Exposure to Diabetes in Utero Is Associated with Earlier Pubertal Timing and Faster Pubertal Growth in the Offspring: The EPOCH Study

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Objective To examine the associations of in utero exposure to maternal diabetes with surrogate measures of offspring pubertal timing (age at peak height velocity [APHV]) and speed of pubertal growth (peak height velocity [PHV]).

Study design Data from 77 exposed and 340 unexposed youth followed from age 2 to 19 years (51% non-Hispanic white, 50% female) were analyzed using the Exploring Perinatal Outcomes among Children study, a historical prospective cohort. Maternal diabetes status was collected from obstetric records, and child heights from 2 years to current age from pediatric records. Other covariates were collected during research visits. The superimposition by translation and rotation method, using height measurements (4-52 per participant), modeled APHV and PHV. Accelerated failure time analyses were used to test whether exposure to maternal diabetes was associated with younger APHV and faster PHV.

Results Adjusting for child's sex, race/ethnicity, and socioeconomic status, median APHV was reached ~3 months earlier in youth exposed to maternal diabetes compared with unexposed youth ($P < .03$). Youth exposed to maternal diabetes had a faster PHV than unexposed youth: exposed girls had 10.5% greater median PHV compared with unexposed girls and exposed boys had a 4.0% greater median PHV compared with unexposed boys ($P < .001$ for exposure by sex interaction).

Conclusions Our findings provide evidence that exposure to maternal diabetes in utero is associated with earlier pubertal timing and faster pubertal growth. Whether earlier puberty or faster speed of pubertal growth mediates the association between maternal diabetes exposure and later chronic disease risk remains to be studied. *(J Pediatr 2019;206:105-12).*

Puberty is a complex physiological process defined by intense hormonal changes and rapid physical growth, leading to psychological and physical maturation. A population-level trend toward earlier pubertal onset has been reported over the last several decades in both boys and girls.[1,2] Numerous studies have investigated the long-term effects of earlier pubertal timing on chronic disease risk in adulthood and have found an association with type 2 diabetes,[3] cardiovascular disease,[4] breast cancer,[5] and all-cause mortality,[6] specifically in girls. In boys, earlier pubertal timing has been associated with higher adiposity,[7] increased blood pressure,[8] and a higher risk of cardiometabolic diseases in adulthood.[9]

Exposure to maternal diabetes during intrauterine life has been shown to result in fetal over-nutrition and endocrine dysfunction.[10,11] Exposure to maternal hyperglycemia causes the developing fetal pancreas to respond by producing additional anabolic hormones and growth factors, which promote growth.[10,12] This exposure has also been linked to increased obesity and cardiometabolic outcomes in the offspring later in life.[11,13-17] It is possible that such exposure also plays a role in the programming of puberty onset and maturation. Given the population-level increase in the prevalence of diabetes during pregnancy and the decrease in the age of pubertal onset,[2,18-21] understanding if exposure to maternal diabetes influences puberty in the offspring is important. However, few researchers have investigated the impact of maternal diabetes during pregnancy on offspring pubertal timing and growth velocity.[22-24]

When measuring pubertal timing and speed of puberty, the gold standard is assessment of Tanner stages by a pediatric endocrinologist.[25-27] The initial

AFT	Accelerated failure time
APHV	Age at peak height velocity
BMI	Body mass index
EPOCH	Early Perinatal Outcomes in Children
GDM	Gestational diabetes mellitus
HPG	Hypothalamic-pituitary-gonadal
KPCO	Kaiser Permanente of Colorado Health Plan
PHV	Peak height velocity
SITAR	Superimposition by translation and rotation

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Supported by the National Institute of Health, National Institute of Diabetes, Digestive, and Kidney Diseases (R01 DK068001). Its contents are the authors' sole responsibility and do not necessarily represent official NIH views. The funders had no role in the design, conduct, or reporting of this work. The authors declare no conflicts of interest.

Portions of this study were presented as an oral presentation at the American Diabetes Association Conference, June 10-14, 2016, New Orleans, Louisiana.

https://doi.org10.1016/j.jpeds.2018.10.053

description of Tanner stages was by visual inspection alone, but because obesity has been significantly increasing in prepubertal children, palpation for thelarche (breast development) and gonadarche (testicular growth) is now considered the best method of assessment. Nonetheless, this type of assessment is difficult to obtain on a large longitudinal cohort. Another measure of pubertal timing in girls is self-reported age of menarche, which is accurate when reported prospectively and in detail. However, there is no simple measure of pubertal development in boys analogous to menarche, which has led to boys being studied less often than girls. An additional hallmark of puberty is a period of rapid growth.[28] As puberty approaches, the growth velocity slows, known as the preadolescent dip, before it suddenly accelerates during midpuberty, resulting in each individual experiencing a peak height velocity (PHV). For girls , the age at peak height velocity (APHV) usually occurs earlier than boys, typically during Tanner stage 3; boys usually reach peak height velocity during Tanner stage 4.[29-31]

In this study, we aimed to examine the association of exposure to maternal diabetes during pregnancy with pubertal timing, estimated using APHV, and speed of pubertal growth, estimated using PHV, using data from an ethnically diverse observational cohort study in Colorado.

Methods

The Exploring Perinatal Outcomes among Children (EPOCH) study is a historical prospective multiethnic cohort study that recruited 604 mother/child dyads in Colorado. Eligible participants were children exposed to maternal diabetes and a random sample of children not exposed. Participants were offspring of singleton pregnancies, born at a single hospital in Denver between 1992 and 2002, whose biological mothers were members of the Kaiser Permanente of Colorado Health Plan (KPCO). Children and their mothers were invited to participate in 2 research visits, at average ages of 10.5 and 16.5 years. Longitudinal heights were obtained from the child's medical records from birth to their current age. For this report, we used data from 417 youth who completed both research visits and had at least 4 or more longitudinal height measurements from 2 years of age to their current age. One particpant was removed from the dataset becaseu of an exteremely unrealistic outcome measure. The study was approved by the appropriate Institutional Review Boards. All participants provided written informed consent, and the youth provided written assent.

Exposure to maternal diabetes was defined as a physician diagnosis of diabetes during the index pregnancy, ascertained from the KPCO perinatal database (details about exposure definition and methodology were previously published[11]). Seventy mothers were diagnosed with gestational diabetes mellitus (GDM), and 7 mothers were diagnosed with type 1 diabetes mellitus prior to pregnancy. Because our research question focused on the effects of hyperglycemia during pregnancy on puberty, we included all diabetes types.

Youth Height and Weight Measurements

Longitudinal heights and weights were obtained from the child's medical records from birth to their current age. For youth with a KPCO enrollment gap or who was no longer a KPCO member, standing heights and weights were obtained from their non-KPCO providers. Longitudinal heights from birth to 2 years of age were excluded from these analyses to focus on the pubertal growth spurt rather than the postnatal growth spurt that occurs the first 2 years of life. The median number of measurements per participant from 2 years of age to current age was 19.

In addition, standard anthropometric measures were recorded at each research visit. Height and weight were measured in light clothing and without shoes. Weight was measured to the nearest 0.1 kg, using a portable electronic SECA scale (SECA, Chino, California). Height was measured to the nearest 0.1 cm, using a portable SECA stadiometer. Height and weight were measured and recorded twice, and an average was taken. Scales and stadiometers were calibrated every 2 months using standard weights for scales and an aluminum measuring rod for the stadiometer. Height and weight taken at the first research visit were used to calculate early childhood body mass index (BMI). Z scores for height and BMI were calculated using data from the National Center for Health Statistics and Centers of Disease Control and Prevention.

Pubertal Timing and Speed of Pubertal Growth

Pubertal timing and speed of pubertal growth were defined by APHV and PHV, respectively, and were estimated using longitudinal height records and superimposition by translation and rotation (SITAR) growth curve analysis.[32] The SITAR method uses a shape invariant spline curve and a nonlinear random-effects model to estimate an average growth curve for the entire sample and each individual's deviation from this average curve. There are 3 subject-specific measures termed size (cm), velocity (PHV), and timing (APHV); conceptually, these subject-specific measures define how much bigger or smaller each child is compared with the population average (size), how much faster and slower the child's growth velocity is compared with the population average (velocity), and how much earlier or later the child experienced peak velocity compared with the population average (timing). The models were fitted with the SITAR package in R.[33] Because SITAR estimates individual measures using the underlying growth curve of the population, 4 separate models were fitted by sex and exposure status (exposed girls, unexposed girls, exposed boys, unexposed boys). The SITAR model allows for the flexibility in fitting the spline curves by adjusting the degrees of freedom (df), in doing so, the optimal models are selected by evaluating the Bayesian information criterion (BIC) score. The lowest BIC score indicates the best fit model. Because of the variability of the longitudinal height measurements, observations with a residual greater than 4 were excluded from the analysis (n = 42), this accounted for <0.7% of the total observations used. SITAR models of height by age were fitted for each group with 4 df for exposed girls, 5 df for unexposed girls, 6 df for exposed boys, and 6 df for unexposed boys. Subject-specific measures size, velocity, and timing were estimated as random effects.

Other Measurements

Race/ethnicity was self-reported at each research visit using the 2000 US Census base questions and categorized as Hispanic (any race), non-Hispanic white, non-Hispanic black, or non-Hispanic other. Maternal prepregnancy BMI (kg/m^2) was calculated from the KPCO measured maternal weight before the last menstrual cycle preceding pregnancy and measured maternal height that was collected at the first research visit. Maternal level of education and total household income at the time of birth were self-reported during the first research visit. Mother's insulin use during pregnancy, delivery method, and child's birth weight were collected from the KPCO perinatal database. Pubertal development at the time of each research visit, including Tanner stage and age of menarche (girls only), was ascertained by child's self-report and are used only to describe the study participants. Using a diagrammatic representation of Tanner staging adapted from Marshall and Tanner,[25,26] Tanner stage based on breast development was used for girls and Tanner stage based on pubic hair was used for boys. Age of menarche was reported to the half year for girls.

Statistical Analyses

Accelerated failure time (AFT) models with a log-logistic distribution were used to evaluate the association between exposure to maternal diabetes and pubertal timing (APHV) and speed of pubertal growth (PHV). A log-logistic distribution was selected to allow modeling for a nonmontonic hazard function that allows for increased hazards during the earlier time periods and decreases at later times. There was no right censoring of any individuals because APHV and PHV were estimated and achieved by all participants. A time-ratio was estimated using the AFT beta coefficients, which can be interpreted as the ratio of the median time-to-event for a given level of a covariant to the referent level. The associations between exposure to maternal diabetes and APHV and PHV were examined separately using 3 main models: an initial base model including adjustment for child's sex and race/ethnicity; a second model including an additional adjustment for potential socioeconomic confounders (mother's education and total household income at birth); and a final model with an additional adjustment for early childhood BMI z score, explored as potential mediator of hypothesized main effects. A potential effect modification by child's sex was evaluated using an interaction term (exposure status*child's sex) in the base models. If the interaction term was not significant based on a P value of <.05, it was removed from the model. As a secondary analysis in a subset of data, we explored the effect of the mother's pre-pregnancy BMI on the relationships of maternal diabetes with pubertal timing and speed of pubertal growth. SAS statistical software v 9.4 (SAS Institute, Inc, Cary, North Carolina) was used for all AFT analyses.

Results

Longitudinal heights (range: 4-52 height measurements per participant; average: 19 height measurements; total: 6332 height measurements) were collected on 417 children (77 exposed and 340 unexposed to maternal diabetes) and included in the analytic cohort. There were no significant differences in exposure status, child's race, or sex between the analytical cohort and the larger EPOCH cohort of 604 participants. Anthropometric and demographic characteristics are summarized in **Table I**. Mean (±SD) current ages of exposed and unexposed youth were 15.8 ± 1.0 and 16.8 ± 1.2 years, respectively ($P < .001$). Of the 77 exposed youth, 44.2% were female and of the 340 unexposed youth, 51.2% were female. Youth exposed to maternal diabetes were heavier at birth than youth unexposed (3392 ± 498 vs 3191 ± 613 g, respectively, $P = .008$). A total of 29% of mothers with diabetes were treated with insulin during their pregnancy. Achieved height z scores were not significantly different between youth exposed to maternal diabetes compared with those unexposed for both research visits (0.35 ± 0.88 and 0.34 ± 0.99, $P = .93$; 0.26 ± 0.88 and 0.17 ± 1.06, $P = .47$, respectively). The mean ages at menarche were 11.9 ± 1.4 and 12.3 ± 1.3 years for exposed and unexposed girls, respectively ($P = .20$). Mean unadjusted APHV (pubertal timing) for exposed and unexposed children were 12.1 ± 1.4 and 12.2 ± 1.4 years, respectively ($P = .62$). Mean unadjusted PHV (speed of pubertal growth) for exposed and unexposed children were 9.3 ± 0.4 and 8.6 ± 0.6 cm/year, respectively ($P < .001$).

Pubertal Timing and Exposure to Maternal Diabetes

Table II shows the association between exposure to maternal diabetes and pubertal timing adjusting for child's sex and race/ethnicity (model 1), as well as additional covariates—socioeconomic characteristics (model 2). The interaction between exposure status and child's sex on APHV was not significant (**Figure**, A). After adjustment for the child's sex and race/ethnicity (model 1), the median age of pubertal timing was 2% younger, or ~3-month age difference, in exposed youth compared with unexposed youth ($\beta = -0.021$, $P = .028$). Boys reached APHV significantly later than girls ($\beta = 0.151$, $P < .001$) and Hispanics and non-Hispanic blacks reached APHV significantly earlier than non-Hispanic whites ($\beta = -0.031$, $P < .001$; $\beta = -0.065$, $P < .001$, respectively). Further adjustment for socioeconomic characteristics (model 2) did not influence our findings. In model 3, when adjusting for early childhood BMI, explored here as a potential mediator, the relationship between exposure to maternal diabetes and APHV was attenuated and became nominally nonsignificant ($\beta = -0.017$, $P = .059$).

Speed of Pubertal Growth and Exposure to Maternal Diabetes

Figure, B shows the effect modification by child's sex of the association between exposure to maternal diabetes and PHV, adjusting for race/ethnicity ($P < .001$). Exposed girls had a 10.5% greater PHV than unexposed girls ($\beta = 0.10$, $P < .001$), and exposed boys had a 4.0% greater PHV compared with unexposed boys ($\beta = 0.04$, $P < .001$). Further adjustment for socioeconomic characteristics did not influence our findings, and further adjustment for early childhood BMI, the proposed

Table I. Characteristics of youth and their mothers by maternal diabetes exposure

	Unexposed to DM (n = 340)			Exposed to DM (n = 77)			
Variables	**n**	**%**	**Mean (SD)**	**n**	**%**	**Mean (SD)**	***P* value**
Current age (y)			16.8 (1.2)	77		15.8 (1.0)	<.001
Sex (female)	174	51.2		34	44.2	34 (44.2)	.27
Child's birthweight (g)			3191 (613)			3392 (498)	.008
Child's height z score at visit 1			0.34 (0.99)			0.35 (0.88)	.93
Child's height z score at visit 2			0.17 (1.06)			0.26 (0.88)	.47
Race/ethnicity							.18
Non-Hispanic white	165	48.5		48	62.3		
Hispanic	126	37.1		22	28.6		
Non-Hispanic black	29	8.5		4	5.2		
Non-Hispanic other	20	5.9		3	3.9		
Self-reported Tanner stage at visit 2*							.71
Prepubertal (TS-1)	0	0		0	0		
Pubertal (TS-2)	3	0.9		0	0		
Pubertal (TS-3)	17	5		4	5.2		
Pubertal (TS-4)	133	39.4		32	41.6		
Pubertal (TS-5)	185	54.7		41	53.3		
Child's age at menarche (female only)			12.3 (1.3)			11.9 (1.4)	.20
Mother's prepregnancy BMI (kg/m2)	235		25.6 (6.0)	63		26.9 (5.7)	.12
Self-reported household income at birth							.51
≤$49 999	155	45.7	155 (45.7)	32	41.6		
≥$50 000	184	54.3	184 (54.3)	45	58.4		
Mother's self-reported education at birth							.83
≤High school	61	17.9		13	16.9		
>High school	279	82.1		64	82.1		
Mother's insulin use during pregnancy (yes)				22	29		
Age at peak height velocity (y)			12.21 (1.35)			12.12 (1.38)	.62
Peak height velocity (cm/y)			8.64 (0.63)			9.30 (0.39)	<.001

DM, diabetes mellitus; *TS*, Tanner stage.
*Girls breast TS; boys pubic hair TS.

mediator, had no effect on the relationship between exposure and PHV (data not shown). In a post hoc analysis, we evaluated the independent effect of exposure on PHV, while controlling for APHV and found that APHV was significantly associated with PHV ($\beta = -0.007$, $P < .001$), but the effect of exposure to maternal diabetes on PHV remained significant and only changed the beta coefficients of exposure about 2% in girls and 6% in boys.

Subset Analyses including Maternal Prepregnancy BMI

Mother/child dyads (N = 298) had available prepregnancy BMI data (78.9% were unexposed; 46% were female). In the subset with available data, the strength of the association between exposure to maternal diabetes and APHV was reduced ($\beta = -0.018$), and the association was not significant ($P = .12$) (**Table III**). Further adjustment for maternal prepregnancy BMI had no additional effect. For speed of pubertal growth, in the subset with available data, we observed similar associations as in the larger dataset and addition of maternal pre-pregnancy BMI had no effect on the relationship between exposure to maternal diabetes and PHV (data not shown). The interaction between exposure to maternal diabetes and child's sex was still significant, where exposed girls had a 10.7% greater PHV compared with unexposed girls ($P < .001$) and exposed boys had a 3.9% greater PHV compared with unexposed boys ($P < .001$), even after adjustment for prepregnancy BMI.

Discussion

In an ethnically diverse population, we found that youth exposed to maternal diabetes during the intrauterine life have an earlier pubertal timing and a faster speed of pubertal growth than youth who were not exposed, independent of child's sex, race/ethnicity, and socioeconomic factors. Increased BMI in early childhood largely mediates the association with earlier pubertal timing but has no effect on the association with the speed of pubertal growth. The difference in the speed of pubertal growth between exposed and unexposed is greater in female than in male offspring and is independent of pubertal timing.

Our finding of a relationship between exposure to maternal diabetes and earlier pubertal timing is consistent with the limited number of other studies that have explored this relationship.[22-24] Kubo et al[23] found that daughters of mothers who were obese prior to pregnancy, based on prepregnancy BMI, and had GDM during their pregnancy, had an earlier pubertal onset compared with girls of mothers who had neither condition. In addition, Monteilh et al[22] found that GDM was associated with a 2-month earlier pubertal onset of pubic hair among boys. The results from these studies showed that the effects of GDM on pubertal timing were similar to our findings of about a 3-month time difference. This difference in pubertal timing shifts the distribution of the population by increasing the number of adolescents who experience earlier

Table II. The association between exposure to maternal diabetes and age at peak height velocity

Variables	Model 1*				Model 2†				Model 3‡			
	TR	β	95% CI	*P* value	TR	β	95% CI	*P* value	TR	β	95% CI	*P* value
Exposure status												
Unexposed to DM	1	Referent	Referent	Referent	1	Referent	Referent	Referent	1	Referent	Referent	Referent
Exposed to DM	0.98	−0.021	(−0.04, −0.002)	.028	0.98	−0.022	(−0.041, −0.003)	.025	0.98	−0.017	(−0.03, 0.001)	.059
Race/ethnicity												
Non-Hispanic white	1	Referent	Referent	Referent	1	Referent	Referent	Referent	1	Referent	Referent	Referent
Non-Hispanic black	0.94	−0.065	(−0.094, −0.036)	<.001	0.94	−0.061	(−0.091, −0.032)	<.001	0.96	−0.043	(−0.069, −0.018)	.001
Hispanic	0.97	−0.031	(−0.047, −0.015)	<.001	0.97	−0.027	(−0.044, −0.01)	.002	0.98	−0.018	(−0.034, −0.003)	.02
Non-Hispanic other	0.97	−0.03	(−0.064, 0.005)	.09	0.97	−0.027	(−0.062, 0.007)	.12	0.98	−0.024	(−0.055, 0.007)	.13
Sex												
Female	1	Referent	Referent	Referent	1	Referent	Referent	Referent	1	Referent	Referent	Referent
Male	1.16	0.151	(0.136, 0.165)	<.001	1.16	0.15	(0.135, 0.165)	<.001	1.17	0.154	(0.141, 0.167)	<.001
Household income												
<$50 000/y					1	Referent	Referent	Referent	1	Referent	Referent	Referent
≥$50 000/y					1.01	0.01	(−0.006, 0.03)	.23	1	0.002	(−0.013, 0.016)	.84
Maternal education												
High school					1	Referent	Referent	Referent	1	Referent	Referent	Referent
Any college					1.01	0.01	(−0.01, 0.03)	.57	1.01	0.006	(−0.013, 0.024)	.84
BMI z score									0.97	−0.026	(−0.032, −0.021)	<.001

*Model 1 adjusted for child's race/ethnicity and sex.
†Model 2 adjusted for child's race/ethnicity, sex, household income, and maternal education.
‡Model 3 adjusted for child's race/ethnicity, sex, household income, maternal education, and child's BMI z score at visit 1.

Figure. The sex difference in the association of exposure to diabetes in utero with **A,** offspring age at peak height velocity and **B,** offspring peak height velocity using a log-logistic AFT model, adjusting for child's race (model 1).

pubertal timing, which has been shown in previous studies to be linked to an increase in chronic disease risk later in life. Grunnet et al found that female offspring of mothers with GDM were 2 times more likely to reach puberty before female offspring of mothers without GDM.[24] However, similar to our results, when controlling for offspring's own BMI, the results were attenuated and became nonsignificant. Childhood BMI has been associated with both exposure to maternal diabetes and pubertal timing,[1,11,34] including in our cohort,[11] and it is, thus, a likely mediator of this relationship. In our study, early childhood BMI seemed to account for most of the association between exposure to maternal diabetes and earlier pubertal timing, but others[23] showed that the relationship still remains significant after adjustment, suggesting potential additional pathways by which exposure to maternal diabetes results in earlier pubertal timing. Further research exploring potential mechanisms by which in utero exposure to maternal diabetes may result in earlier pubertal timing is warranted.

Looking at a different measure of pubertal timing, age of menarche for girls only, our study found a nonsignificant effect

Table III. The effect of adjustment for prepregnancy BMI on the association between exposure to maternal diabetes in utero and age at peak height in a subset (n = 298)

	Model 1*				Model 2†			
Variables	**TR**	***B***	**95% CI**	***P* value**	**TR**	**β**	**95% CI**	***P* value**
Exposure status								
Unexposed to DM	1	Referent	Referent	Referent	1	Referent	Referent	Referent
Exposed to DM	0.98	−0.018	(−0.041, 0.005)	.12	0.99	−0.012	(−0.035, 0.01)	.28
Race/Ethnicity								
Non-Hispanic white	1	Referent	Referent	Referent	1	Referent	Referent	Referent
Non-Hispanic black	**0.94**	**−0.059**	**(−0.094, −0.023)**	**.001**	**0.96**	**−0.046**	**(−0.082, −0.011)**	**.01**
Hispanic	**0.97**	**−0.029**	**(−0.05, −0.009)**	**.005**	**0.98**	**−0.023**	**(−0.043, 0.002)**	**.03**
Non-Hispanic other	0.99	−0.012	(−0.054, 0.03)	.58	0.99	−0.006	(−0.048, 0.035)	.76
Sex								
Female	1	Referent	Referent	Referent	1	Referent	Referent	Referent
Male	**1.17**	**0.154**	**(0.135, 0.173)**	**<.001**	**1.17**	**0.156**	**(0.138, 0.174)**	**<.001**
Prepregnancy BMI					**1**	**−0.003**	**(−0.004, −0.001)**	**<.001**

TR, time-ratio.
*Adjusted for child's race/ethnicity, and sex.
†Adjusted for child's race/ethnicity, sex, and maternal prepregnancy BMI.

of exposure to maternal diabetes during pregnancy on pubertal timing (results not shown). However, this variable was collected to the half-year in our study (ie, 12.0 years at age of menarche or 12.5 years at age of menarche) and, therefore, may have not been sensitive enough to detect an effect of exposure to maternal diabetes on menarcheal age.

During normal pubertal development, maturation of the hypothalamic-pituitary-gonadal (HPG) axis, along with increased adrenal androgen and growth hormone secretion, drive achievement of pubertal milestones and growth. Previous animal and human studies have shown that maternal diabetes and obesity are associated with offspring adiposity and metabolic dysfunction.[11,13-17,35] In a previous report from our cohort, we found that adolescents exposed to diabetes in utero had significantly higher fasting insulin levels, compared with unexposed adolescents.[35] Thus, it is plausible that hyperinsulinemia seen in exposed offspring may permanently alter the HPG axis and subsequent sex hormone secretion.[36] Sex hormone alterations may explain the sex differences we observed in the association between exposure to maternal diabetes and speed of pubertal growth. Also, researchers have shown that pubertal timing is related to physical growth,[37,38] so we explored whether our results of exposure to maternal diabetes being associated with PHV may be explained by the earlier APHV. However, we found that the effect of exposure to maternal diabetes on PHV remained significant even after controlling for APHV, suggesting that the observed effect on the speed of pubertal growth is not explained by an earlier pubertal timing. Further study of these potential mechanisms is important, as linear growth is an important biomarker of a child's development and overall health.

The difference in the size of the association between maternal diabetes and pubertal timing vs pubertal growth observed in our study may be related to the multiple hormonal pathways associated with pubertal onset and maturation. Pubertal timing is primarily dependent on the reemergence of gonadotropin-releasing hormone secretion, which is the initial step in the HPG axis, while pubertal growth is not only dependent on the HPG axis, but also the Growth hormone/Insulin-like growth factor 1 (GH/IGF-1) axis and the interaction of these axes.[39,40] It is likely that exposure to maternal diabetes influences these axes and their associated hormones differently, resulting in the somewhat larger effect of maternal diabetes exposure on pubertal speed vs pubertal timing.

We also explored the effect of additional adjustment for maternal prepregnancy BMI on the relationship between exposure to maternal diabetes and pubertal timing and speed of pubertal growth in the offspring, albeit only in a subset with available data. Previous studies looking at the effect of maternal diabetes on puberty measures have not explored the influence prepregnancy BMI. We were only able to explore this in a subset, in which, because of the smaller sample size, the relationship between exposure to maternal diabetes in utero and pubertal timing was not significant, even without controlling for maternal prepregnancy BMI. Additional adjustment for maternal prepregnancy BMI had no further effect. Because prepregnancy BMI is highly related to maternal diabetes, it may be part of the fetal overnutrition pathway,[41] in which case this modeling may also result in over adjustment. Nevertheless, adjustment for maternal prepregnancy BMI had no effect on the association between exposure to maternal diabetes and speed of pubertal growth.

Although our findings represent an important addition to the existing evidence regarding risk factors for earlier puberty, further investigation into potentially responsible mediators, specifically hormones related to the GH-IGF-1 and HPG axes, is needed. In addition, further study is required to understand the role that puberty may play on the relationship between exposure to diabetes in utero and subsequent disease risk in the offspring. It is possible that puberty may be another critical or sensitive period in the lifecycle when the effects of in utero exposure to maternal diabetes may be enhanced via biological programming.

This prospective study is one of the largest multi-ethnic cohorts to investigate the relationships between maternal diabetes and offspring pubertal outcomes. Estimating

accurately the timing and intensity of puberty is challenging, and the current methods, such as using height as a measure of pubertal timing or estimating the mean age at a given Tanner stage or the transition from one stage to another, have some variability in their estimates. However, in this study, we focused on using height as a measure of pubertal timing and intensity because this is a valid measure of pubertal timing and we had longitudinal height measures on individuals from 6 to 19 years of age. Also, we wanted to be able to compare these pubertal measures between boys and girls, which is not possible using Tanner stages. The height measurements used in calculating APHV and PHV were not obtained in a standardized fashion, which may have introduced some variability and decreased the precision of the APHV and PHV estimates, attenuating the associations of interest. Additionally, we have not yet followed the cohort long enough to have data on achieved adult height, and therefore we cannot address the question of whether the observed difference in the speed of pubertal growth according to exposure status will affect final achieved height. Because achieved height at 2 times points during childhood and adolescence was not affected, we speculate that exposure to diabetes in utero may not affect achieved adult height but rather the shape of childhood growth trajectory. Unfortunately, our study was unable to control for genetic factors associated with pubertal timing and growth. However, this would not bias our results unless the genes in question were also associated with maternal diabetes, which has not been shown to date. Further research is needed to examine whether the relationship between exposure to maternal diabetes and pubertal development mediates, at least in part, the increased risk of obesity and cardiometabolic outcomes associated with this exposure. Such findings may then provide evidence for life-stage targeted interventions aimed at reducing or halting the transgenerational vicious cycle of diabetes and obesity.

In summary, these novel findings provide evidence that exposure to diabetes during the intrauterine life may affect pubertal development and growth in the offspring and support the hypothesis that perinatal exposures are among the multiple contributors to the general trend of earlier puberty seen over the last couple of decades. ■

We thank the EPOCH participants, their families, and the study staff for their dedicated contribution to this work. We also thank Dr Tim Cole (UCL Institute of Child Health, London, United Kingdom) for his guidance in using the SITAR method.

Submitted for publication Jul 28, 2018; last revision received Oct 1, 2018; accepted Oct 24, 2018

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