = 1,320)	No (n = 284)	P value
Maternal			
Age at pregnancy OGTT (years)	30.0 (5.4)	28.3 (5.7)	<0.001
Primiparous	658 (49.8%)	132 (46.6%)	0.33
BMI at pregnancy OGTT (kg/m^2)	28.1 (4.4)	29.0 (5.5)	0.02
BMI category at pregnancy OGTT			
<28.5 kg/m^2	809 (61.3%)	154 (54.4%)	0.007
28.5–32.9 kg/m^2	345 (26.2%)	74 (26.2%)	
≥33 kg/m^2	165 (12.5%)	55 (19.4%)	
Education (years)	15.0 (2.8)	14.1 (2.6)	<0.001
Pregnancy OGTT glucose			
FPG (mmol/L)	4.6 (0.3)	4.6 (0.3)	0.39
1-h PG (mmol/L)	7.4 (1.6)	7.4 (1.6)	0.42
2-h PG (mmol/L)	6.0 (1.1)	6.1 (1.2)	0.58
AUC PG (mmol/L/h)	12.8 (2.0)	12.7 (2.1)	0.68
Smoked cigarettes during pregnancy	280 (21.2%)	105 (37.1%)	<0.001
Drank alcohol during pregnancy	359 (27.2%)	71 (25.1%)	0.47
Married or cohabiting during pregnancy	1,127 (85.4%)	223 (78.8%)	0.006
Offspring			
Female sex	639 (48.4%)	134 (47.3%)	0.75
Birth weight z score	−0.11 (0.96)	−0.18 (0.98)	0.28
LGA	99 (7.5%)	19 (6.8%)	0.67
Neonatal sum of skinfolds	12.3 (10.8, 14.1)	12.2 (10.7, 14.1)	0.66
Cord C-peptide concentration (µg/L)	0.99 (0.70, 1.40)	0.95 (0.70, 1.20)	0.24
Age at follow-up (years)	6.3 (0.5)		
Age range (years)	5.2–7.7		
BMI at follow-up (kg/m^2)†	16.4 (1.9)		
BMI z score at follow-up	0.43 (1.01)		
BMI z score category			
≥85th percentile	318 (24.1%)		
≥95th percentile	143 (10.9%)		
≥99th percentile	62 (4.7%)		
Sum of skinfolds at follow-up (mm)‡	23.5 (range 18.6–28.2)		

Data represent the mean (SD) or the geometric mean (interquartile range), unless otherwise indicated. †BMI available in 1,317 offspring. ‡Sum of skinfolds available in 1,311 offspring.

Table 2—Linear regression analysis examining relation between offspring adiposity and maternal gestational OGTT glucose and cord C-peptide concentrations

	Dependent variables			
	Offspring BMI z score		Offspring sum of skinfolds*	
	Simple regression	Adjusted model†	Simple regression	Adjusted model†
FPG	0.31‡ (0.14, 0.48) (n = 1,317)	−0.00 (−0.17, 0.17) (n = 1,316)	0.040§ (0.016, 0.064) (n = 1,311)	0.009 (−0.015, 0.032) (n = 1,310)
1-h PG	0.02 (−0.01, 0.06) (n = 1,316)	−0.02 (−0.06, 0.01) (n = 1,315)	0.003 (−0.002, 0.008) (n = 1,310)	−0.001 (−0.006, 0.003) (n = 1,309)
2-h PG	0.03 (−0.02, 0.07) (n = 1,317)	−0.04 (−0.08, 0.01) (n = 1,316)	0.005 (−0.002, 0.012) (n = 1,311)	0.000 (−0.007, 0.006) (n = 1,310)
AUC PG	0.02 (0.00, 0.05) (n = 1,316)	−0.02 (−0.05, 0.01) (n = 1,315)	0.003 (−0.001, 0.007) (n = 1,310)	−0.001 (−0.004, 0.003) (n = 1,309)
Cord C-peptide‖	0.24 (−0.02, 0.50) (n = 1,115)	−0.06 (−0.15, 0.03) (n = 1,114)	0.035 (−0.003, 0.073) (n = 1,110)	−0.007 (−0.019, 0.005) (n = 1,109)

Data are mean (interquartile range). *log10 transformed. †Adjusted for maternal BMI at OGTT (kg/m^2), offspring birth weight z score, age at study (years), and sex. ‡$P < 0.001$. §$P < 0.01$. ‖log$_{10}$ transformed with regression coefficient representing an increase in the dependent variable per 10-fold increase in cord C-peptide concentration.

Neither the addition of quadratic terms nor the fitting of restricted cubic splines provided any evidence of nonlinearity in the relationships among any of the OGTT glucose measures and offspring BMI z score or sum of skinfolds (data not shown).

CONCLUSIONS

Our principal finding was that increasing postload maternal glycemia during pregnancy, short of overt diabetes, was not independently associated with excess adiposity in the offspring at 5–7 years of age after carefully controlling for confounding variables, and this was consistently observed for offspring adiposity whether expressed as BMI or skinfold thickness. Maternal pregnancy BMI and offspring birth weight were both independent predictors of offspring overweight (BMI z score ≥85th percentile), but only maternal BMI principally accounted for the relationship between maternal FPG concentration and later offspring adiposity, underpinning the importance of this factor. As in our previous study of this cohort at an offspring age of 2–3 years (17), cord C-peptide concentration did not predict later offspring adiposity.

In this article, we examined the relation between untreated mild gestational hyperglycemia and later offspring obesity. Few studies have examined this association, and they had conflicting results. The only long-term follow-up from a randomized controlled trial is that of Gillman et al. (11) at an offspring age of 4–5 years. In this primarily white South Australian cohort, the authors reported similar BMI values in the offspring of mothers with and without glucose-lowering intervention targeting mild GDM during pregnancy. By contrast, two previous observational studies showed an increased risk of offspring overweight and/or obesity with mild gestational hyperglycemia. In a large multiethnic U.S. epidemiological study involving 9,439 children, Hillier et al. (12) showed an 82% increased risk of obesity in 5- to 7-year-old offspring of mothers with gestational hyperglycemia levels lower than those of the National Diabetes Data Group criteria but higher than the more stringent Carpenter and

Table 3—Logistic regression analysis showing risk of excess offspring adiposity with maternal gestational OGTT glucose and GDM status

	Offspring			
	BMI z score			
	≥85th percentile (n = 1,316)	≥95th percentile (n = 1,316)	≥99th percentile (n = 1,316)	Sum of skinfolds ≥90th percentile (n = 1,310)
FPG				
Unadjusted	2.01 (1.37–2.96)†	2.37 (1.41–3.98)‡	4.32 (2.07–9.04)†	2.48 (1.44–4.26)‡
Adjusted model*	1.16 (0.76–1.76)	1.34 (0.76–2.35)	2.32 (1.05–5.13)	1.61 (0.90–2.89)
1-h PG unadjusted	1.06 (0.98–1.15)	1.01 (0.91–1.13)	1.06 (0.90–1.24)	1.02 (0.91–1.14)
2-h PG unadjusted	1.10 (0.99–1.23)	0.99 (0.85–1.15)	0.94 (0.75–1.18)	0.99 (0.84–1.16)
AUC PG unadjusted	1.06 (1.00–1.13)	1.02 (0.93–1.11)	1.04 (0.92–1.18)	1.02 (0.93–1.12)
GDM				
Unadjusted	1.62 (1.17–2.25)‡	1.56 (1.01–2.41)	1.37 (0.72–2.63)	1.30 (0.81–2.09)
Adjusted model*	1.18 (0.84–1.67)			

Data are OR (95% CI) for one unit rise in OGTT glucose measures and for GDM (excluding unblinded participants) compared with no GDM. Sex-specific cutoffs were used for the sum of skinfolds ≥90th percentile. *Adjusted for maternal OGTT BMI and offspring birth weight z score. †$P < 0.001$. ‡$P < 0.01$.

Table 4—Logistic regression showing association between maternal FPG and excess offspring adiposity controlled for maternal BMI and birth weight z score

	BMI z score ≥85th percentile		BMI z score ≥95th percentile		BMI z score ≥99th percentile		Sum of skinfolds ≥90th percentile	
	OR	P	OR	P	OR	P	OR	P
Model 1								
FPG	2.01	<0.001	2.37	0.001	4.32	<0.001	2.48	0.001
Model 2								
FPG	1.27	0.27	1.33	0.32	2.39	0.03	1.54	0.14
Mat BMI	1.12	<0.001	1.14	<0.001	1.14	<0.001	1.12	<0.001
Model 3								
FPG	1.71	0.008	2.22	0.003	3.76	<0.001	2.47	0.001
Bwt z score	1.36	<0.001	1.09	0.37	1.17	0.25	0.97	0.77
Model 4								
FPG	1.16	0.49	1.34	0.32	2.32	0.04	1.61	0.11
Mat BMI	1.11	<0.001	1.15	<0.001	1.14	<0.001	1.12	<0.001
Bwt z score	1.28	<0.001	0.99	0.91	1.07	0.62	0.90	0.28

Sex-specific cutoffs were used for the sum of skinfolds in ≥90th percentile. Bwt z score, offspring birth weight z score; Mat BMI, maternal BMI at OGTT.

Coustan criteria and who did not receive glucose-lowering treatment. The comparator group comprised women with normal results on a screening glucose challenge test. In addition, compared with the latter reference group, the offspring of women with treated GDM diagnosed by National Diabetes Data Group criteria did not show an excess risk for obesity. However, of note in this study, there was no adjustment for maternal BMI. In another study, Deierlein et al. (14) studied the offspring of women who had tested positive on a 50-g, 1-h glucose challenge test but were subsequently not found to have GDM on a 3-h, 100-g OGTT and therefore had not received glucose-lowering treatment. In this predominantly white U.S. cohort, the authors showed that, even after adjusting for maternal BMI, there was a doubling in the risk for overweight/obesity in offspring who were 3 years of age when the maternal gestational 1-h 50-g post–glucose challenge test glucose concentration was ≥130 mg/dL (7.2 mmol/L) compared with ≤100 mg/dL (5.6 mmol/L).

Other observational studies (8–10) have examined the risk of obesity in the offspring of mothers in whom clinical GDM, as opposed to mild untreated hyperglycemia, was diagnosed and, concordant with our results, did not find an association. Two recent systematic reviews also did not find an increase in offspring obesity (15) or BMI z score (21) with maternal GDM.

While several studies (13,22–25) in adolescents reported an association between maternal GDM and increased obesity risk, they often share the problem of nonadjustment for maternal BMI. Furthermore, a recent study (26) reported maternal prepregnancy BMI to be the strongest predictor of later offspring obesity independent of maternal GDM. The importance of adjusting for maternal BMI in studies examining long-term outcomes with maternal GDM has been highlighted recently (15), and our results would support this. However, there are data showing that adjusting for maternal overweight and/or obesity does not always sway results toward the null. For example, a recently published prospective observational study (25) in >28,000 children from a historical cohort (1959–1965) showed that a diagnosis of maternal GDM was related to an excess risk of offspring overweight at 4 and 7 years of age even after adjustment for maternal BMI. Similarly, as noted above, Deierlein et al. (14) showed increased risk after controlling for maternal BMI.

What might be the reasons for such discordance in evidence? One possibility is that obesity is manifested earlier in populations at higher risk for diabetes such as that reported in the classic studies among the Pima Indians (27). It is also possible that there exists a glycemic threshold above which the risk for offspring obesity increases. Evidence to support this comes from the clear increase in offspring obesity with more overt types of diabetes, including type 1 diabetes (4,27,28), and from the study of Baptiste-Roberts et al. (25) in which

the diagnostic criteria for GDM were much higher than those used in contemporary cohorts. Similarly, in a study by Lawlor et al. (9), gestational glycosuria, and not GDM status, was associated with later offspring obesity, suggesting that the increased risk occurred with a greater degree of gestational hyperglycemia. It is also possible that postnatal influences may also be operative, whereby obesity is only manifested when a "glycemically primed" offspring from intrauterine life experiences a "second hit," for example, from an obesogenic environment, a hypothesis that could be tested further in future studies.

Finally, the relation of maternal glycemia to extreme obesity (BMI ≥99th percentile) in the offspring is of interest. Flores and Lin (22) reported an increased risk of extreme obesity in the offspring with maternal GDM in a cohort of 6,800 children of kindergarten age, independent of maternal severe obesity. Although we found a similar association, it was significant only at the conventional 5% level of significance, and not at the stricter 1% level that we adopted, to make allowance for the large number of analyses we performed. The fact that we have replicated their findings in a geographically and ethnically different cohort adds further weight to the argument that the association between maternal glycemia and extreme obesity is real. Future studies should examine this specific issue.

Our study has several strengths. A unique feature of the HAPO cohort was the double blinding of OGTT glucose

during pregnancy, thus decreasing the susceptibility to plausible confounding from interventions for GDM during pregnancy, an issue affecting many previous studies. The methodological rigor involved in the measurement of biochemical and anthropometric data with adherence to a strict research study protocol was replicated in the follow-up of the offspring. The follow-up rate was also high, at 82%. It should, however, be noted that the data relate to a white European cohort with a moderate GDM prevalence (17.1%, by WHO 2013 criteria), and that the offspring age of 5–7 years may not be directly extrapolated to other populations.

In conclusion, this study has shown that in a white European cohort, hyperglycemia in pregnancy, short of overt diabetes, is not associated with an increased risk for offspring obesity at ages 5–7 years. It is possible that such risk is manifested only at a later age, and a study of offspring 10–12 years of age from the HAPO study is now in progress at 10 of the original 15 HAPO centers (the HAPO Follow-Up Study).

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