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Drilling and Production Activity Related to Unconventional Gas Development and Severity of Preterm Birth

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BACKGROUND: Studies of unconventional gas development (UGD) and preterm birth (PTB) have not presented risk estimates by well development phase or trimester.

OBJECTIVE: We examined phase and trimester-specific associations between UGD activity and PTB.

METHODS: We conducted a case–control study of women with singleton births in the Barnett Shale area, Texas, from 30 November 2010 to 29 November 2012. We individually age- and race/ethnicity-matched five controls to each PTB case ($n = 13{,}328$) and truncated controls' time at risk according to the matched case's gestational age. We created phase-specific UGD-activity metrics: *a*) inverse squared distance–weighted (IDW) count of wells in the drilling phase ≤ 0.5 mi (804.7 meters) of the residence and *b*) IDW sum of natural gas produced ≤ 0.5 mi of the residence. We also constructed trimester- and gestation-specific metrics. Metrics were categorized as follows: zero wells (reference), first, second, third tertiles of UGD activity. Analyses were repeated by PTB severity: extreme, very, and moderate (<28, 28 to <32, and 32 to <37 completed weeks). Data were analyzed using conditional logistic regression.

RESULTS: We found increased odds of PTB in the third tertile of the UGD drilling {odds ratio (OR) = 1.20 [95% confidence interval (CI): 1.06, 1.37]} and UGD-production [OR = 1.15 (1.05, 1.26)] metrics. Among women in the third tertile of UGD-production, associations were strongest in trimesters one [OR = 1.18 (1.02, 1.37)] and two [OR = 1.14 (0.99, 1.31). The greatest risk was observed for extremely PTB [third tertile ORs: UGD drilling, 2.00 (1.23, 3.24); UGD production, 1.53 (1.03–2.27)].

CONCLUSIONS: We found evidence of differences in phase- and trimester-specific associations of UGD and PTB and indication of particular risk associated with extremely preterm birth. Future studies should focus on quantifying specific chemical and nonchemical stressors associated with UGD. https://doi.org/10.1289/EHP2622

Introduction

Recent innovations in oil and gas extraction have led to increased use of unconventional gas development (UGD) strategies (U.S. EIA 2010). UGD involves high-volume hydraulic fracturing ("fracking") coupled with directional or horizontal drilling (Rahm 2011) to extract oil and gas from previously untapped shale formations. UGD includes a process of injecting a pressurized mixture of large volumes of water, sand, and potentially hazardous chemicals into wellbores, fracturing the rock and enabling outflow of trapped oil or gas (U.S. EPA 2013).

In addition to potential chemical contamination from fracking fluid, the industrial processes and equipment surrounding UGD, such as condensate tanks, well head compressors, pumps, and processing facilities, may contribute to air or water contamination (Fontenot et al. 2013; Moore et al. 2014; Vengosh et al. 2014). Additionally, heavy use of diesel trucks and equipment can result in increased ambient concentrations of particulate matter and diesel particulate matter during various phases of UGD (Coons and Walker 2008; Litovitz et al. 2013; Moore et al. 2014; Zielinska et al. 2011). Airborne volatile organic compounds (VOCs; e.g., benzene) and polycyclic aromatic hydrocarbons (PAHs; e.g., naphthalene, benzo[*a*]pyrene) have been detected near well drilling sites in several states (Colborn et al. 2014; Macey et al. 2014; McKenzie et al. 2012; TCEQ 2010).

Many contaminants associated specifically with UGD have been identified as reproductive or developmental toxicants (Elliott et al. 2017). Chemicals associated with UGD may also act as endocrine disruptors (EDs) (Elliott et al. 2017; Kassotis et al. 2014; Kassotis et al. 2016), often at levels far below regulatory thresholds (Vandenberg et al. 2012; Welshons et al. 2003). Human and animal studies demonstrate that endocrine-disrupting chemicals can alter reproductive function and interfere with normal fetal development (Lupo et al. 2011; Maffini et al. 2006; Webb et al. 2014). Further, nonchemical stressors such as noise and light pollution and community and social disruption may also be present in areas where well development activity is prevalent (Adgate et al. 2014; Korfmacher et al. 2013). It has been suggested that nonchemical stressors may affect susceptibility to chemical stressors by increasing allostatic load (McEwen 1998; Morello-Frosch and Shenassa 2006).

Previous studies have indicated positive associations between maternal residential proximity to well development activity (including UGD-specific activity) and adverse perinatal outcomes (Casey et al. 2016; McKenzie et al. 2014; Stacy et al. 2015; Whitworth et al. 2017), with some conflicting results regarding preterm birth. Whitworth et al. (2017) and Casey et al. (2016) each reported statistically significant positive associations between maternal residential proximity to UGD and preterm birth, whereas McKenzie et al. (2014) found a statistically significant negative association. Although Stacy et al. (2015) found no association between preterm birth and UGD among women in the highest two exposure quartiles, they reported statistically significantly decreased odds of preterm birth among women classified in the second exposure quartile. Exposure to UGD-related contaminants may affect preterm birth via oxidative stress and inflammation (Li et al. 2017; Slama et al. 2008) or via endocrine disruption (Balise et al. 2016; Elliott et al. 2017; Kassotis et al. 2014, 2016). Moreover, given potential increased psychosocial stressors associated with living

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near drilling sites, a maternal stress response may be activated, stimulating parturition (Brou et al. 2012; Menon et al. 2016).

Although existing studies provide some evidence of increased risk of preterm birth among women who live near UGD, they have not addressed potential critical windows of susceptibility and timing of prenatal exposure relative to gestation. Because UGD activities and emissions may vary by phase of well development, we hypothesized that risks associated with proximity to such activities would also vary (Brown et al. 2015; McKenzie et al. 2012; Rich et al. 2014). To our knowledge, previous studies have not published separate relative risk estimates for the association between UGD activity and preterm birth by well development phase, nor have specific relative risks been examined within pregnancy trimesters. Given this gap, we conducted a case–control study of preterm births nested within a cohort of women in the Barnett Shale region in Texas. Our goals were to examine the association between maternal residential proximity to UGD and preterm birth separately during two well development phases and to explore whether these associations varied by trimester.

Methods

Study Population

We conducted a case–control study nested within the cohort of 166,966 women with a singleton birth in the 24 counties covering the Barnett Shale area, Texas (Whitworth et al. 2017). This birth cohort was constructed based on all birth records in the study area from 30 November 2010 to 29 November 2012 obtained from the Texas Department of State Health Services, Center for Health Statistics. Two estimates of gestational age were recorded on the birth record: one based on the woman's reported last menstrual period (LMP) and a second clinical-based estimate. Implausible birth weight for gestational age combinations were corrected using methods described by Basso and Wilcox (2010). Records missing both the LMP-based and clinical-based estimates of gestational age were excluded ($n=28$), as were records for which both estimates indicated a gestational age either <22 wk or >44 completed weeks ($n=185$). An additional 227 ($\sim 0.1\%$) records were excluded for implausible birth weight for gestational age estimates, leaving 166,526 births.

A total of 366 records had a post office box or incomplete information regarding the maternal residential address at birth. Of the remaining 166,160 birth records, street-level geocoded location of the maternal residential address was available for 164,991 records: 161,810 were geocoded by the TX DSHS, and we manually geocoded 3,180 records in ArcMap 10.2.1 (ESRI). We subsequently excluded 1,164 births because the geocoded location of the maternal residence at birth was mapped outside the study area.

Preterm Birth

Among the 163,827 singleton births with an available estimate of gestational age and geocoded maternal address at birth, we identified all cases of preterm birth, defined as completed gestational age <37 wk. The control group consisted of term births (i.e., completed gestational age ≥37 wk) and was randomly selected and individually matched with cases by maternal age group (≤20, 21–25, 26–30, 31–35, and ≥35 wk) and race/ethnicity (non-Hispanic black, Hispanic, non-Hispanic white, and other). We identified 13,549 cases of preterm birth and selected five controls per case for a total of 67,745 controls. By definition, controls will have a longer time at risk than cases of preterm birth owing to their longer gestation. Thus, for the present analysis, we truncated controls' time at risk based on the gestational age of the matched case.

Exposure Assessment

We used a commercially available site, DrillingInfo (www.drillinginfo.com), to obtain data for all active UGD wells in the Barnett Shale between 1 January 2010 and 29 November 2012. We included data for wells as far back as January 2010 to characterize UGD activity across gestation for the earliest births in our study. DrillingInfo is updated on a bimonthly basis, and data used in this study were queried on 12 May 2015. For each UGD well in the 24-county Barnett Shale area, we obtained latitude and longitude, spud date (i.e., the date on which ground was broken in the process of well development), and most recent completion date [i.e., the date on which installation of well casing and hydraulic fracturing was completed (Wood et al. 2011)]. We also obtained the well-level monthly gas production as estimated by DrillingInfo in units of 1,000 cubic feet of natural gas (MCF). We then estimated daily gas production for each well assuming equal production throughout the month by dividing the estimated monthly gas production by the number of days in the month. UGD wells that were permitted but had not yet been drilled were not included in this study. We identified 14,351 unique UGD wells.

We estimated UGD activity proximal to the maternal residence at birth by first creating geographic buffers representing a 0.5-mi (804.7 meters) radius around the residence for each woman in the study. Then, for each woman during her time at risk during pregnancy, we calculated the geodesic distance from the residence to each well located within the 0.5-mi buffer. This distance was selected *a priori* given previous work identifying increased risk for PTB within 0.5 mi of UGD activity (Whitworth et al. 2017) as well as a health impact assessment (McKenzie et al. 2012) indicating elevated hazard indices when residing within 0.5-mi of UGD activity.

In addition to creating metrics representing activity across the at-risk pregnancy period, we also calculated trimester-specific metrics that captured activity during each of the three trimesters, defined as the first 13 wk (trimester 1), weeks 14–27 (trimester 2), and weeks ≥28 (trimester 3) (Nguyen and Wilcox 2005). Moreover, we created separate UGD activity metrics reflecting drilling and production activity within 0.5 mi of the residence. We created the UGD drilling metric according to

$$\mathrm{UGD}_{\mathrm{drilling}} = \sum_{i=1}^{n} \frac{1}{d_i^2},$$

where i is a given well in the drilling phase within 0.5 mi of the maternal residence during the period of interest (i.e., trimesters 1, 2, or 3, or the entire pregnancy), d is the exact geodesic line distance between well i and the residence, and n is the total number of wells in the drilling phase within 0.5 mi of the maternal residence. We used a similar calculation to construct the UGD production metric:

$$\mathrm{UGD}_{\mathrm{production}} = \sum_{i=1}^{n} \frac{\sum MCF}{d_i^2},$$

where ΣMCF represents the cumulative daily gas produced over the period of interest (i.e., trimesters 1, 2, or 3, or the entire pregnancy), and n is the total number of wells in the production phase within 0.5 mi (804.7 meters) of the maternal residence. All other terms are as in the UGD drilling metric. We categorized UGD drilling and production metrics by tertiles among controls with at least one well within 0.5 mi of the residence in the drilling or production phase, respectively. Women with zero UGD drilling and production wells within 0.5 mi of the residence served as the common referent group. Preliminary analyses of continuous IDW measures revealed weak correlation between the drilling and production metrics (Pearson's $\rho = 0.23$) and between their respective tertiles (Spearman's $\rho = 0.34$); thus, analyses proceeded by treating the two measures as independent.

Statistical Analysis

The following covariates were recorded from birth records: maternal education (<high school, high school graduate, some college, college graduate), parity (0, ≥1), smoking during pregnancy (yes/no), prepregnancy body mass index (BMI; $\leq 18.5\ \text{kg/m}^2$, $18.5\text{–}24.9\ \text{kg/m}^2$, $25.0\text{–}29.9\ \text{kg/m}^2$, $30.0\text{–}34.9\ \text{kg/m}^2$, $\geq 35.0\ \text{kg/m}^2$), infant sex, and previous poor pregnancy outcome (including a previous preterm birth, small-for-gestational age or intrauterine-growth restricted infant, or perinatal death/pregnancy termination) (yes/no). Timing and frequency of prenatal care was represented using the Kotelchuck Adequacy of Prenatal Care Utilization Index (APCUI; inadequate, intermediate, adequate, adequate plus, unknown) (Kotelchuck 1994). The "unknown" category includes women for whom the date of the first prenatal visit or the number of prenatal visits is missing, but for whom the birth record indicates that prenatal care was received. The "adequate plus" category represents women who have more than the recommended number of prenatal care visits, presumably because of high-risk pregnancies (Kotelchuck 1994). Given the consistent association between distance to the nearest major roadway (a proxy for traffic-related air pollution) with adverse pregnancy outcomes in previous studies (Stieb et al. 2012), we also created a variable representing maternal residential distance to the nearest major roadway. Briefly, we used maps from the Texas Department of Transportation (TXDOT 2015) to isolate roadways classified as interstates or major arteries according to the Federal Highway Functional Classification System and calculated the exact line distance from these roads to each woman's residence. For analysis, this variable was dichotomized based on whether there was a major roadway within 300 meters of the residence (Wu et al. 2011).

We implemented conditional logistic regression to examine the association between UGD drilling and production metrics and preterm birth during the entire pregnancy and for each trimester. Because cases and controls were matched on maternal age and race/ethnicity, these variables were not included in regression models. To enhance the comparability of phase- and trimester-specific models, we included the following set of covariates that were statistically significantly ($p < 0.05$) associated with preterm birth in all final adjusted models: prepregnancy BMI, education, smoking during pregnancy, infant sex, previous poor pregnancy outcome, and the Adequacy of Prenatal Care Utilization Index. Owing to missing data for some covariates, the final sample size for analysis was 13,332 cases and 66,933 controls, individually matched on maternal age and race/ethnicity. We computed p-values for linear trend by including the UGD variable in the regression model as a continuous variable.

Because preterm birth is heterogeneous and risk factors may vary according to the severity of prematurity (Moutquin 2003), we conducted sensitivity analyses evaluating associations according to the following multilevel categorization of preterm birth as defined by the World Health Organization (March of Dimes et al. 2012): extremely preterm (<28 completed weeks), very preterm (28 to <32 completed weeks), and moderately preterm (32 to <37 completed weeks). Subcategories were modeled simultaneously in a polytomous regression. All analyses were performed using SAS version 9.4 (SAS Institute Inc.), Stata version 13.1 (StataCorp LP), or ArcMap version 10.2.1 (ESRI). This study was approved by the UTHealth Committee for the Protection of Human Subjects and the TX DSHS Institutional Review Board (IRB). Further, given that this study relied on secondary data analysis of existing records, informed consent was not required.

Results

The mean age of study subjects was 27.5 y [standard deviation (SD) cases = 6.5, controls = 6.4) (Table 1). Most of the women in this study identified as Hispanic (37.9%); one-third (33.3%) of the women identified as non-Hispanic white, and 22.8% identified as non-Hispanic black. Slightly more cases than controls were overweight (13.2% vs. 12.3%) or obese (10.4% vs. 9.1%). Cases were also more likely to report smoking during pregnancy (5.9% vs. 4.2%), to not have a college degree (81.0% vs. 77.2%), to have a history of a poor pregnancy outcome (2.2% vs. 1.6%), and to have male infants (54.6% vs. 51.0%). Although similar proportions of cases and controls were classified as having inadequate utilization of prenatal care, a larger proportion of controls had intermediate (15.2% vs. 8.0%) or adequate (42.4% vs. 19.1%) prenatal care utilization, and far more cases were classified as having adequate plus (41.8% vs. 16.1%) prenatal care utilization, potentially indicating high-risk pregnancies. Parity was similar for cases and controls. The distribution of covariates by preterm birth severity was similar with some exceptions: A higher proportion of extremely preterm birth was observed among women who were non-Hispanic black, had BMI $\geq 35\ \text{kg/m}^2$, and had an unknown APCUI (see Table S1).

Table 1. Characteristics of women with a singleton birth in the Barnett Shale between 30 November 2010 and 29 November 2012 by preterm birth case status (cases, $n = 13{,}549$; controls, $n = 67{,}745$).

Characteristic	Cases *n* (%)	Controls *n* (%)
Maternal age in years, mean ± SD	27.5 ± 6.5	27.5 ± 6.4
<20	2,218 (16.4)	11,090 (16.4)
21–25	3,359 (24.8)	16,795 (24.8)
26–30	3,436 (25.4)	17,180 (25.4)
31–35	2,787 (20.6)	13,935 (20.6)
≥36	1749 (12.9)	8,745 (12.9)
Race/ethnicity		
Hispanic	5,137 (37.9)	25,685 (37.9)
Non-Hispanic white	4,514 (33.3)	22,570 (33.3)
Non-Hispanic black	3,083 (22.8)	15,415 (22.8)
Other	815 (6.0)	4,075 (6.0)
Prepregnancy BMI (kg/m^2)		
<18.5	620 (4.6)	2,519 (3.7)
18.5–24.9	6,642 (49.0)	34,733 (51.3)
25.0–29.9	2,984 (22.0)	15,657 (23.1)
30–34.9	1,780 (13.1)	8,330 (12.3)
≥35.0	1,414 (10.4)	6,133 (9.1)
Missing	109 (0.8)	373 (0.6)
Maternal education		
<High school	3,038 (22.4)	14,322 (21.1)
High school graduate	4,484 (33.1)	20,869 (30.8)
Some college	3,460 (25.5)	17,077 (25.2)
College degree	2,550 (18.8)	15,442 (22.8)
Missing	17 (<0.1)	35 (<0.1)
Adequacy of prenatal care utilization		
Inadequate	3,016 (22.3)	15,046 (22.2)
Intermediate	1,080 (8.0)	10,323 (15.2)
Adequate	2,590 (19.1)	28,724 (42.4)
Adequate plus	5,657 (41.8)	10,877 (16.1)
Unknown	1,206 (8.9)	2,775 (4.1)
Smoked during pregnancy		
No	12,644 (93.3)	64,496 (95.2)
Yes	804 (5.9)	2,812 (4.2)
Missing	101 (0.7)	437 (0.6)
Previous poor pregnancy outcome[a]		
No	13,251 (97.8)	66,635 (98.4)
Yes	298 (2.2)	1,110 (1.6)
Infant sex		
Male	7,402 (54.6)	34,525 (51.0)
Female	6,147 (45.4)	33,220 (49.0)

Note: BMI, body mass index; SD, standard deviation.
[a]Includes previous preterm birth, small-for-gestational age, intrauterine growth restriction, and perinatal death/pregnancy termination.

Table 2. Adjusted associations between unconventional gas development (UGD) activity during pregnancy and preterm birth among 80,257 women with a singleton birth in the Barnett Shale, 30 November 2010–29 November 2012.

	UGD-Drilling Activity			UGD-Production Activity		
Exposure	*n*	Cases	aOR[a] (95% CI)	*n*	Cases	aOR[a] (95% CI)
0 Wells	68,256	11,290	Reference	68,256	11,290	Reference
1st Tertile	1,813	283	1.03 (0.90, 1.18)	3,502	577	1.07 (0.97, 1.17)
2nd Tertile	1,831	295	1.03 (0.90, 1.18)	3,519	608	1.13 (1.02, 1.24)
3rd Tertile	1,912	342	1.20 (1.06, 1.37)	3,621	635	1.15 (1.05, 1.26)
p-Trend[b]			<0.01			<0.01

Note: aOR, adjusted odds ratio; CI, confidence interval.
[a]ORs were derived using conditional logistic regression, and five controls were individually matched to each case on maternal age (≤20, 21–25, 26–30, 31–35, ≥35 y) and race/ethnicity (non-Hispanic black, Hispanic, non-Hispanic white, other). The time at risk of each control was truncated based on the gestational age of the matched case. ORs were adjusted for prepregnancy body mass index, maternal education, smoking, Adequacy of Prenatal Care Utilization index, previous poor pregnancy outcome, and infant sex.
[b]Computed by including the UGD variable in the regression model as a continuous variable.

Relative to women with no UGD wells near their homes, we observed odds ratios (ORs) near the null value for women in the first {OR = 1.03 [95% confidence interval (CI): 0.90, 1.18]} and second [OR = 1.03 (95% CI: 0.90, 1.18)] tertiles of UGD drilling activity during pregnancy. In contrast, women classified in the highest tertile of drilling activity had 20% higher odds of preterm birth (95% CI: 6%, 37%) compared with women with no UGD wells. Increasing, albeit moderate, associations were observed between UGD production activity during pregnancy and preterm birth across all tertiles (Table 2). We observed statistically significant ($p < 0.01$) p-values for trend across tertiles of each metric.

Trimester-specific associations between maternal residential proximity to UGD activity and preterm birth are presented in Table 3. Among women classified in the highest tertile of UGD drilling activity, we observed little trimester-specific variability in associations with preterm birth (increase in odds ranged from 19–24%). Among women living near the greatest density of UGD production activity, we observed the strongest associations with preterm birth in the first two trimesters.

We also examined the associations by preterm birth severity (extremely, very, and moderately preterm) using polytomous regression (Table 4). Owing to small cell counts, we were unable to explore trimester-specific associations among these subtypes. This analysis revealed the strongest associations between UGD activity and extremely preterm births. Compared with women with no UGD wells within 0.5 mi of their homes, women classified in the highest tertile of the UGD drilling or production activity metrics had 2.0 (95% CI: 1.23, 3.24) and 1.53 (95% CI: 1.03, 2.27) times the odds of extremely preterm birth, respectively. We observed only modest associations between UGD activity and moderately preterm birth among women classified in the highest tertiles of the UGD drilling [OR = 1.18 (95% CI: 1.03, 1.36)] and production [OR = 1.15 (95% CI: 1.04, 1.27)] metrics. Little evidence was observed for an association between UGD activity and very preterm birth.

Discussion

In this large case–control study nested within a cohort, we observed evidence of a positive association between maternal residential proximity to UGD activity and preterm birth. We observed evidence of UGD phase-specific differences in risk of preterm birth, although the magnitude of differences was small. We observed little difference in trimester-specific risk associated with UGD drilling activity, but our results appear to suggest slightly greater risk of preterm birth associated with UGD production activity earlier in pregnancy. Not only is our study the first to examine phase and trimester-specific UGD associations with preterm birth, but given our large sample size, we were also able to examine potential differences in risk according to severity of preterm birth. We found

Table 3. Adjusted associations between unconventional gas development (UGD) activity during pregnancy and preterm birth among 80,257 women with a singleton birth in the Barnett Shale, 30 November 2010–29 November 2012.

	UGD-Drilling Activity			UGD-Production Activity		
Exposure	*n*	Cases	aOR[a] (95% CI)	*n*	Cases	aOR[a] (95% CI)
Trimester One						
0 Wells	68,256	11,290	Reference	68,256	11,290	Reference
1st Tertile	1,482	227	1.03 (0.88, 1.19)	4,937	791	1.03 (0.95, 1.12)
2nd Tertile	1,116	169	0.96 (0.80, 1.14)	3,081	558	1.20 (1.09, 1.33)
3rd Tertile	898	167	1.24 (1.03, 1.49)	1,408	252	1.18 (1.02, 1.37)
p-trend[b]			0.11			<0.01
Trimester Two						
0 Wells	68,256	11,290	Reference	68,256	11,290	Reference
1st Tertile	1,380	233	1.10 (0.94, 1.28)	5,135	820	1.02 (0.94, 1.11)
2nd Tertile	1,077	183	1.15 (0.96, 1.33)	3,324	594	1.19 (1.08, 1.31)
3rd Tertile	878	161	1.21 (1.00, 1.45)	1,574	279	1.14 (0.99, 1.31)
p-trendb			<0.01			<0.01
Trimester Three						
0 Wells	68,256	11,290	Reference	68,256	11,290	Reference
1st Tertile	799	134	1.13 (0.93, 1.39)	5,994	1,024	1.10 (1.02, 1.19)
2nd Tertile	527	82	0.95 (0.73, 1.22)	2,508	451	1.19 (1.06, 1.33)
3rd Tertile	358	63	1.19 (0.89, 1.60)	745	109	0.89 (0.72, 1.10)
p-Trend[b]			0.31			0.01

Note: aOR, adjusted odds ratio; CI, confidence interval.
[a]ORs were derived using conditional logistic regression, and five controls were individually matched to each case on maternal age (≤20, 21–25, 26–30, 31–35, ≥35 y) and race/ethnicity (non-Hispanic black, Hispanic, non-Hispanic white, other). The time at risk of each control was truncated based on the gestational age of the matched case. ORs were adjusted for prepregnancy body mass index, maternal education, smoking, Adequacy of Prenatal Care Utilization index, previous poor pregnancy outcome, and infant sex.
[b]Computed by including the UGD variable in the regression model as a continuous variable.

Table 4. Adjusted associations between unconventional gas development (UGD) activity during pregnancy and severity of preterm birth among 80,257 women with a singleton birth in the Barnett Shale, 30 November 2010–29 November 2012.

	UGD-Drilling Activity			UGD-Production Activity		
Exposure	*n*	Cases	aOR[a] (95% CI)	*n*	Cases	aOR[a] (95% CI)
Extremely preterm						
0 Wells	68,256	873	Reference	68,256	873	Reference
1st Tertile	1,813	15	1.00 (0.56, 1.81)	3,502	49	1.22 (0.86, 1.74)
2nd Tertile	1,831	13	0.66 (0.35, 1.22)	3,519	46	1.14 (0.80, 1.63)
3rd Tertile	1,912	28	2.00 (1.23, 3.24)	3,621	38	1.53 (1.03, 2.27)
p-trend[b]			0.12			0.03
Very preterm						
0 Wells	68,256	1,194	Reference	68,256	1,194	Reference
1st Tertile	1,813	31	1.31 (0.87, 1.98)	3,502	48	0.86 (0.62, 1.20)
2nd Tertile	1,831	32	0.95 (0.63, 1.42)	3,519	61	1.19 (0.88, 1.60)
3rd Tertile	1,912	27	0.97 (0.62, 1.52)	3,621	54	1.01 (0.74, 1.39)
p-trend[b]			0.98			0.67
Moderately preterm						
0 Wells	68,256	9,223	Reference	68,256	9,223	Reference
1st Tertile	1,813	237	1.00 (0.86, 1.17)	3,502	480	1.08 (0.97, 1.20)
2nd Tertile	1,831	250	1.06 (0.92, 1.23)	3,519	501	1.12 (1.01, 1.24)
3rd Tertile	1,912	287	1.18 (1.03, 1.36)	3,621	543	1.15 (1.04, 1.27)
p-Trend[b]			0.02			<0.01

Note: aOR, adjusted odds ratio; CI, confidence interval.
[a]ORs were derived using conditional logistic regression, and five controls were individually matched to each case on maternal age (≤20, 21–25, 26–30, 31–35, ≥35 y) and race/ethnicity (non-Hispanic black, Hispanic, non-Hispanic white, other). The time at risk of each control was truncated based on the gestational age of the matched case. ORs were adjusted for prepregnancy body mass index, maternal education, smoking, Adequacy of Prenatal Care Utilization index, previous poor pregnancy outcome, and infant sex.
[b]Computed by including the UGD variable in the regression model as a continuous variable.

the strongest associations between UGD activity, regardless of phase, and extremely preterm birth.

Few previous studies have examined UGD activity in relation to preterm birth. A previous analysis of women in the Barnett Shale, without consideration of drilling phase, indicated increased odds of preterm birth associated with maternal residential proximity to UGD activity regardless of whether UGD activity was captured within 0.5-, 2-, or 10-mile (804.7-, 3,218.7-, or 16,093.4-meter) residential buffers (third-tertile ORs ranging from 1.14–1.15) (Whitworth et al. 2017). Two previous studies conducted in the Marcellus Shale, in Pennsylvania, reported conflicting results. Casey et al. (2016) considered all active UGD wells in the state during a woman's pregnancy and reported a positive association between UGD activity and preterm birth [fourth vs. first quartile OR = 1.9 (95% CI: 1.2, 2.9)]. Although they did not present ORs among extremely or very preterm births, Casey et al. (2016) did restrict their analysis to moderate and late preterm births [fourth vs. first quartile OR = 1.5 (95% CI: 1.0, 2.4)]. In addition, although Casey et al. (2016) initially constructed individual phase-specific metrics, because of high collinearity between them (ρ, 0.6–0.9), they were each z-transformed and summed to create a final metric of total UGD activity; the authors did not present risk estimates by phase (Casey et al. 2016). Stacy et al. (2015) considered wells that were active during the year of the child's birth and that were located within 10 miles (16,093.4 meters) of a woman's residence; they found no association with preterm birth. In a study conducted in Colorado, McKenzie et al. (2014) reported a small protective effect between increased well development activity and preterm birth, but like Stacy et al. (2015), they included active wells within 10 miles of the maternal residence at any time during the year of the child's birth. Further, no distinction was made between conventional and unconventional drilling in that study. In sensitivity analyses, McKenzie et al. (2014) also reported associations for well development activity within smaller residential buffers [i.e., 2 and 5 miles (3,218.7 and 8,046.7 meters)] and preterm birth; in each of these analyses, the protective effect observed among women in the highest tertile disappeared. Interestingly, we found the strongest association with UGD activity among extremely preterm births, with little evidence of an association with very preterm births and only a modest association with moderately preterm births. To our knowledge, ours is the first study to examine the association between UGD activity and preterm birth severity.

Identifying potential critical windows of susceptibility during pregnancy when exposures may have particularly harmful effects on the fetus has been identified as a methodologic challenge in studying the relationship between environmental exposures and perinatal health end points (Woodruff et al. 2009). It has been posited that early pregnancy may be important because it is during this period that development and attachment of the placenta occurs, and initial genetic programming is determined (Ritz and Wilhelm 2008; Woodruff et al. 2009). However, a consensus as to the most important critical window of susceptibility for preterm birth has not been reached and may vary given the severity of preterm birth as well as different exposures. Although previous studies investigating the association between UGD and preterm birth have not examined windows of susceptibility, evidence from studies evaluating air pollution impacts on fetal growth and preterm birth indicate potentially stronger effects during the first and third trimesters (Ritz and Wilhelm 2008; Woodruff et al. 2009). In the present study, trimester-specific differences in risk associated with UGD drilling activity were minimal. However, our results are suggestive of greater risk of preterm birth associated with UGD production activity in the first two trimesters. Although the correlation between trimester-specific drilling metrics was relatively small (Pearson's $\rho = 0.16$–0.18), there was relatively high correlation between trimester-specific production metrics (Pearson's $\rho = 0.54$–0.85), likely because of the long duration of the production period over the life cycle of a well. Thus, our ability to detect independent associations by trimester was limited.

Maternal residential proximity to UGD encompasses a range of potential exposures, including chemical contamination of ambient air and drinking water, as well as nonchemical stressors. Although it is possible that local water sources may be contaminated owing to UGD activity, water contamination is episodic in nature (U.S. EPA 2016). Further, the population of the present study in the Barnett Shale is primarily from urban and suburban areas and is not likely to rely on private water sources. However, UGD activities that may result in increased ambient air contamination (e.g., the use of diesel-powered equipment, generators, and trucks) occur continuously throughout the drilling process. Modeling of ambient air pollution in the Barnett Shale has implicated UGD as a contributor to ambient ozone concentrations in the area (Olaguer 2012), which may also indicate increased concentrations of volatile organic compounds (VOCs) because ozone is a secondary pollutant formed in reactions between nitrogen oxides and VOCs in the presence of sunlight. UGD has also been associated with increased ambient concentrations of benzene (Bunch et al. 2014; Halliday et al. 2016; Macey et al. 2014; Pétron et al. 2014; Rich et al. 2014; Warneke et al. 2014; Zielinska et al. 2011).

To our knowledge, ours is the first study to report relative risk estimates of the association between UGD and preterm birth by well development phase. Even so, the data we obtained for wells only permitted classification of two broad phases encompassing either drilling or production. Unfortunately, we did not have access to dates that would allow a more refined distinction (e.g., we did not have access to specific dates of hydraulic fracturing). Thus, the drilling phase as defined in our study is presumed to include activities related to drilling of the wellbore and installation of well casing, as well as hydraulic fracturing. Although the drilling phase represents a shorter period of intense activity involving heavy diesel-powered equipment and trucks, the use of chemicals related to hydraulic fracturing, and flow-back of "produced" water, the production phase represents a longer period involving the flowback of gas, condensate, and produced water, as well as possible on-site storage of these materials (Rahm 2011). Additionally, diesel trucks may be used during the production phase in servicing the well or transporting materials (Rahm 2011). Previous studies have indicated differences in potential exposure to air pollutants by UGD phase, although studies have been inconsistent in terms of the relative impact of each phase on air quality (Colborn et al. 2014; NYSDEC 2011). Although the estimated risk of delivering an extremely preterm baby was higher among women classified in the highest versus lowest category of both UGD drilling and production activity, the magnitude of this association was much greater for drilling activity.

Because adverse birth outcomes such as preterm birth can result from many variations of cascading physiological responses, identification of specific causal agents from complex environmental mixtures has not been firmly established (Slama et al. 2008; Wright 2017). However, several potential mechanisms have been proposed. Endocrine disruption is a possible mechanism through which many UGD-related contaminants may affect preterm birth (Balise et al. 2016; Elliott et al. 2017; Kassotis et al. 2016). Air pollution in particular has been posited to affect preterm birth through mechanisms related to oxidative stress, inflammatory pathways, or endothelial dysfunction (Li et al. 2017; Slama et al. 2008; Wright 2017). In addition to chemical contamination, UGD activity has been associated with increased nonchemical stressors [see the directed acyclic graph developed by Casey and Schwartz (2016)], including noise and light pollution (Adgate et al. 2014). Such nonchemical stressors may heighten susceptibility to chemical stressors by affecting women's allostatic load (Morello-Frosch and Shenassa 2006). Maternal stress may also influence preterm birth through "dysregulated parturition," a theory in which the human stress response leads to a release of hormones that may influence parturition (Brou et al. 2012; Menon et al. 2016).

Our study was strengthened by the large sample size, which allowed for evaluation of preterm birth severity as well as trimester-specific UGD activity. Additionally, the use of the matched case–control design allowed us to correct the exposure period of the matched control and thus to account for the fact that women with preterm births may otherwise be assigned lower exposure values by virtue of their shorter gestation (Slama et al. 2008). The potential for selection bias in this study is minimized owing to the nested nature of the study and because controls were randomly selected from the full source cohort; thus, our results should be comparable to those of a cohort analysis (Kass and Gold 2007). Unfortunately, because we were relying only on birth records, and thus because UGD activity was based on the maternal residence at birth, we were unable to assess the potential impact of maternal mobility during pregnancy. Although previous studies have indicated that just under one-third of women in Texas move during pregnancy (Canfield et al. 2006), Lupo et al. (2010) conducted another study among women in Texas and reported that among the women who changed residences during pregnancy, the new residence generally was not far from the original residence, and assignment of area-level exposure was not largely affected. In addition, women who moved tended to move to areas with similar demographic and neighborhood characteristics (Lupo et al. 2010). Thus, on average, the expected direction of any bias resulting from mobility during pregnancy would be toward the null. Additionally, the UGD activity metric used in our study is nonspecific; it does not measure exposure *per se*. However, our goal was to examine potential harmful effects resulting from living in close proximity to UGD, which encompasses myriad exposures from a variety of chemical and nonchemical stressors and which may occur through a variety of pathways.

Conclusions

In conclusion, this large population-based case–control study adds to the evidence of adverse perinatal health impacts associated with maternal residential proximity to UGD activity in a diverse population. Our findings also suggest that associations between UGD and preterm birth may be strongest for extremely preterm births. Given the range of potential chemical and nonchemical exposures associated with UGD, it is imperative to conduct comprehensive studies to characterize specific exposures experienced by individuals affected by UGD. These data are critical to fully understand risk and to inform prevention strategies.

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