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Impact of Parental Obesity on Neonatal Markers of Inflammation and Immune Response

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Abstract

Background/Objectives—Maternal obesity may influence neonatal and childhood morbidities through increased inflammation and/or altered immune response. Less is known about paternal obesity. We hypothesized that excessive parental weight contributes to elevated inflammation and altered immunoglobulin (Ig) profiles in neonates.

Subjects/Methods—In the Upstate KIDS Study maternal pre-pregnancy body mass index (BMI) was obtained from vital records and paternal BMI from maternal report. Biomarkers were measured from newborn dried blood spots (DBS) among neonates whose parents provided consent. Inflammatory scores were calculated by assigning one point for each of 5 pro-inflammatory biomarkers above the median and one point for an anti-inflammatory cytokine below the median. Linear regression models and generalized estimating equations were used to estimate mean differences (β) and 95% confidence intervals (CI) in the inflammatory score and Ig levels by parental overweight/obesity status compared to normal weight.

Results—Among 2974 pregnancies, 51% were complicated by excessive maternal weight (BMI>25), 73% by excessive paternal weight, and 28% by excessive gestational weight gain. Maternal BMI categories of overweight (BMI 25.0-29.9) and obese class II/III (BMI≥35) were

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

associated with increased neonatal inflammation scores (β=0.12, 95% CI: 0.02, 0.21; p=0.02, and β=0.13, CI: −0.002, 0.26; p=0.05, respectively) but no increase was observed in the obese class I group (BMI 30-34.9). Mothers with class I and class II/III obesity had newborns with increased IgM levels (β=0.11, CI: 0.04, 0.17; p=0.001 and β=0.12, CI: 0.05, 0.19); p<0.001, respectively). Paternal groups of overweight, obese class I and obese class II/III had decreased neonatal IgM levels (β=−0.08, CI: −0.13,-0.03, p=0.001; β=−0.07, CI: −0.13, −0.01, p=0.029 and β=−0.11, CI: −0.19,-0.04, p=0.003, respectively).

Conclusions—Excessive maternal weight was generally associated with increased inflammation and IgM supporting previous observations of maternal obesity and immune dysregulation in offspring. The role of paternal obesity requires further study.

INTRODUCTION

In the United States, the Centers for Disease Control and Prevention reported that 44.3% of pregnancies were complicated by excessive maternal weight in 2014.[1] The influence of maternal weight and gestational weight gain on both perinatal health and transgenerational health are subjects of frequent study, and the effect of paternal obesity on offspring is increasingly gaining interest.[2, 3]

Apart from the impact of maternal obesity on increasing numerous fetal and perinatal health risks,[4-7] studies also demonstrate continued long-term risks for offspring including childhood obesity,[8, 9] metabolic dysregulation,[9] asthma[2, 10] and increased inflammation.[10-12] Additionally, as defined by the 2009 Institute of Medicine (IOM) guidelines, [13] low as well as excessive gestational weight gain (EGWG) are associated with increased infant mortality,[14, 15] large for gestational age, and neonatal intensive care admissions.[16] Furthermore, there is considerable concern that EGWG is predictive of childhood obesity as supported by animal[17] and epidemiologic data.[18] Given the morbidities associated with excessive maternal weight and our understanding of the relationship between adiposity and inflammation, it has been postulated that maternal obesity causes increased intrauterine inflammation in both fetal and placental circuits.[19-21] However, there are limited data available on the effect of maternal obesity on neonatal inflammatory markers and immunoglobulin (Ig) levels such that specific aspects of this pathophysiology remain uncertain.[10, 20-24]

There are also limited data on the impact of paternal obesity on offspring health. A few epidemiologic studies have evaluated paternal obesity and offspring morbidity with intriguing results.[2, 11, 25] Paternal obesity may increase the risk of obesity,[25] cardiovascular disease,[2] and inflammation[11] in offspring. Animal data indicate that paternal obesity alters seminal fluid[26] and in general, altered seminal fluid can affect the metabolic phenotype of offspring.[27] Additionally, Soubry and colleagues identified altered neonatal methylation patterns associated with paternal obesity.[3] Ultimately, further research is needed to fully understand the role of paternal obesity on child health. Also of note, assessing paternal obesity may help us understand the extent to which intrauterine programming associated with maternal obesity contributes to offspring morbidities.[28]

To help identify biologic pathways through which both maternal and paternal obesity affect neonatal health, we evaluated associations between maternal and paternal obesity, gestational weight gain, and biomarkers of neonatal inflammation and immune activity as measured in newborn dried blood spots (DBS) while accounting for sociodemographic and lifestyle risk factors.

MATERIALS AND METHODS

Study Population

The Upstate KIDS study is a population-based birth cohort designed to study the effects of infertility treatment on child health and development.[29] Mothers were recruited after live births in New York State (excluding New York City) between 2008 and 2010. Enrollment occurred approximately 4 months postpartum, at which time baseline questionnaires were completed. At 8 months postpartum, we asked for parents' permission to use residual newborn DBS from the state newborn screening program to measure biomarker levels. The current analysis includes children whose parents agreed to consent for use (n=2310 infants excluded).[30] In addition, we limited investigations to singletons and twins (n=92 triplets/quadruplets excluded), mothers with baseline questionnaire data (n=198 children excluded), infants with information for at least one biomarker of interest (n=12 children excluded), and mothers with body mass index (BMI) information (n=4 children excluded). Our final study sample included 3555 children (born to 2974 mothers). The Institutional Review Boards (IRB) of the New York State Department of Health (#07-097) and the University at Albany (#08-179) approved the study, and both IRB-serving institutes entered into a reliance agreement with the National Institutes of Health. Parents provided written informed consent upon enrollment.

Exposures & Covariates

Maternal obesity was defined using pre-pregnancy body mass index, calculated as maternal weight in kilograms over height (in meters) squared;[31] these anthropometrics were obtained from birth certificates or maternal report at baseline where missing (~2%). Maternal obesity was categorized into five categories based on standard BMI cut-offs: underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese class I (30.0-34.9 kg/m^2), and obese classes II and III (>35 kg/m^2).[31] Paternal obesity was similarly defined, using calculated BMI obtained from maternal report of paternal height and weight and categorized into 4 groups: underweight and normal weight (<24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese class I (30.0-34.9 kg/m^2), and obese classes II and III (>35 kg/m^2). Underweight and normal weight men were grouped together as only 30 men were classified as being underweight. We based our definitions for low (LGWG), appropriate (AGWG), and EGWG on the 2009 IOM recommendations specific to pre-pregnancy BMI categories and infant plurality.[13]

Covariate information on maternal age and insurance, as well as infant characteristics, including birth weight, gestational age, and gender were obtained from birth certificates. Information on maternal race and ethnicity, education, smoking and drinking during pregnancy, married/living as married, and dietary supplementation during pregnancy were

obtained from the baseline questionnaire. Paternal weight and height were obtained from maternal report on this questionnaire.

Outcomes

Inflammatory biomarker and Ig levels were measured from DBS taken 2-3 days after birth. Blood spots were initially stored at 4°C by the New York State Newborn Screening Program but frozen after retrieval. The elution of analytes from the DBS punches and their preparation for the Luminex assays were performed as previously described for analysis of immunoglobulins.[30, 32] Inflammatory biomarkers and Igs collected from the blood spots were measured as part of the Kit A, Obesity, and Ig Panels (R&D Systems, Minneapolis, MN, USA) and further analyzed using the Luminex^{100} analyzer with xPONTENT 3.1 software (Luminex System, Austin, TX, USA). The specific inflammatory markers of interest, processed using Luminex^{100}, included c-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and four interleukins: interleukin 1 alpha (IL-1α), interleukin 1 receptor antagonist (IL-1ra), interleukin 6 (IL-6), and interleukin 8 (IL-8). Igs measured via Luminex^{100} included IgA, IgM, IgG subclasses. IgE was analyzed using ELISA (MABTECH Inc., Cincinnati, OH, USA). Intra-assay coefficients of variation (CV) were 8.6% for CRP, 8.4% for TNF-α and ranged from 10.1 – 16.9% for the interleukins. Intra-assay CVs for all Ig's ranged from 4.8%– 12.0%. Batch effects were corrected for in the biomarkers of interest using ComBat[33], a statistical program that removes measurement error introduced when samples are processed in multiple batches. ComBat was implemented in R.[34]

These inflammatory markers were selected *a priori* based on literature describing biological pathways involved in inflammation.[35, 36] Each newborn was assigned one point for a value above the population median level for each pro-inflammatory biomarker (IL-1α, IL-6, IL-8, CRP, TNF-α), and for the anti-inflammatory biomarker, IL-1ra, one point was given for a value below the median level. The points for each inflammatory biomarker were then summed in order to derive an overall inflammation score with scores ranging from 0 to 6 for each child.[37]

Statistical Analyses

Chi-square and t-tests were used to compare and contrast parental and neonatal characteristics by maternal obesity status for all pregnancies, which included all singletons and one randomly selected twin (versus both twins; n=2974 pregnancies). Regression analyses were performed on the entire cohort (n = 3555 neonates). Multiple imputation was used for missing biomarker and covariate information when needed (marital status, paternal BMI, private insurance, smoking during pregnancy, and parity). CRP and all Igs were log transformed for normality. Generalized estimating equations with robust standard errors were used for the entire cohort to account for correlated observations among the twins. We estimated associations between parental obesity and an overall neonatal inflammation score, as well as continuous levels of individual biomarkers and Igs. Maternal obesity analyses were adjusted for maternal age, race and ethnicity, education, insurance, smoking during pregnancy, alcohol use during pregnancy, dietary supplementation during pregnancy, parity,

infant plurality, and pate rnal BMI. Paternal obesity models were adjusted for the same confounders (except for paternal BMI) and additionally adjusted for maternal BMI.

In secondary analyses, similar models were used to examine the association between GWG and continuous levels of biomarkers and Igs in the full cohort. Models were adjusted for the same covariates as in the parental obesity models. However, both paternal and maternal BMI were additionally included in the models. Eleven children were removed from GWG analyses due to missing exposure information (n=3544 infants).

Sampling weights were used in all analyses to account for the study design, which oversampled on singletons conceived with infertility treatment and twin births. An additional sampling weight was applied to account for biomarker consent and availability in our study sample. A p-value of <0.05 was statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Parental and infant characteristics among 2974 pregnancies are described in Table 1. Previously, the study examined differences between parents who consented for use of newborn DBS and those who did not, finding small absolute differences in sociodemographic factors.[30] Infant sex, plurality, and gestational age were equally represented across categories of maternal BMI. As expected, mean birth weights and gestational weight gains were significantly different between categories: the prevalence of EGWG was highest among mothers classified as overweight and obese class I and mothers classified as underweight had the lowest mean newborn birth weight. Mothers with the highest and lowest BMIs were among the least likely to be insured or married and mothers with the highest BMIs were less likely to complete more years of education. Paternal BMI also varied between maternal BMI categories with increased paternal BMI associated with increased maternal BMI. We show distributions of the biomarkers as measured in DBS stratified by parental BMI in Supplemental Tables 1 & 2.

Unadjusted and adjusted mean differences (β) in continuous measures of neonatal biomarkers and Igs were estimated across maternal BMI groups (Table 2). After adjustment, maternal overweight and obesity class II/III categories were associated with increased neonatal CRP levels (β=0.11, 95% CI [confidence interval]:0.04, 0.17; p=0.001 and β= 0.10, 95% CI:0.02, 0.19; p=0.02 respectively), but the difference associated with obesity class I was smaller in magnitude and did not reach statistical significance. The difference in log units equated to percent changes of 11.6% (95% CI:4.08%, 18.53%) in the overweight group and 10.5% (95% CI:2.02%, 20.92%) in the obese class II/III groups compared to the normal weight group. Being overweight was also associated with an increased neonatal inflammation score after adjustment (β=0.12 points, 95% CI:0.02-0.21; p=0.022). We did not identify significant associations between maternal BMI and TNF-α levels (data not shown).

Maternal BMI was similarly variably associated with Ig levels. Increased neonatal IgM levels were noted among mothers with class I (β=0.11, 95% CI:0.04, 0.17; p=0.001) and

class II/III obesity (β=0.12, 95% CI:0.05, 0.19; p=<0.001) after adjustment (Table 2) and a linear trend across categories of BMI was confirmed (p<0.01). Extremes of BMI (underweight and obesity class II/III) were associated with decreases in neonatal IgG4. Being underweight was also associated with decreased neonatal IgG2 after adjustment.

In both unadjusted and adjusted models, paternal overweight or obesity was not associated with the neonatal inflammation score or CRP (Table 3). In contrast to maternal obesity, paternal membership in overweight or obese (all classes) BMI groups was associated with decreased neonatal IgM levels after adjustment (Table 3). This inverse trend was confirmed upon evaluating for a linear trend (p=< 0.01). No other significant associations between Ig levels and paternal obesity.

EGWG was associated with decreased IgG3 levels (β=−0.06, 95% CI:−0.10, −0.01; p=0.022) compared with neonates of mothers in the AGWG group (Table 4). Though not significant, we noted a trend toward decreased IgA levels among neonates exposed to EGWG (p = 0.09). Otherwise, no associations were identified between EGWG and newborn inflammation.

DISCUSSION

To our knowledge, this is the largest study examining associations between parental BMI and GWG and neonatal markers of inflammation and immune function. We identified associations between maternal BMI categories and neonatal inflammation, as well as parental BMI categories and neonatal IgM and IgG subclass levels. Increasing CRP levels were not consistently identified among neonates born to overweight or obese mothers, as those born to mothers in the obese class I group did not have significantly increased CRP levels relative to those born to normal weight mothers, while those born to mothers in the overweight or obese class II/III did. Interestingly, our results suggest that neonatal IgM levels were decreased among those born to fathers with high BMI (relative to normal and underweight fathers) and may be increased among those born to mothers with higher BMI.

Inflammatory Markers

The elevated inflammation score and CRP levels identified in infants of overweight and obese class II/III mothers compared to infants born to normal weight mothers is consistent with our hypothesis and previous literature. It is well documented that obesity is a state of low grade inflammation regardless of gravid status.[21, 38-41] Aye et al. identified both increased maternal inflammation and upregulated placental inflammatory pathways associated with obesity among pregnant women.[21] Basu et al. demonstrated elevated CRP and IL-6 levels in obese compared to non-obese mothers among 120 mothers.[41] Stewart et al. identified consistently elevated CRP in obese mothers throughout pregnancy and on postpartum evaluations compared to non-obese mothers.[38] Despite observing elevated inflammation scores and CRP levels, we identified no difference in TNF-α levels between our neonates of overweight versus non-overweight mothers. Interestingly, both Stewart et al. and Basu et al. identified increased maternal CRP levels but no difference in TNF-α levels in maternal circulation between different BMI categories.[38, 41] With additional data from direct adipose tissue and stromal cell evaluation, it is apparent that TNF-α is highly produced in

stromal vascular cells of obese mothers despite normal or low circulatory levels.[41] Thus, it is possible that TNF-α is most active locally in a paracrine fashion, and therefore, systemic levels are not adequately reflective. Although these data come from maternal subjects, it is plausible that our TNF-α findings reflect the same scenario and only direct adipose tissue evaluation of our neonates would have detected TNF-α differences.

As to the underlying mechanism connecting maternal inflammation and neonatal inflammation, much is postulated but little is known. Summative data in mice are inconclusive as to whether maternal adiposity-induced inflammatory cytokines traverse the placental barrier.[22] Of the few human studies exploring this topic, negligible amounts of IL-1[42] and TNF-α[43], cross the placenta, but moderate amounts of IL-6 do so.[43] Additionally, there is evidence to suggest that maternal pro-inflammatory T-helper (Th)1 and Th17 cells may cross the placenta which would then promote fetal production of inflammatory cytokines.[44] Lastly, Heerwagan and colleagues postulate that irrespective of direct cytokine or immune-cell transfer, excessive lipid delivery to fetal tissues secondary to maternal adiposity promotes fetal production of pro-inflammatory cytokines.[20] Thus, there is evidence to support both direct and indirect inflammation transfer from mother to offspring in the setting of maternal obesity.

Although we identified increased inflammation in neonates with mothers of overweight and obese class II/III, we failed to observe this finding in neonates of mothers with class I obesity. This finding is unexpected and the interpretation is unclear. In understanding the pathophysiologic nature between excessive weight and inflammation, the systemic inflammation associated with obesity is at least partially a direct result of adipose tissue production of inflammatory cytokines. Given this, we might expect a linear increase in inflammatory cytokines among pregnant women (and likely their offspring) with increasing BMI. Previous studies observed increased circulating inflammatory markers in mothers with obesity but did not separate maternal obesity further into classes which may mask any otherwise detectable differences.[38, 41] When we grouped all overweight mothers (BMI>25) together, we observed an elevated total inflammation score. Thus, it is unclear if there is truly an unexpected normalization in neonates of obese class I compared to overweight mothers. One mechanism to explain this finding would be the concept of protective adaptation[19] which is overwhelmed in extreme obesity. We also evaluated the possibility of clinical sequelae affecting our results. For example, an imbalance of cesarean rates between the maternal BMI groups could affect neonatal inflammation levels. However, in sensitivity analyses, removing those who had a NICU admission, cesarean delivery, and adjusting for birthweight and gestational age, as well as stratifying by plurality in several models did not change the obese class I results (data not shown). More investigation is needed to evaluate this hypothesis.

To our knowledge, this is the first study to evaluate for associations of neonatal markers of inflammation and paternal weight status and we found no association. Although they did not use neonatal data, Lieb et al. found increased inflammation in offspring who had two parents with obesity and no independent effect of maternal or paternal obesity, raising the possibility that paternal obesity may have additive effects on offspring.[11] We also evaluated the combined maternal and paternal obesity effect on neonatal inflammation and found no

significant pattern (data not shown). Our negative results may indicate a specificity for the associations with maternal obesity [28] and suggest that the association of paternal obesity with offspring obesity is not mediated through neonatal inflammation. Animal data from Binder et al. suggest that paternal obesity alters seminal fluid as obese mice produce semen with significantly altered concentrations of insulin, leptin, estradiol, and carbohydrate metabolites when compared to non-obese mice but no difference in semen IL-6, TNF-α or cortisol concentrations.[26] An additional animal investigation has demonstrated that altered seminal fluid created by seminal vesicle excision produces increased adiposity and impaired metabolic function in offspring[27] but it is unclear if this alteration adequately reflects the seminal disruption caused by paternal obesity and whether such alteration ultimately effects the neonatal systemic inflammatory environment. Lastly, embryonic genetic and epigenetic alteration secondary to paternal obesity is being increasingly investigated with mixed results.[3, 26, 45] For example, paternal obesity appears to be associated with decreased methylation of the gene encoding insulin like growth factor-2, which is a paternally expressed gene involved in growth.[45] However, such genetic alterations have provided no definitive link between paternal obesity and neonatal inflammatory pathways.

Immunoglobulin Profile

In addition to evaluating inflammatory biomarkers, we complemented our study by evaluating the Ig profile of neonates. Overall, there is a paucity of literature exploring neonatal Ig profiles in the context of parental obesity and interpretation of neonatal Ig levels is not without difficulty, as there is a differential transfer across the placental barrier. It is generally accepted that IgG is readily transferred across the placental barrier, but the remaining Igs are less likely to transfer and may only do so in pathologic states.[46] Keeping this in mind, the IgM and IgE levels collected from neonates mainly represent neonatal origin and can be interpreted as such.[47] Altered IgE has been demonstrated in neonates exposed to maternal psychosocial stress[48], perinatal infections[49], and toxin exposure.[50] Elevated IgE is associated with atopy and asthma (because of it's role in type 1 hypersensitivity) and researchers have identified associations between childhood wheezing and maternal obesity,[51-53] but few investigators have assessed IgE abnormalities among children associated with maternal obesity.[24, 54] Bolte et al. identified increased serum IgE levels in children with increased birth weight [54], whereas Kumar et al. identified decreased serum IgE levels in neonates with maternal obesity.[24] We did not find consistent associations between neonatal IgE and parental obesity, but we identified associations with IgM. We found a positive association between increasing maternal BMI and neonatal IgM levels and a negative association between increasing paternal weight and neonatal IgM levels. Taking into account our finding that maternal and paternal BMI are correlated, the net effect of neonatal IgM must incorporate these opposing factors and it is unclear if one parental influence takes precedence. IgM is an important player in responses to acute infection via complement activation, opsonization and phagocytosis of foreign or infective material.[55] The association between maternal BMI and neonatal IgM levels may partly be explained by an increased incidence of perinatal infection associated with maternal obesity.[46, 56] For example, Kankuri et al. describe in elevated relative risk peripartum sepsis in mother's with BMI > 30, RR = 4.9 (95% CI 2.9-8.5).[56] Additionally, a proportion of circulating IgM is derived from germline production without foreign antigen exposure.[57] It has been

demonstrated that these natural antibodies have high affinity for oxidative stress related antigens[58, 59] thus it can be postulated increased neonatal IgM may be due to increased fetal oxidative stress in newborns exposed to maternal obesity.

Strengths & Limitations

The timing of DBS collections and the initial storage conditions might have affected results. Little normative data is available describing inflammatory biomarker kinetics in the early neonatal period. IL-6 and CRP have been described to have a physiologic surge at 24 hours of life in healthy term neonates with stable values at 48 hours.[60] Thus our collection spans throughout this anticipated surge; however, in our design there was no systematic timing of collection to believe that a particular parental BMI category would be selected for specific collection timing and as such it is unlikely that timing of collection biased our results. Degradation of cytokines and to less extent, Igs could have impacted levels but should also not have been differential with respect to parental obesity status. Additionally, given the observational nature of our study, residual confounding from unmeasured factors cannot be ruled out. Finally, inaccuracies of parental weight and GWG may have induced random measurement error.

The strength of this study lies in the large population based sample to allow generalizability and data on variables to minimize potential confounding. In addition to having a large sample size, we used high throughput processing for biochemical evaluations for a thorough evaluation of the inflammatory and immunoglobulin profiles. We uniquely used a summative inflammatory score combining biomarker data to reduce multiple testing. Furthermore, our study presents successful use of the newborn DBS specimen which is a resource available throughout the world with vast potential applications. Finally, this study uniquely captured paternal information which is marginally represented in the literature.

Conclusion

Maternal BMI status appears to be associated with increased neonatal systemic inflammation as evidenced by newborn DBS evaluation, but the extent of excess weight may have variable effects and paternal BMI status appears to have no association. Neonatal Ig levels may be associated with maternal and paternal BMI status with opposite effects specifically seen in neonatal IgM levels. Confirmatory, prospective data are needed to support these findings and further delineate causality as well as clinical correlations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics by pre-pregnancy BMI of participants consenting to use of dried blood spots in the Upstate KIDS Study.

Characteristics[a,b]		Obese Class II/III	Obese Class I	Overweight	Underweight	Normal weight	P-value
		(>35.0 kg/m^2)	(30.0-34.9 kg/m^2)	(25-29.9 kg/m^2)	(<18.5 kg/m^2)	(18.5-24.9 kg/m^2)	
Mothers	N=2974	380	373	773	64	1384	
Age (y)[b]		30.2 (6.0)	30.9 (5.8)	31.6 (6.0)	29.0 (6.5)	31.1 (5.8)	0.0002
Non-Hispanic white[c]		317 (83.4)	317 (85.0)	648 (83.8)	48 (75.0)	1161 (83.9)	0.3961
Privately insured		267 (70.3)	295 (79.3)	629 (81.5)	40 (62.5)	1130 (81.7)	<0.0001
Married		318 (84.8)	337 (91.8)	694 (90.8)	55 (85.9)	1263 (92.5)	0.0001
College degree or higher		138 (36.3)	175 (46.9)	442 (57.2)	34 (53.1)	885 (64.0)	<0.0001
Alcohol use during pregnancy		32 (8.4)	39 (10.5)	99 (12.8)	8 (12.5)	235 (17.0)	<0.0001
Any dietary supplementation during pregnancy		294 (77.4)	293 (78.9)	615 (79.6)	48 (75.0)	1146 (82.8)	0.047
Smoking during pregnancy		63 (16.6)	47 (12.6)	93 (12.0)	15 (23.4)	125 (9.0)	<0.0001
Any infertility treatment		134 (35.3)	116 (31.1)	246 (31.8)	14 (21.9)	446 (32.3)	0.2856
Nulliparous		162 (42.9)	150 (40.5)	344 (44.7)	36 (57.1)	667 (48.7)	0.0092
Gestational weight gain[d]							<0.0001
LGWG		128 (33.9)	62 (16.7)	102 (13.2)	19 (29.7)	326 (23.7)	
AGWG		103 (27.3)	89 (23.9)	212 (27.4)	30 (46.9)	595 (43.2)	
EGWG		147 (38.9)	221 (59.4)	459 (59.4)	15 (23.4)	455 (33.1)	
Paternal BMI							<0.0001
Thin and normal (<25 kg/m^2)		44 (12.9)	66 (19.3)	174 (24.0)	24 (41.4)	437 (34.2)	
Overweight (25-29.9 kg/m^2)		112 (32.9)	112 (32.8)	327 (45.0)	628 (49.1)	25 (43.1)	
Obese class I (30.0-34.9 kg/m^2)		86 (25.3)	100 (29.2)	162 (22.3)	7 (12.1)	151 (11.8)	
Obese class II/III (>35.0 kg/m^2)		98 (28.8)	64 (18.7)	63 (8.7)	2 (3.5)	62 (4.9)	
Infants[e]	N=2974	380	373	773	64	1384	
Males		207 (54.5)	192 (51.5)	397 (51.4)	36 (56.3)	699 (50.5)	0.6488
Singletons		300 (79.0)	296 (79.4)	608 (78.7)	52 (81.3)	1107 (80.0)	0.9475
Birth weight (g)[b]		3252.3 (765.4)	3265.7 (633.7)	3237.7 (680.8)	2947.2 (747.7)	3153.2 (655.3)	<0.0001
Gestational age (weeks)[b]		37.9 (2.5)	38.2 (2.1)	38.1 (2.3)	37.9 (2.7)	38.2 (2.4)	0.4293

Abbreviations: y, years; LGWG, low gestational weight gain; AGWG, appropriate gestational weight gain; EGWG, excessive gestational weight gain; BMI, body mass index; g, grams. All data reported as n (%) excepted where annotated ([b]) which indicates mean (standard deviation).

[a]Number of participants missing information for characteristics: 2 for health insurance, 38 for marital status, 1 for alcohol use during pregnancy, 1 for smoking during pregnancy, 23 for parity, 11 for gestational weight gain, 230 for paternal obesity/body mass index

[c]Percentage of non-Hispanic black in cohort: 16.4%

[d]Gestational weight gain = 2009 IOM guidelines: LGWG is <12.5 kg for underweight women, <11.5 kg for normal weight women, <7.0 kg for overweight women, and <5.0 kg for obese women (classes I and II) delivering singletons. LGWG is <17.0 kg for underweight and normal weight women, <14.0 kg for overweight women, and <11.0 kg for obese women (classes I and II) delivering twins. AGWG is between 12.5-18.0 kg for underweight women, between 11.5-16.0 kg for normal weight women, between 7.0-11.5 kg for overweight women, and between 5.0-9.0 kg for

obese women (classes I and II) delivering singletons. AGWG is between 17.0-25.0 kg for underweight and normal weight women, between 14.0-23.0 kg for overweight women, and between 11.0-19.0 kg for obese women (classes I and II) delivering twins. EGWG is >18.0 kg for underweight women, >16.0 kg for normal weight women, >11.5 pounds for overweight women, and >9.0 kg for obese women (classes I and II) delivering singletons. EGWG is >25.0 kg for underweight and normal weight women, >23.0 kg for overweight women, and >19.0 kg for obese women (classes I and II) delivering twins.

[e]Total sample size is restricted to descriptive cohort n = 2974, all singletons and one twin selected at random in the Upstate KIDS birth cohort.

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Table 2

Mean differences (beta, 95% CI) between pre-pregnancy body mass index and neonatal markers of inflammation and immunoglobulin levels in the Upstate KIDS Study.

Neonatal Biomarkers[a] **Total n = 3555**	**Obese Class II/III (>35.0 kg/m^2) n = 458**		**Obese Class I (30.0-34.9 kg/m^2) n = 445**		**Overweight (25.0-29.9 kg/m^2) n = 927**		**Underweight (<18.5 kg/m^2) n = 74**	
	Unadjusted	***Adjusted***	***Unadjusted***	***Adjusted***	***Unadjusted***	***Adjusted***	***Unadjusted***	***Adjusted***
Inflammation score	**0.14 (0.02,0.27)**	0.13 (−0.002,0.26)	−0.02 (−0.15,0.10)	−0.01 (−0.13,0.11)	**0.11 (0.01,0.20)**	**0.12 (0.02,0.21)**	0.1 (−0.16,0.37)	0.02 (−0.24,0.29)
CRP[b]	**0.1 (0.02,0.18)**	**0.1 (0.02,0.19)**	0.02 (−0.06,0.10)	0.03 (−0.05,0.12)	**0.09 (0.03,0.16)**	**0.11 (0.04,0.17)**	0.07 (−0.10,0.23)	0.02 (−0.15,0.18)
IgE[c]	−0.002 (−0.09,0.09)	−0.01 (−0.11,0.08)	−0.05 (−0.14,0.04)	−0.06 (−0.15,0.03)	−0.001 (−0.07,0.06)	−0.01 (−0.07,0.06)	−0.05 (−0.22,0.12)	−0.01 (−0.11,0.08)
IgA[c]	−0.01 (−0.07,0.06)	−0.01 (−0.07,0.06)	0.02 (−0.04,0.08)	0.03 (−0.04,0.09)	−0.01 (−0.05,0.04)	−0.004 (−0.05,0.04)	−0.003 (−0.12,0.11)	−0.02 (−0.14,0.09)
IgM[c]	**0.08 (0.02,0.14)**	**0.12 (0.05,0.19)**	**0.07 (0.01,0.13)**	**0.11 (0.04,0.17)**	−0.02 (−0.06,0.03)	0.002 (−0.04,0.05)	−0.04 (−0.15,0.07)	−0.04 (−0.16,0.07)
IgG1[c]	**−0.04 (−0.08,−0.01)**	−0.03 (−0.07,0.004)	−0.002 (−0.04,0.04)	0.01 (−0.03,0.05)	−0.004 (−0.02,0.02)	0.003 (−0.02,0.03)	−0.02 (−0.09,0.05)	−0.03 (−0.09,0.04)
IgG2[c]	−0.01 (−0.10,0.07)	0.02 (−0.06,0.11)	0.001 (−0.08,0.08)	0.03 (−0.05,0.11)	−0.03 (−0.09,0.03)	−0.02 (−0.07,0.04)	**−0.16 (−0.30,−0.02)**	**−0.17 (−0.31,−0.02)**
IgG3[c]	−0.05 (−0.11,0.02)	−0.067 (−0.14,0.003)	0.02 (−0.06, 0.10)	0.01 (−0.07,0.10)	−0.0002 (−0.05, 0.05)	0.001 (−0.05,0.05)	0.01 (−0.11,0.13)	−0.01 (−0.13,0.11)
IgG4[c]	**−0.19 (−0.33,−0.04)**	**−0.17 (−0.31,−0.02)**	−0.1 (−0.26,0.05)	−0.08 (−0.24,0.08)	−0.01 (−0.11,0.09)	−0.0002 (−0.10, 0.10)	**−0.37 (−0.64,−0.11)**	**−0.4 (−0.66,−0.13)**

Abbreviations: CI, confidence interval; CRP, C-reactive protein; TNF, tumor necrosis factor; (IL)-1ra, interleukin-1 receptor antagonist; Ig, immunoglobulin.

Adjusted for maternal age; white race; attainment of college degree or higher; private insurance; smoking, alcohol use, and dietary supplementation during pregnancy; parity; infant plurality; and paternal body mass index.

Significant differences (P<0.05) are in **bold.**

[a] Infants born to normal weight women (body mass index=18.5-24.9 kg/m2) served as the reference group: n=1651.

[b] log mg/L

[c] log ng/mL

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Table 3

Mean differences (beta, 95% CI) between paternal body mass index and neonatal markers of inflammation and immunoglobulin levels in the Upstate KIDS Study.

Neonatal Biomarkers[a]	**Obese Class II/III (>35.0 kg/m^2)**		**Obese Class I (30.0-34.9 kg/m^2)**		**Overweight (25.0-29.9 kg/m^2)**	
Total n = 3555	**n = 379**		**n = 666**		**n = 1551**	
	Unadjusted	***Adjusted***	***Unadjusted***	***Adjusted***	***Unadjusted***	***Adjusted***
Inflammation score	0.08 (−0.08,0.23)	0.07 (−0.09,0.23)	0.03 (−0.09,0.15)	0.05 (−0.07,0.17)	−0.03 (−0.13,0.08)	0.003 (−0.10,0.11)
CRP[b]	0.01 (−0.08,0.11)	0.004 (−0.10,0.10)	0.01 (−0.07,0.09)	0.01 (−0.07,0.09)	0.005 (−0.06,0.07)	0.02 (−0.04,0.09)
IgE[c]	0.04 (−0.06,0.14)	0.04 (−0.06,0.15)	−0.02 (−0.10,0.06)	−0.02 (−0.10,0.07)	0.01 (−0.06,0.08)	0.01 (−0.06,0.08)
IgA[c]	0.002 (−0.06,0.07)	0.02 (−0.05,0.09)	−0.03 (−0.09,0.03)	−0.01 (−0.07,0.05)	−0.01 (−0.06,0.04)	−0.0001 (−0.05,0.05)
IgM[c]	**−0.08 (−0.15,−0.01)**	**−0.11 (−0.19,−0.04)**	−0.05 (−0.11,0.01)	**−0.07 (−0.13,−0.01)**	**−0.07 (−0.12,−0.03)**	**−0.08 (−0.13,−0.03)**
IgG1[c]	−0.04 (−0.08,0.0005)	−0.03 (−0.07,0.02)	−0.01 (−0.04,0.02)	−0.001 (−0.03,0.03)	0.005 (−0.02,0.03)	0.01 (−0.02,0.04)
IgG2[c]	−0.01 (−0.10,0.08)	−0.03 (−0.12,0.06)	−0.04 (−0.11,0.03)	−0.06 (−0.13,0.02)	0.02 (−0.03,0.08)	0.01 (−0.04,0.07)
IgG3[c]	−0.07 (−0.15,0.01)	−0.05 (−0.13,0.04)	**−0.07 (−0.12,−0.01)**	−0.04 (−0.10,0.02)	−0.03 (−0.08,0.02)	−0.01 (−0.06,0.04)
IgG4[c]	−0.09 (−0.27,0.08)	−0.03 (−0.21,0.15)	−0.01 (−0.14,0.12)	0.02 (−0.11,0.15)	0.06 (−0.06,0.18)	0.08 (−0.04,0.19)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; TNF, tumor necrosis factor; (IL)-1ra, interleukin-1 receptor antagonist; Ig, immunoglobulin.

Adjusted for maternal age; white race; attainment of college degree or higher; private insurance; smoking and alcohol use during pregnancy; parity; infant plurality; and pre-pregnancy body mass index. Significant differences (P<0.05) are in **bold.**

[a] Infants born to thin and normal weight men (body mass index= <25.0 kg/m2) served as the reference group: n=959.

[b] log mg/L

[c] log ng/mL

Table 4

Mean differences (beta, 95% CI) between gestational weight gain and neonatal markers of inflammation and immunoglobulin levels in the Upstate KIDS Study.

Neonatal Biomarkers[a] **Total n = 3544**	**EGWG**[b] **n = 1408**		**LGWG**[b] **n = 852**	
	Unadjusted	***Adjusted***	***Unadjusted***	***Adjusted***
Inflammation score	0.07 (−0.02,0.15)	0.02 (−0.07,0.11)	−0.03 (−0.15,0.09)	−0.03 (−0.14,0.09)
CRP[c]	**0.10 (0.04,0.16)**	0.05 (−0.01,0.11)	−0.02 (−0.09,0.06)	−0.01 (−0.08,0.06)
IgE[d]	−0.04 (−0.10,0.02)	−0.04 (−0.10,0.02)	0.02 (−0.05,0.10)	0.02 (−0.05,0.10)
IgA[d]	−0.02 (−0.06,0.02)	−0.03 (−0.08,0.01)	0.04 (−0.02,0.09)	0.04 (−0.02,0.09)
IgM[d]	0.02 (−0.02,0.06)	0.002 (−0.04,0.04)	0.02 (−0.03,0.07)	0.01 (−0.05,0.06)
IgG1[d]	0.003 (−0.02,0.03)	−0.0004 (−0.03,0.02)	−0.03 (−0.06,0.01)	−0.02 (−0.06,0.01)
IgG2[d]	−0.02 (−0.08,0.03)	−0.03 (−0.08,0.03)	0.04 (−0.03,0.11)	0.05 (−0.01,0.12)
IgG3[d]	−0.04 (−0.09,0.007)	**−0.06 (−0.10,−0.01)**	−0.03 (−0.09,0.03)	−0.02 (−0.08,0.04)
IgG4[d]	0.01 (−0.09,0.11)	0.01 (−0.09, 0.11)	−0.09 (−0.22,0.03)	−0.06 (−0.19,0.07)

Abbreviations: CI, confidence interval; EGWG, excessive gestational weight gain; LGWG, low gestational weight gain; CRP, C-reactive protein; TNF, tumor necrosis factor; (IL)-1ra, interleukin-1 receptor antagonist; Ig,immunoglobulin.

Adjusted for maternal age; white race; attainment of college degree or higher; private insurance; smoking, alcohol use, and dietary supplementation during pregnancy; parity; infant plurality; paternal body mass index; and pre-pregnancy body mass index.

Significant differences (P<0.05) are in **bold.**

[a] Infants born to women with appropriate gestational weight gain (AGWG) served as the reference. Total sample size for reference group: n=1284.

[b] Gestational weight gain =,2009 IOM guidelines: LGWG is <12.5 kg for underweight women, <11.5 kg for normal weight women, <7.0 kg for overweight women, and <5.0 kg for obese women (classes I and II) delivering singletons. LGWG is <17.0 kg for underweight and normal weight women, <14.0 kg for overweight women, and <11.0 kg for obese women (classes I and II) delivering twins. AGWG is between 12.5-18.0 kg for underweight women, between 11.5-16.0 kg for normal weight women, between 7.0-11.5 kg for overweight women, and between 5.0-9.0 kg for obese women (classes I and II) delivering singletons. AGWG is between 17.0-25.0 kg for underweight and normal weight women, between 14.0-23.0 kg for overweight women, and between 11.0-19.0 kg for obese women (classes I and II) delivering twins. EGWG is >18.0 kg for underweight women, >16.0 kg for normal weight women, >11.5 pounds for overweight women, and >9.0 kg for obese women (classes I and II) delivering singletons. EGWG is >25.0 kg for underweight and normal weight women, >23.0 kg for overweight women, and >19.0 kg for obese women (classes I and II) delivering twins.

[c] log mg/L

[d] log ng/mL