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Prenatal exposure to phthalates and maternal metabolic outcomes in a high-risk pregnant Latina population

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Abstract

Background: Phthalates are a group of endocrine disrupting chemicals that are heavily used throughout industry in flexible plastic and personal-care products. As a result, detectable levels of their metabolites are readily found in humans. Some studies have shown associations of phthalates with diabetes, but associations with gestational diabetes mellitus (GDM) are less clear.

Objective: To investigate the association of 11 prenatal urinary phthalate metabolites and development of GDM, impaired glucose tolerance (IGT), continuous plasma glucose level, and excessive gestational weight gain (GWG) in a population of pregnant Latina women (N=415) enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort study.

Methods: Phthalate metabolite levels were measured via mass spectrometry from two urine samples collected in the end of the first and second trimester. Maternal plasma glucose levels, prior diabetes diagnosis, GDM diagnosis, and weight gain were abstracted from medical records. Multiple regression was used to evaluate the association between the average of the two urinary phthalate metabolites levels and maternal metabolic outcomes. In our sensitivity analysis, phthalate levels were categorized by level (as quartiles of exposure) and by timing of urine sample collection (as taken in first and second half of pregnancy).

Results: Consistent with findings from a nationally representative sample, all of the individual phthalate metabolites were detected in majority of mothers. Thirty-one mothers (7.5%) were diagnosed with GDM, 49 mothers (14.7%) displayed IGT, and 223 mothers (55.1%) gained an

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excessive amount of weight during their pregnancy. MEP concentrations were associated with an increased odds of excessive GWG (OR: 1.1, 95% CI: 1.0 to 1.3). We did not find an association between any phthalate metabolite and any maternal glucose outcome.

Conclusion: Contrary to previous studies, our findings do not support an association of prenatal phthalate levels and increased odds for hyperglycemia, IGT, or GDM. But, we did find an increased odds of excessive GWG, a well-known risk factor for GDM.

Keywords

Phthalates; Endocrine Disruptors; Gestational Diabetes; Impaired glucose tolerance; Gestational Weight Gain; Pregnancy

1. Introduction

Gestational diabetes mellitus (GDM) is a medical condition in which glucose intolerance develops during pregnancy, resulting in a prolonged state of hyperglycemia (American Diabetes Association (ADA) 2019). Worldwide prevalence of GDM has significantly increased over the past two decades, disproportionately affecting different racial and ethnic populations (Casagrande et al. 2018; Ferrara 2007; Zhu and Zhang 2016). GDM diagnoses are associated with increased risk of preeclampsia, macrosomia, maternal and infant birth trauma, cesarean delivery, and neonatal morbidity (Ehrenberg et al. 2004; Kwik et al. 2007; Yogev et al. 2004) and with both mother and child at increased risk of developing Type 2 diabetes (Bianco and Josefson 2019; Boney 2005; England et al. 2009). Even when blood glucose levels fall below GDM diagnostic criteria, higher glucose levels have been associated with increased risk to mother (HAPO 2008) and child (Scholtens et al. 2019).

The exact pathophysiology of GDM is not fully understood. During pregnancy, a natural state of declining insulin sensitivity occurs due to the influence of hormones and other factors, which allows higher concentrations of glucose to be diverted to the fetus. In GDM, pancreatic beta cells do not produce sufficient amounts of insulin to overcome this natural state of insulin resistance (Plows et al. 2018). While lifestyle factors, such as weight gain, play an important role in development of GDM, endocrine-disrupting chemicals (EDCs) may also be contributing (Chevalier and Fénichel 2015; Ehrlich et al. 2016). One of these EDCs is the class of chemicals known as phthalates.

Phthalates are widely used industrial compounds whose basic structures consists of diester phthalic acids (1,2 -benzenedicarboxlyic acid) (Wang et al. 2019). Every year, global industry uses 18 billion pounds of various phthalates as solvents, plasticizers, and additives in a wide range of products, including plastic food containers, personal-care products (i.e. make-up, lotions, and shampoos), medical devices, plastic toys, vinyl-flooring, PVC piping, and shower curtains (Supplemental Table S1) (Latini 2005). As additives, phthalates are not chemically connected to the products, causing them to disperse during states of agitation, storage, or use (Wang et al. 2019). As result, phthalates are ubiquitous contaminants in the environment (Latini 2005). National studies have shown that 94% of Americans have detectable phthalate levels in their urine (Zota et al. 2014), with minority populations having significantly higher levels than their white peers (Silva et al. 2004).

Phthalates may promote GDM development through interaction with peroxisome proliferator-activated receptors (PPARs), nuclear receptors that control transcription of genes that affect lipid storage and carbohydrate metabolism (Casals-Casas et al. 2008; Desvergne et al. 2009; Gibson et al. 2012). In non-pregnant populations, several epidemiologic studies have shown that certain phthalate metabolites are associated with increased risk of type 2 diabetes mellitus and obesity (Stojanoska et al. 2017). The literature exploring phthalate metabolites' impact on development of GDM and other metabolic disorders during pregnancy is less consistent(Bellavia et al. 2017; Fisher et al. 2018; James-Todd et al. 2018, 2016; Robledo et al. 2015; Shaffer et al. 2019; Shapiro et al. 2015). However, four out of the seven cohort studies have shown positive association between monoethyl phthalate (MEP), a urinary metabolite of diethyl phthalate found in personal-care products, and GDM or GDM risk factors (Bellavia et al. 2017; James-Todd et al. 2018, 2016; Shaffer et al. 2019). Most studies were completed in mainly white and high-socioeconomic population.

To our knowledge, no study has investigated the association of phthalates on mothers' risk of developing GDM, experiencing hyperglycemia, and gaining excessive weight during pregnancy in a Latina population who are high-risk for both development of GDM and exposure to phthalates. We used data from The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) to investigate association of phthalate levels and GDM development among Latina mothers in a Californian farmworker community. Previous CHAMACOS investigations have shown associations between maternal prenatal MEP, MBP, and DEHP concentration and increased risk of childhood obesity (Harley et al. 2017). We hypothesized that higher maternal concentrations of MEP and possibly other phthalate metabolite would be associated with GDM, higher blood glucose levels, impaired glucose tolerance (IGT), and gestational weight gain (GWG).

2. Methods

2.1 Study Population

Study participants were pregnant women enrolled in the CHAMACOS study, a prospective birth cohort in a farmworker community in the Salinas Valley, California. Participants were recruited between October 1999 to October 2000 from six partnering health clinics where they were receiving prenatal care. Women were eligible to participate if they were 18 years or older, spoke English or Spanish, qualified for Medicaid, were less than 20 weeks gestation, and were planning on delivering at the county hospital. Altogether, 601 women were enrolled. This study was approved by the Institutional Review Board (IRB) of the University of California, Berkeley. For this analysis we excluded: 7 women (1.2%) with a prior diagnosis of type 1 or type 2 diabetes mellitus; 22 women (3.7%) who did not identify as Latina; and 157 women (26.1%) who were missing urinary phthalate biomarker samples, for a total of 415 mothers (69.1%). Of these, 334 mothers (80.5%) had complete data on glucose levels from a screening glucose challenge test (GCT) conducted between 24–28 weeks gestation, 411 mothers (99.0%) had information on GDM diagnosis, and 405 mothers (97.6%) had information on weight gain during pregnancy. Mothers who were excluded (i.e. no phthalate measurement, did not identify as Latina, and had a preexisting diabetes diagnosis) were similar to included women on all characteristics except excluded women

were more likely to have been born in the United States, to have smoked during pregnancy, and to have gained excessive amount of weight during their pregnancy (Supplemental Table S2).

2.2 Data Collection

Mothers completed interviews near the end of the first and second trimesters of pregnancy (mean: 14.2 ± 5.0 and 26.9 ± 2.4 weeks gestation). All interviews were completed in English or Spanish through structured questionnaires. Basic demographic information, including age, marital status, education, household income, smoking status, diet, and sugar-sweetened beverage consumption were asked. We also gathered health information including prior diabetes diagnosis, pre-pregnancy weight, and date of last menstrual period. Information on pregnancy weight gain, gestational duration, and gestational diabetes diagnosis were abstracted from maternal medical records by a registered nurse.

2.3 Phthalate Biomarker Measurement

Urine samples were collected in polypropylene urine cups at both pregnancy interviews, transferred into glass vials, and stored at −80 °C until shipment to the CDC in Atlanta, Georgia for analysis.

Urine samples were analyzed for 11 phthalate metabolites from 8 parent compounds (Table 1). Analytical methods used solid-phase extraction and isotope dilution high-performance liquid chromatography electrospray ionization-tandem mass spectrometry (Silva et al. 2007). Phthalate metabolite concentrations were recorded in ng/ml of urine with limits of detection (LOD) ranging from 0.2 to 0.6 ng/ml. Concentrations that fell below the LOD were assigned the instrumental reading values. If instrumental readings were not available then values <LOD were randomly imputed from the log-normal distribution utilizing maximum likelihood estimation (Lubin et al. 2004).

A hand-help refractometer measured urinary-specific gravity (National Instrument Company Inc., Baltimore, Maryland). Phthalate metabolite concentrations were corrected for urinary dilution using the formula (analyte concentration x 0.24)/sample specific gravity-1) (Mahalingaiah et al. 2008). For participants missing specific gravity measurements at baseline (N=70) and at 26 weeks GA (N=4), urinary-specific gravity was imputed utilizing urinary creatinine concentrations.

Out of 415 participants, 395 participants (95%) completed both phthalate measurements; for those women with only one measurement, the single measurement was used as the pregnancy average.

2.4 Maternal Glycemic Outcomes

Glucose testing was completed as part of the mother's routine prenatal care following a two-step strategy, starting with a non-fasting screening glucose challenge test (GCT). If participants had elevated glucose levels on the GCT, they proceeded to a fasting, 3-hour diagnostic oral glucose tolerance test (OGTT). The GCT entailed a non-fasting 50g glucose load test with plasma glucose levels taken at 1 hour. Average gestational age at time of the

GCT was 26.4 weeks (SD± 1.1 weeks). The follow-up OGTT entailed a fasting 100g glucose load test with plasma glucose levels taken at fasting, 1 hour, 2 hour, and 3 hour. Results from these tests were obtained by a registered nurse through a medical record review.

Maternal IGT and GDM status was defined using the Carpenter-Coustan diagnostic criteria (Carpenter and Coustan 1982). IGT was defined as plasma glucose level ≥140 mg/dl on the initial screening GCT (i.e. the level that would trigger referral for OGTT), regardless of OGTT results. Women were considered to have a GDM diagnosis if either 1) maternal plasma glucose levels on the OGTT exceeded at least two of the following plasma levels: fasting 95 mg/dL (5.3 mmol/L), 1 hr 180 mg/dL (10.0 mmol/L); 2 hr 155 mg/dL (8.6 mmol/L); 3hr 140 mg/dL (7.8 mmol/L) (N=27)(ADA2019) or 2) OGTT glucose levels were missing but there was a diagnosis of GDM in the maternal medical records (N=5).

2.5 Maternal Gestational Weight Gain

Total GWG was calculated by subtracting pre-pregnancy weight from maternal weight at birth. Pre-pregnancy BMI was calculated utilizing measured height and self-reported pre-pregnancy weight. If self-reported pre-pregnancy weight was missing (N = 60), it was imputed based on weight at the first prenatal visit. GWG was evaluated as both a continuous and a categorical outcome (inadequate/adequate vs excessive GWG) based on the Institute of Medicine guidelines (IOM 2009).

2.6 Statistical Analysis

Maternal prenatal phthalate exposure was analyzed as early pregnancy (<20 weeks gestation), late pregnancy (≥ 20 weeks gestation), and the average of the two urinary phthalate concentrations. Phthalate concentrations were examined as continuous (log_2-transformed) and categorical (quartiles) variables. A ΣDEHP variable was created by summing the DEHP metabolites: MEHP, MEHHP, MEOHP, and MECCP. All other metabolites were analyzed individually.

Using multivariable logistic regression, we examined the association of maternal prenatal phthalate metabolite concentrations with development of GDM, IGT, and excessive GWG. The relationship between maternal prenatal phthalate metabolites and continuous GCT glucose levels was examined using multi-variable linear regression. Regression analyses were performed using Stata/IC 16.0.

2.7 Confounders

Potential confounders were selected *a priori* using a directed acyclic graph (Supplemental Figure S1). All maternal glycemic models controlled for maternal age, household poverty status, marital status, maternal education, country of birth, pre-pregnancy BMI, and sugar-sweetened beverage consumption during pregnancy. Covariates were characterized as shown in Table 1, with the exception of pre-pregnancy BMI which was used a continuous variable in the models. GWG was not included in glycemic models because of its strong correlation to pre-pregnancy BMI (Santos et al. 2018) and the possibility of it being on the causal pathway. Smoking during pregnancy (N=15) was tested but not included in the models

because the number of smokers was too low to support analysis and because no mothers who smoked developed GDM or IGT. Although 3 pregnancies resulted in twin births, this was not controlled for in the model because no mothers who had a multiple gestational birth had a GDM or IGT outcomes.

Results:

3.1 Study Characteristics

Demographic characteristics of 415 mothers are displayed in Table 1. Mothers in the study tended to have low-socioeconomic status with 63.4% living below the federal poverty threshold and only 18.7% achieving at least a high school diploma. Majority of the mothers were born in Mexico, younger than 30 years old, and living with their partner. Most mothers were obese or overweight before pregnancy. Majority of women reported drinking at least 2 sugar-sweetened beverages a day. Examination of glycemic outcomes showed 14.7% of mothers experiencing IGT and 7.5% participants developing GDM.

Distribution of prenatal urinary phthalates between the two measurements is displayed in Table 2. Most women had detectable urinary phthalate metabolites, with detection frequencies for all individual phthalate concentrations ranging from 87.7% to 100%. We observed the highest concentrations for MEP, followed by MBP. Our metabolite concentrations were similar to those of a nationally representative sample (CDC 2009).

3.2 Covariate analysis

Table 3 presents the individual prenatal urinary phthalate's geometric means for mothers' pre-pregnancy BMI and recommended weight gain during pregnancy. A dose-relationship was seen with increasing pre-pregnancy BMI across all 8 phthalate metabolites, with obese women having higher geometric means of all measured phthalates than women with normal BMI. However, only MiBP, MBzP, MCOP, and ΣDEHP were statically significant. Phthalate metabolite levels were not found to be significantly associated with recommended weight gain during pregnancy in bivariate analyses. Higher pre-pregnancy BMI was significantly associated with IGT, GDM, and excessive GWG (not shown). Other risk factors for GDM in this population were older age, lower income, and lower education; older age was also a risk factor for IGT.

3.3 Multivariable analysis

Table 4 presents the results of the multivariable regressions examining relationship between prenatal urinary phthalates and GDM, IGT, and excessive GWG as dichotomous outcomes and glucose levels on GCT as a continuous outcome. No association between exposure and maternal glycemic outcomes was observed, however MEP concentrations were associated with a slightly increased odds of excessive GWG (OR: 1.1 CI 1.0–1.3). We also found no associations with glycemic outcomes when phthalate concentrations were examined as quartiles of exposure (Supplemental Table S3) or when phthalates were divided into first and second halves of pregnancy (Supplemental Table S4–S5). Lastly, relative risks were calculated and the results were substantively the same.

3. Discussion

We found, in a pregnant Latina population, higher urinary concentrations of MEP, a metabolite of diethyl phthalate, were associated with excessive weight gain during pregnancy. Additionally, mothers who were obese and overweight prior to pregnancy had higher mean concentrations of MiBP, MBzP, MCOP, and ΣDEHP metabolites than mothers whose BMI were normal or underweight. Contrary to other studies, we found no associations between any phthalate metabolite and GDM, IGT, or having higher levels of plasma glucose.

Previous studies have connected maternal urinary MEP metabolite concentrations with increased GDM (Shaffer et al. 2019), IGT (James-Todd et al. 2016), plasma glucose levels (James-Todd et al. 2018), GWG (Bellavia et al. 2017; James-Todd et al. 2016), and first trimester BMI (Bellavia et al. 2017). In the Boston Lifecodes' pregnancy cohort (N=350), James-Todd et al. found that MEP metabolite concentrations were associated with maternal experience of impaired glucose tolerance (IGT), defined as a blood glucose level ≥140 mg/dL on the screening glucose challenge test (GCT), and with excessive gestational weight gain (James-Todd et al. 2016). A second study in a different population found a positive relationship between urinary MEP metabolite concentrations and continuous glucose levels and a negative relationship between MiBP and glucose levels (James-Todd et al. 2018). Lastly, among pregnant women participating in the The Infant and Development and Environment Study (TIDES) (N=701), a significant positive relationship was seen between the average of two trimester's urinary MEP metabolites and risk of GDM, but not IGT or a continuous plasma glucose (Shaffer et al. 2019). However, three cohort studies that have investigated phthalates and a maternal glycemic outcome have failed to find these associations (Fisher et al. 2018; Robledo et al. 2015; Shapiro et al. 2015), including in the largest cohort to date (N=1274) (Shapiro et al. 2015).

Varying results could be attributed to differences in phthalate measurement methods. Some studies, including this one, collected more than one phthalate measurement (Shaffer et al. 2019; James-Todd et al. 2016, James-Todd et al. 2018), while other studies relied on a single phthalate measurement taken early during pregnancy (Fisher et al. 2018; Robledo et al. 2015; Shapiro et al. 2015). Due to the nature of phthalates' short half-life in the body, usage of one phthalate measurement in pregnancy may not accurately reflect a mother's average prenatal phthalate exposure (Fisher et al. 2015).

Furthermore, phthalates may have varying impact at different times in pregnancy. Past studies have found associations between MEP and prenatal maternal glycemic outcomes using MEP levels from second trimester (James-Todd et al. 2018, 2016) and an average 1st trimester and 3rd trimester (Shaffer et al. 2019). But, these studies did not find association when only 1st trimester MEP levels were used. When we looked at specific time points (early vs. late pregnancy), we still found no associations with any of the glycemic outcomes.

Our study used phthalate measurements taken on average at 14.2 weeks (SD ± 5.1) and 26.9 weeks (SD ± 2.4). However, the standard deviation of the collection windows were wide, especially the first measurement with 95% of participants providing their sample between

9.2 weeks and 19.2 weeks. Due to this, we may not be capturing phthalate levels during the critical period where phthalates would have their largest impact.

Usage of different diagnostic criteria for GDM could also explain differences in results. Shaffer et al. utilized Carpenter-Coustan thresholds for GDM diagnosis on the GCT while Shapiro et al. followed Canadian GDM diagnostic guidelines, and Fisher et al. followed a one-step OGTT process. These differences have considerable impact on how many women would qualify as cases in each study (Ferrara et al. 2002; Schwartz et al. 1999).

Our study used both Carpenter-Coustan and medical records' ICD-9 coding to diagnosis GDM. Of the thirty-one mothers diagnosed with GDM, five were diagnosed using only ICD-9 coding without recorded OGTT values. It is possible that these five mothers may have been wrongly coded and may not truly had GDM. However, sensitivity analyses using only the mothers diagnosed with GDM from Carpenter-Coustan criteria similarly showed no associations.

Possible biological mechanisms linking phthalates to metabolic disorders center around phthalates' ability to bind to the nuclear hormone receptor superfamily PPAR and estrogen receptors (Chen et al. 2009; Desvergne et al. 2009). PPARs are widely expressed throughout human tissues. Their receptors are found in adipocytes, hepatocytes, muscle and endothelial cells where they play an important role in the regulation of glucose and lipid homeostasis (Grygiel-Górniak 2014). Of specific interest is PPAR gamma whose physiologic role includes regulation of adipocyte differentiation and maturation (Spiegelman 1998). Both in vitro and in vivo studies have shown that certain phthalates binding to PPAR gamma promotes adipogenesis (Bility 2004; Feige et al. 2007)(Güven et al. 2016).

Estrogen alpha and beta receptors also exert influence across multiple energy metabolism pathways from glucose transport to glycolysis to the Krebs cycle (Chen et al. 2009). A growing body of literature supports phthalates' ability to bind to estrogen receptors exerting an estrogenic effect which could lead to weight gain (Chen et al. 2014; Güven et al. 2016; Harris et al. 1997). Güven et al. showed that MEP acts as both an estrogenic and PPAR gamma agonist (Güven et al. 2016). Although MEP was not associated with hyperglycemia in our study it was associated with GWG, which is known risk factor for metabolic disorders.

There are some limitations to this study. First, multiple comparison were completed during our analysis. Thus, our association between MEP and excessive GWG could be due to chance. However, our finding is supported by the fact that MEP was also associated with child obesity in this same cohort and with GWG in other studies (Harley et al. 2017). Second, selection bias may have been introduced during exclusions. A total of 186 participants, representing 31% of initial participants were excluded in our analysis. However, the majority of exclusions were due to not having a large enough urine sample to complete a phthalate measurement, making the exclusions likely to be missing at random. Third, literature has shown that urinary phthalates measurements have low reproducibility and sensitivity throughout pregnancy (Fisher et al. 2015). Our study relied on two phthalate measurements, which, although better than a single measure, still may not accurately reflect

true participant average across their pregnancy. Additionally, time of day has also been shown to be a significant predictor of certain phthalate levels with MEP having higher levels in the morning while MCPP and DEHP metabolites have higher levels in the evening (Fisher et al. 2015). Our study did not standardize or adjust for time of day during our analysis. Both may have led to non-differential misclassification bias during the exposure assessment, which would have biased results towards the null. Fourth, while we adjusted for multiple known GDM risk factors including maternal age, household poverty status, marital status, maternal education, country of birth, pre-pregnancy BMI, and sugar beverage consumption during pregnancy, we were not able to account for family history of T2DM. Lastly, our sample size may have been too small to detect statistically significant associations between MEP and IGT or GDM.

Despite limitations, our study has multiple strengths. To our knowledge, our study is the first study to be completed in a Latina U.S. population who are at higher risk of GDM, obesity, and phthalate exposure. Majority of past study participants have been white, high income, and highly educated, a population that literature has characterized as low risk for development of GDM and lower exposure rates to phthalates than their Latina peers (Casagrande et al. 2018; Silva et. al 2004). Our study is also the first to adjust for aspects of maternal diet, which can have great impact on development of GDM and weight gain.

While our study did not find a significant relationship with phthalates and maternal glycemic outcomes, our results show a significant association between MEP metabolite and excessive GWG and between certain phthalates and higher pre-pregnancy BMI. This adds to the growing consensus that suggests MEP may play a role in metabolic dysfunction during pregnancy. To fully understand MEP's metabolic impact during pregnancy, more research is needed to identify GDM's critical window, including measures of phthalates at multiple times during pregnancy. Other areas of interest that future research could explore include MEP and its role in long-term maternal weight gain extending after pregnancy, which increases a mother's risk of developing chronic disease later in life.

4. Conclusion

Our study found that the phthalate metabolite MEP slightly increased the odds of a woman experiencing GWG, a well-established risk factor for development of GDM. Our study contributes to the growing body of literature that had identified an association with MEP and a metabolic disorder during pregnancy. Moreover, it adds to the discussion of whether regulation of phthalates in personal care products, an industry that is widely unregulated, is needed and whether the medical community should be counseling patients on potential harms of phthalates in pre-conception and prenatal appointments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Urinary phthalate metabolites were widely detected in a Latina pregnant population
- Maternal phthalate concentrations were not associated with gestational diabetes
- Maternal MEP concentrations were associated with excessive gestational weight gain

Table 1:

Demographic characteristics of cohort (N=415), CHAMACOS study, 1999–2000

	N	(%)
Maternal Age		
8–24	181	43.6%
25–29	133	32.1%
30–34	67	16.1%
35–45	34	8.2%
Income		
Below Poverty Threshold	263	63.4%
Above Poverty Threshold	152	36.6%
Marital Status		
Not Married	78	18.8%
Married/Living as Married	337	81.2%
Maternal Education		
≤ 6th grade	184	44.3%
7–12th grade	154	37.1%
≤High School Graduate	77	18.6%
Maternal Country of Birth		
Mexico	364	87.7%
US and Other	51	12.3%
Pre-pregnancy BMI		
Normal or Underweight	157	37.8%
Overweight	162	39.0%
Obese	96	23.1%
Weight Gain during Pregnancy		
Below adequate weight gain	64	15.8%
Adequate weight gain	118	29.1%
Above adequate weight gain	223	55.1%
Parity		
0	139	33.5%
1	118	28.4%
2+	158	38.1%
Smoking during Pregnancy		
No	400	96.4%
Yes	15	3.6%
Sugar Beverage Consumption		
<1 per day	81	20.0%
1 per day	112	27.7%
+2 per day	212	52.4%
Impaired Glucose Tolerance (>140 mg/dl)		
No	285	85.3%

	N	(%)
Yes	49	14.7%
Gestational Diabetes Mellitus		
No	383	92.5%
Yes	31	7.5%
Excessive Gestational Weight Gain		
No	182	44.9%
Yes	223	55.1%

Table 2:

Distribution of uncorrected and specific-gravity corrected (italics) prenatal urinary phthalate metabolites, CHAMACOS study 1999–2000

Phthalate Metabolite	% > LOD		Average of two measurements				
	1st measurement[a]	2nd measurement[b]	Geo. Mean	25th%	50th%	75th%	95th%
MEP (ng/ml)	100.0%	99.8%	184.6	78.2	181.5	422.5	1287.8
			236.7	*105.5*	*230.5*	*520.1*	*1662.8*
MBP (ng/ml)	98.3%	100%	22.9	12.3	21.9	45.9	107.8
			28.5	*16.0*	*27.2*	*51.1*	*121.2*
MiBP (ng.ml)	92.5%	94.9%	2.7	1.5	2.8	5.4	15.8
			3.3	*1.8*	*3.4*	*6.3*	*16.3*
MBzP (ng/ml)	97.6%	98.7%	7.2	3.8	7.8	14.9	34.4
			8.9	*4.9*	*9.4*	*17.8*	*40.2*
ΣDEHP (nmol/ml)	NA	NA	0.2	0.1	0.2	0.3	0.8
			0.2	*0.1*	*0.2*	*0.4*	*0.9*
MCPP (ng.ml)	87.6%	93.7%	1.7	1	2.1	3.2	6.3
			2.1	*1.3*	*2.4*	*3.7*	*7.0*
MCOP (ng/ml)	97.3%	96.7%	2.9	1.7	3.1	4.9	10.5
			3.7	*2.3*	*3.8*	*5.5*	*10.8*
MCNP (ng.ml)	95.4%	97%	1.8	1.2	1.9	3	6.0
			2.2	*1.5*	*2.3*	*3.3*	*7.4*

Abbreviations: LOD = limit of detection

[a] Mean 14.2 SD ± 5.0 weeks gestation

[b] Mean 26.9 SD ± 2.4 weeks gestation

Table 3:

Phthalate concentrations according to maternal pre-pregnancy BMI and GWG

	Urinary Phthalate Metabolites[a]							
	MEP	**MBP**	**MiBP**	**MBzP**	**ΣDEHP**	**MCPP**	**MCOP**	**MCNP**
Pre-pregnancy BMI								
Normal Weight or Below	217.3	25.3†	2.9**	7.3***	0.2**	1.9†	3.4*	2.2
Overweight	236.3	29.6	3.2	8.9	0.2	2.1	3.6	2.2
Obese	272.8	32.5	4.5	12.5	0.3	2.5	4.4	2.5
Weight Gain During Pregnancy[b]								
Below or Adequate weight gain	210.2†	27.7	3.4	8.6	0.2	2.2	3.8	2.3
Above adequate weight gain	264.5	29.1	3.3	9.2	0.2	2.1	3.6	2.2

[a] Urinary Metabolite Concentrations geometric means of the $\log^2$ and SG adjusted

[b] Internal Medicine recommended weight gain

† <0.1

* <0.05

** ≤0.01

Table 4.

Association of urinary phthalate metabolites and maternal glycemic outcomes

Maternal Glycemic Outcome	GDM[a]	IGT[b]	GCT Glucose Level (continuous)	Excessive GWG[c]
	AOR[d] (95% CI) N =405	AOR[d] (95% CI) N = 316	ABeta[d] (95% CI) N=316	AOR[d] (95% CI) N = 396
Phthalate Metabolite[e]				
MEP	1.1 (0.9, 1.4)	1.0 (0.8, 1.2)	− 1.0 (−2.8, 0.9)	1.1 (1.0, 1.3)*
MBP	1.0 (0.8, 1.5)	0.9 (0.7, 1.2)	− 0.9 (−3.3, 1.5)	1.1 (0.9, 1.3)
MIBP	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	− 0.3 (−2.5, 1.9)	1.0 (0.9, 1.2)
MBZP	1.1 (0.8, 1.5)	0.9 (0.7, 1.2)	− 1.0 (−3.4, 1.3)	1.1 (0.9, 1.2)
ΣDEHP	1.2 (0.8, 1.7)	0.9 (0.7, 1.3)	− 0.4 (−3.2, 2.4)	1.1 (0.9, 1.3)
MCPP	1.0 (0.7, 1.4)	1.0 (0.7, 1.3)	− 0.9 (−3.4, 1.6)	0.9 (0.8, 1.1)
MCOP	1.1 (0.7, 1.6)	1.0 (0.7, 1.4)	− 1.0 (−4.2, 2.3)	1.0 (0.8, 1.2)
MCNP	0.8 (0.6, 1.2)	1.0 (0.7, 1.3)	− 0.5 (−3.6, 2.6)	0.9 (0.8, 1.1)

Abbreviations: GDM = Gestational Diabetes Mellitus; IGT = Impaired Glucose Tolerance; GCT = Glucose Challenge Test; AOR = Adjusted Odds Ratio; CI = Confidence Interval; ABeta = Adjusted Beta

[a] GDM determined by medical record review

[b] IGT determined on GCT with glucose threshold value ≥140 mg/dl

[c] Excessive GWG determined by Institute of Medicine guidelines

[d] AOR were adjusted for maternal age, income, maternal education, marital status, sugar beverage consumption, country of birth, maternal pre-pregnancy BMI

[e] Phthalate variable were average of two urinary samples. Variables were logged for normality and adjusted for specific gravity

* <0.05

** ≤0.01