Etiology and evaluation of stillbirth in patients with obesity

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ABSTRACT
Objective: Maternal obesity is a risk factor for stillbirth, but whether or not the etiology of stillbirth differs in gravidas with and without obesity is unknown. We categorized stillbirths in a contemporary cohort to test the hypothesis that the etiology of stillbirth is different in gravidas with and without obesity.

Methods: This retrospective cohort study included all gravidas with a stillbirth ≥20 weeks’ gestation between 2010 and 2017 and a normal mid-trimester anatomic survey by ultrasound assessment at a large academic institution. Pregnancies were excluded if delivery data were unavailable, a multifetal gestation was present, or there was an antenatally diagnosed fetal structural or genetic anomaly. Our primary exposure was maternal obesity, defined as a body mass index (BMI) ≥30 kg/m² at the time of anatomic survey. Our primary outcome was stillbirth etiology, as classified by the initial causes of fetal death tool from the Stillbirth Collaborative Research Network and includes maternal, obstetric, hematologic, fetal, infectious, placental, other, or unexplained categories. Our secondary outcomes included the evaluation performed on each stillbirth, compliance with the recommended stillbirth evaluation by the American College of Obstetricians and Gynecologists (ACOG), and the percentage of abnormal results for each of the tests ordered for stillbirth evaluation.

Results: Of 118 stillbirths meeting the inclusion criteria, 44 (37.3%) occurred in gravidas with obesity and 74 (62.7%) were in patients without obesity. An obstetric complication was the most commonly identified etiology for stillbirth, found in 40.9% of cases with obesity versus in 29.7% of cases without obesity (aOR 1.09, 95% CI 0.47–2.66). The likelihood of any specific etiology of stillbirth was not significantly different in gravidas of the two weight groups, after controlling for confounders. However, assignment to the unexplained stillbirth category was significantly less common in women with obesity, compared to those without obesity (aOR 0.18, 95% CI 0.05–0.67). There was no difference in testing performed on each stillbirth between the groups. Compliance with the ACOG-recommended diagnostic evaluation for stillbirth was similar in the two groups but was only performed in 10.2% of all cases of stillbirth. Placental pathology was the test most likely to yield an abnormal result in both groups, but the percentage of abnormal results for this and all other tests was the same in the presence and absence of obesity.

Conclusion: There is no specific etiology of stillbirth seen in gravidas with obesity, compared to those without obesity, after controlling for maternal confounders. We surmise that the evaluation recommended for stillbirth assessment in the general population is appropriate for stillbirth evaluation in gravidas with obesity. Testing pursued was similar between groups, but compliance with ACOG recommendations for testing after stillbirth was deficient in the cohort. Future work should aim to identify and address barriers to completing the recommended stillbirth evaluation.

Introduction

The incidence of stillbirth in the United States is estimated to be one in 160 pregnancies [1]. There are a multitude of potential etiologies for stillbirth, including maternal medical conditions, obstetric complications, hematologic disorders, fetal genetic or structural abnormalities, infections, and placental etiologies [2–4]. Obesity is a significant risk factor for stillbirth,
with more than a two-fold increased odds of stillbirth in this group compared to the non-obese population [5–7]. What is unclear is if obesity plays a role in stillbirth in the absence of comorbidities, such as hypertensive disease or diabetes mellitus. That is to say, a selective cause for stillbirth in gravidas with obesity has not been identified [5–7]. With the prevalence of obesity approaching 40% in gravidas 20–39 years of age, identification of specific causes for stillbirth in this population is imperative for both patient counseling and prevention efforts [8].

An etiology for stillbirth is not identified in up to 50% of cases, which may be due to an incomplete evaluation or a lack of positive findings on a thorough workup [2,3,9–11]. Recent guidance from the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine reinforce the previously published 2009 recommendation that evaluation of stillbirth should include fetal autopsy, gross and histologic examination of the placenta, cord, and membranes, and genetic evaluation, with additional testing based on the clinical scenario [12]. This renewed recommendation was partly based on results from a large prospective cohort of over 500 stillbirths, in which the rate of unexplained stillbirth was only 24% after evaluation with fetal autopsy, placental pathology, and genetic evaluation [13]. This systematic approach informs patients and providers as to the risk of stillbirth recurrence and can guide future pregnancy management. Data regarding compliance with the ACOG-recommended diagnostic evaluation for stillbirth is generally lacking.

We aimed to investigate the stillbirth etiology and evaluation pursued in a cohort including patients with and without obesity.

Materials and methods

This study was approved by the Washington University School of Medicine Human Research Protection Office. We conducted a retrospective cohort study of gravidas diagnosed with a stillbirth beyond 20 weeks’ gestation and delivered between 2010 and 2017, based on the definition of stillbirth in the state of Missouri. This time frame included stillbirths after the 2009 ACOG stillbirth evaluation recommendations were published, which have since been updated [12]. Maternal body mass index (BMI) was calculated using the height and weight recorded at the ultrasound visit for the mid-trimester anatomic survey, and a BMI ≥ 30.0 kg/m² defined obesity, as designated by the Center for Disease Control and Prevention (CDC). Obesity class was assigned based on CDC definitions: Class 1 obesity BMI 30.0–34.9 kg/m², class 2 obesity BMI 35.0–39.9 kg/m², and class 3 obesity BMI ≥ 40.0 kg/m². Patients with a BMI < 30 kg/m² were assigned to the group without obesity. The latter group included patients with a BMI of 25.0–29.9 kg/m² (overweight), of 18.5–24.9 kg/m² (normal weight) and <18.5 kg/m² (underweight). All included cases had a normal anatomic survey at the mid-trimester ultrasound assessment at our institution. Gravidas were excluded for multifetal gestation, antenatally diagnosed fetal structural anomaly or confirmed genetic abnormality in the fetus, or if delivery and stillbirth evaluation data were unavailable.

Ultrasound details, maternal demographic data, medical, surgical, and obstetrical histories were obtained from medical chart review. Race and ethnicity were based on patient self-report. The GA at stillbirth was defined as the GA in weeks based on estimated due date (EDD) calculated from last menstrual period (LMP) or ultrasound-assigned EDD if discordant from LMP at the time of confirmation of absent fetal cardiac activity. Maternal and fetal chart reviews were conducted for the stillbirth evaluations performed, which included fetal autopsy, placental pathology, fetal genetic evaluation, maternal indirect coombs, antiphospholipid antibody syndrome (APS) titers, urine drug screen (UDS), fetomaternal hemorrhage evaluation, congenital infection evaluation for syphilis, parvovirus, and other infections selectively done, hemoglobin A₁c, thrombophilia evaluation, and thyroid-stimulating hormone (TSH). If a test was not found in our medical system or in clinician notes, it was assumed to have not been performed. The evaluation was designated complete if fetal autopsy, placental pathology, and genetic evaluation were obtained, as recommended by ACOG [12]. The cause of stillbirth was assigned by independent review of testing results by the primary author, who is a practicing obstetrician who was blinded to maternal BMI. The stillbirth etiologies were categorized based on the Stillbirth Collaborative Research Network initial causes of fetal death (INCODE) tool [4]. The INCODE tool divides the etiology for stillbirth into eight categories: (1) maternal medical complications during pregnancy, (2) obstetrical complications, (3) maternal or fetal hematologic conditions, (4) fetal genetic, structural, or karyotypic abnormalities, (5) infection of the chorionic-placenta-placenta, fetus, or both but excluding fetal membrane infection, (6) pathologic placental conditions, (7) other pertinent conditions, and (8) unknown. Etiologies were further classified based on the likelihood that the stillbirth was caused by the
complicating factor, as recommended by the INCODE tool. For example, hypertensive disease alone is not categorized as an etiology for stillbirth based on this tool; however, hypertensive disease with associated fetal growth restriction is classified as a possible cause for stillbirth, while hypertensive disease with associated eclampsia is classified as a probable cause for stillbirth. Cases could be assigned multiple etiologies.

The primary outcome was the etiology of stillbirth, which we defined as a “possible” or “probable” etiology based on the INCODE tool. Secondary outcomes included the evaluation ordered for each stillbirth, compliance with ACOG-recommended evaluation, and the percentage of abnormal results for each test performed during stillbirth evaluation. An abnormal result on any diagnostic test was considered contributory if the results aided in the assignment of a “possible” or “probable” etiology for the stillbirth. The outcomes were compared between gravidas with and without obesity. As a secondary analysis, we also compared etiology of stillbirth in patients with obesity to those with a normal weight.

All statistical tests were two-tailed, performed using STATA 12.1 (Statacorp, College Station, TX), and significant at a p-value < .05. No a priori sample size calculation was performed as all eligible stillbirths during the study period were included; however, a post hoc power analysis was performed to assess our ability to detect differences between gravidas with and without obesity based on our fixed sample size. Comparisons between gravidas with and without obesity were done with the Mann-Whitney U test, chi-square test, or Fisher’s exact test, as appropriate. The Multivariable logistic regression was used to account for confounders and to estimate adjusted odds ratios (aORs). After backward stepwise elimination considering factors that were statistically different in univariate analysis, biologic plausibility, and factors with > 10% impact on model, the final model controlled for chronic hypertension and preexisting diabetes mellitus. The final model was assessed with the Hosmer-Lemeshow goodness-of-fit test.

Results

A total of 147 stillbirths occurring during the study period after a normal singleton anatomic survey were identified. Twenty-nine cases were excluded for missing delivery data. The remaining 118 cases were included, with 44 (37.3%) patients having obesity and 74 (62.7%) patients not having obesity. The former category included 16 (13.6%) gravidas with class 1 obesity, 10 (8.5%) with class 2 obesity, and 18 (15.3%) with class 3 obesity. The latter category included 26 (22.0%) overweight, 45 (38.1%) normal weight, and three (2.5%) underweight patients.

Gravidas with obesity and a stillbirth were more likely to self-identify as Black or have preexisting hypertension or diabetes mellitus than gravidas without obesity and a stillbirth (Table 1). Maternal age, GA at stillbirth, incidence of nulliparity, insurance type, use of in vitro fertilization, and fetal sex were not significantly different between groups. There were no cases of stillbirth beyond 41 weeks’ gestation.

An etiology of stillbirth was identified in 72.9% of all cases, with 50.6% of etiologies classified as probable and 22.3% as possible. An obstetrical complication was the most common cause of stillbirth in the entire cohort, identified in 33.9% of the cases (Table 2). An obstetric complication leading directly to stillbirth was identified in 40.9% of patients with obesity compared to 29.7% of patients without obesity (aOR 1.09,
A placental source of stillbirth was seen in 33.1% of total cases. A placental etiology was equally likely in gravidas with and without obesity (38.6% vs 29.7%, aOR 1.35, 95% CI 0.56–3.24). Maternal medical complications contributing to stillbirth were seen in 29.7% among the entire cohort, and stillbirths in this category were more common in patients with obesity, compared to those without obesity (40.9% vs 23.0%, OR 2.32, 95% CI 1.03–5.21); however, after adjusting for preexisting chronic hypertension and diabetes, this difference was no longer significant (aOR 0.60, 95% CI 0.18–2.04). Hematologic, fetal, and infectious etiologies were rare in our cohort, occurring in 3.4%, 3.4%, and 0.9% of cases, respectively, with no difference seen between gravidas with and without obesity.

Stillbirths with unexplained etiology accounted for 27.1% of total cases, and there was a significant difference in rate of unexplained stillbirth among patients with and without obesity (6.8% vs 39.2%, aOR 0.18, 95% CI 0.05–0.67).

Only 12 (10.2%) of the 118 stillbirth cases had complete diagnostic testing, and there were no differences in rate of compliance based on whether maternal obesity was present (11.4% vs. 9.5%; p = .74). Most stillbirths (87.3%) had at least one of the three diagnostic components recommended by ACOG, and 33.0% had at least two of the three components performed. Women with obesity were no more or less likely to have one or two recommended diagnostic components performed compared to women without obesity. Among the cases, placental pathology was performed in 77.1% of cases, genetic evaluation in 33.9% of cases, and autopsy in 19.5% of cases. The most common additional tests ordered were indirect coombs (97.5%), antiphospholipid antibody testing (58.5%), UDS (40.7%), and congenital infection evaluation (35.6%). The utilization of these specific tests was similar in patients with and without obesity (Supplemental Table 1).

The likelihood of any abnormal test result to identify an etiology for stillbirth was also similar in patients with and without obesity (Supplemental Table 2). Placental pathology identified a stillbirth cause in 42/91 cases (46.2%) in which it was performed. Fetal genetic identified an etiology for stillbirth in 10.0% of cases in which it was performed, while fetal autopsy identified an etiology for stillbirth in 13.0% of cases in which it was performed. Of the remaining diagnostic tests pursued, hemoglobin A1C was abnormal and identified a cause of stillbirth in 6/24 (25.0%) cases tested, and abnormal thrombophilia testing assigned a stillbirth etiology in 2/17 (11.8%) cases in which this evaluation was performed.

Our secondary analysis comparing the etiology of stillbirth in patients with obesity to those with a normal weight included 89 stillbirth cases, 44 (49.4%) of which occurred in patients with obesity. A placental etiology was the most common identified stillbirth etiology occurring in 38.6% of patients with obesity and 35.6% of patients without obesity (aOR 1.06, 95% CI 0.41–2.73). As in the main cohort, a maternal etiology of stillbirth was more likely to be seen in gravidas with obesity (40.9% versus 17.8%), but this difference was no longer significant after controlling for preexisting hypertension and diabetes mellitus (aOR 0.99, 95% CI 0.27–3.67). The risk of unexplained stillbirth continued to be lower in the group with obesity (aOR 0.22, 95% CI 0.06–0.86).

### Discussion

In our cohort, there were no differences in stillbirth etiology between patients with and without obesity, after accounting for maternal hypertension and diabetes mellitus. This suggests that there is not an obesity-related malady that accounts for the well-described two-fold higher risk for stillbirth in gravidas with obesity with structurally normal fetuses [5–7]. The test most likely to be abnormal, and thereby to identify a cause of stillbirth, is placental gross and histologic examination. Indeed, placental etiologies were the second most common cause of stillbirth among all patients in the cohort, with no difference in patients

| Etiology     | All (n = 118) | Obesity (n = 44) | No obesity (n = 74) | OR (95% CI) | aOR* (95% CI) |
|--------------|--------------|-----------------|-------------------|------------|--------------|
| Maternal     | 35 (29.7)    | 18 (40.9)       | 17 (23.0)         | 2.32 (1.03–5.21) | 0.60 (0.18–2.04) |
| Obstetric    | 40 (33.9)    | 18 (40.9)       | 22 (29.7)         | 1.64 (0.75–3.57) | 1.09 (0.47–2.66) |
| Hematologic  | 4 (3.4)      | 3 (6.8)         | 1 (1.4)           | 5.34 (0.54–53.0) | 6.01 (0.54–67.3) |
| Fetal        | 4 (3.4)      | 2 (4.6)         | 2 (2.7)           | 1.71 (0.23–12.6) | 2.85 (0.38–21.4) |
| Infectious   | 1 (0.9)      | 1 (2.3)         | 0 (0.0)           |             |               |
| Placental    | 39 (33.1)    | 17 (38.6)       | 22 (29.7)         | 1.49 (0.68–3.26) | 1.35 (0.56–3.24) |
| Other        | 0 (0.0)      | 0 (0.0)         | 0 (0.0)           |             |               |
| Unexplained  | 32 (27.1)    | 3 (6.8)         | 29 (39.2)         | 0.11 (0.03–0.40) | 0.18 (0.05–0.67) |

Data represented as n (%)

*Adjusted for chronic hypertension and preexisting diabetes. Bold values represent p < 0.05.
with and without obesity. Notably, compliance with ACOG recommendations for stillbirth evaluation is deficient in our cohort.

The association between obesity and stillbirth is well supported in the literature, but any independent effect of obesity on stillbirth remains unknown [7,14–16]. Comorbidities in this population, such as hypertension and diabetes mellitus, are confounders in determining the relationship between obesity and stillbirth [5,7,16–18]. Bodnar et al. reported that gravidas with obesity had a higher prevalence of placentopathic disease, fetal abnormalities, and maternal medical conditions compared to gravidas without obesity [14]. Our study demonstrated similar findings of higher unadjusted rates of maternal etiologies of stillbirth, but a difference in rate of stillbirth due to maternal etiology vanished after adjusting for preexisting hypertension and diabetes mellitus.

The diagnostic yield of placental pathology and fetal genetic evaluation among all patients in our cohort was similar to rates previously reported in the literature [13,19,20]. Placental pathology was abnormal in 46% of cases and genetics were abnormal in 10% of cases. However, the rate of abnormal autopsy was significantly lower in our cohort than in the literature, which is likely explained by our exclusion of fetuses with abnormal anatomic surveys. Moreover, the low numbers of autopsy in our cohort may also contribute to this difference.

Our overall rate of identification of stillbirth etiology was lower than the rate reported by Page et al. and this likely reflects our cohort’s low compliance with ACOG-recommended stillbirth evaluation, but may also be related to our small sample size [13]. Unfortunately, no formal stillbirth evaluation protocol was in place to guide providers during the time period studied. Additionally, we are unable to comment on why the recommended tests were not performed. It is unclear where diagnostic evaluation was declined by the patient, cost-prohibitive due to inadequate insurance coverage, or not recommended by the clinical team. Whatever the reason, it is clear from previous data that complete evaluation decreases the rate of unexplained stillbirth, and its importance should be stressed to clinicians and patients.

Our study found no difference in the performed evaluation between gravidas with and without obesity. This finding is reassuring as gravidas with obesity, like many other marginalized groups, may be subject to biases in healthcare — providers may not pursue a complete workup of stillbirth and attribute the stillbirth simply to obesity or its associated comorbidities, risking missing other etiologies rather than performing a thorough evaluation. However, we did identify a higher rate of medical comorbidities in gravidas with obesity. While preconception control of hypertension and diabetes is not known in this cohort, preconception evaluation of those considering pregnancy with obesity would allow for optimization of comorbidities and may combat the increased risk of stillbirth in this population.

A strength of our study is the cohort of patients with stillbirths which includes significant diversity in terms of maternal age, medical comorbidities, and racial/ethnic background, making our results generalizable. Twenty percent of gravidas included were of advanced maternal age and over 60% of cases occurred in gravidas who identified as Black. It is well-known that race is a social construct, but social determinants continue to play a large role in and likely impact pregnancy outcomes. We also included gravidas with hypertension and diabetes mellitus, allowing for adjustment of these confounders in our analysis. Lastly, an obstetrician familiar with how to interpret genetic, pathology, and laboratory reports reviewed all medical records to categorize stillbirth etiology using the validated INCODE tool developed by the Stillbirth Collaborative Research Network [4].

The retrospective nature of our study is a limitation, and our results are subject to bias. We controlled for this bias by independent review of each stillbirth case by a practicing obstetrician blinded to maternal BMI. We chose to exclude known structurally and genetically anomalous fetuses which yielded a lower estimate of stillbirth due to fetal causes; however, this approach was utilized to examine the etiology in cases with unexpected stillbirths. This methodology also created a sample size limitation, despite the collection of 8 years of data. Fortunately, this speaks to the relative rarity of stillbirth as an outcome. Despite our limited sample size, we had >90% power to detect a difference in rates of unexplained stillbirth in patients with and without obesity. However, to detect a meaningful difference in the etiology of stillbirth between patients with and without obesity and in the absence of comorbidities, we would need a stillbirth cohort approximately four times larger than our current cohort. Given the rate of chronic hypertension and diabetes concurrent with obesity was over 50% in our population, a sample size of gravidas without comorbidities would be unfeasible. Additionally, we did not examine any other potential etiologies of stillbirth outside those included in the INCODE tool. Obesity is known to be a proinflammatory state, and previous
studies have shown increased placental inflammation in neonates born to gravidas with obesity [21]. Additionally, hormones important to placental transport have been shown to be altered in the setting of obesity including high levels of insulin and leptin [22]. Future research should examine the impact of these and other changes on stillbirth etiologies in the setting of obesity.

In summary, after accounting for common medical comorbidities associated with obesity, stillbirth etiology is similar in gravidas with and without obesity, with an obstetric and placental causes most common in both groups. We recommend a protocol for stillbirth evaluation as described by the recent ACOG bulletin which includes placental, genetic, and autopsy evaluations at a minimum, with additional testing as indicated by the clinical scenario [12]. The results of this study have important implications for patient counseling as identifying an etiology of stillbirth can not only help with the coping process but can also offer important information regarding risks and management of future pregnancies. Future work should attempt to identify and address barriers to completion of the ACOG-recommended stillbirth evaluation. Additionally, we should continue to investigate modifiable risk factors for obstetric and placental etiologies of stillbirth and the role of antenatal testing among those at risk of placental abnormalities to decrease stillbirth risk.

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