The association of euploid miscarriage with obesity

Jacqueline C. Lee, M.D.,[a] Lia A. Bernardi, M.D., M.S.C.I.,[b] and Christina E. Boots, M.D., M.S.C.I.[b]

[a] Department of Obstetrics and Gynecology, McGaw Medical Center of Northwestern University, Chicago, Illinois; and
[b] Fertility and Reproductive Medicine, Northwestern Medical Group, Chicago, Illinois

Objective: To determine whether the frequency of euploid miscarriage is increased in obese women with early pregnancy loss.
Design: Retrospective cohort study.
Setting: Academic medical center.
Patient(s): A total of 2,620 women with cytogenetic analysis results from products of conception after a pregnancy loss <20 weeks gestation from 2006–2018.
Intervention(s): None.
Main Outcome Measure(s): Frequency of euploid miscarriage was compared in obese (body mass index [BMI] $\geq 30 \text{ kg/m}^2$) versus non-obese (BMI <30 kg/m^2) patients.
Result(s): A total of 2,620 women with a mean (± standard deviation) age at time of loss of 34.9 years (± 4.9) and mean (± standard deviation) BMI of 25.3 kg/m^2 (±5.5) were included in the final analysis. After adjusting for age and race, obese women were 56% more likely to have a euploid pregnancy loss compared with nonobese women (odds ratio 1.56; 95% confidence interval 1.32–1.92). Within the cohort, 63.8% of the losses were aneuploid, of which 41% were trisomies, 8% were monosomies, and 7% were polyploidies. Of the euploid losses, 50.1% were 46,XX and 49.9% were 46,XY, which suggests that the rate of maternal cell contamination was low.
Conclusion(s): Obese women have an increased frequency of euploid miscarriage when compared with nonobese women. (Fertil Steril Rep® 2020;1:142–8. ©2020 by American Society for Reproductive Medicine.)
Key Words: Early pregnancy loss, euploid, karyotype, obesity, cytogenetics

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/xfre00047

O besity is a major epidemic that influences health worldwide. The United States National Center for Health Statistics estimated that 34.4% of reproductive aged women (ages 20–39 years) are affected by obesity (1). Obesity is linked to a wide range of negative health outcomes. Specifically, obesity is associated with reproductive issues such as ovulatory dysfunction, menstrual abnormalities, and impaired fertility (2). Obesity also is associated with an increased rate of pregnancy loss, and evidence suggests that increased rates of pregnancy loss occur in obese women who undergo assisted reproduction as well (3–5).

The etiology of many miscarriages is unknown and typically evaluation for an underlying cause of a pregnancy loss is not initiated until two or more losses occur (6). When pregnancy losses are evaluated, >50% of miscarriages are secondary to chromosomal errors, namely, numeric chromosomal abnormalities that arise secondary to errors in maternal gametogenesis (7). Providers who care for women with early pregnancy loss have the option to send products of conception for chromosome analysis. If abnormal, these genetic results can provide an explanation for a pregnancy loss, which has been shown to correlate with lower rates of anxiety and self-blame following a pregnancy loss (8) However, data show that a euploid miscarriage is a risk factor for subsequent euploid miscarriage, suggesting maternal rather than chromosomal factors are the cause for spontaneous miscarriage and further evaluation should be performed (9).

The pathophysiology behind how obesity increases the risk of pregnancy loss is unclear. Data have shown that obesity also increases the risk for insulin resistance, thyroid dysfunction, leptin resistance, impaired steroidogenesis, and poor oocyte quality, all of which can contribute to early miscarriage (10, 11). If oocyte quality is so impaired that meiosis becomes inefficient, then obese women should have higher rates of aneuploidy. This association has been demonstrated in

https://doi.org/10.1016/j.xfre.2020.05.011

the obese mouse model where spindle defects and chromosome misalignments were increased significantly in oocytes of mice fed a high-fat diet when compared with controls (12). On the other hand, if these other comorbidities and alterations in the uterine milieu are strong, then obese women will be more likely to have a euploid loss (13).

Data from a study of women with recurrent early pregnancy loss showed an increased rate of euploid pregnancy loss in the obese population (13). Our hypothesis is that obese women in the general population also have a higher rate of euploid miscarriage compared with their nonobese counterparts. The objective of this study was to determine whether obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2 is a risk factor for euploid miscarriage in women of reproductive age. This study included an unselected cohort of women from a large academic medical center that cares for patients in diverse clinical settings, including general gynecology (private and academic), emergency department, labor and delivery, and reproductive endocrinology and infertility clinic.

MATERIALS AND METHODS

Northwestern University Institutional Review Board approval was obtained for this retrospective cohort study. A data analyst at Northwestern University queried the Northwestern Enterprise Data Warehouse (EDW). The EDW is a data repository that spans all clinical sites associated with Northwestern Memorial HealthCare and the Northwestern University Feinberg School of Medicine and contains patient information from 1996 onward. Financial support was obtained from the Northwestern University EDW Pilot Data Program. Inclusion criteria consisted of women ≥ 18 years of age between January 2006 and January 2018 with pregnancy losses of ≤ 20 weeks' gestation who had genetic analysis of their products of conception by conventional cytogenetics with resulting karyotypes reported. Specifically, karyotype results were limited to those specimens with an associated diagnosis code of "missed abortion," "spontaneous abortion," "recurrent pregnancy loss," "recurrent miscarriage," "incomplete abortion," or "recurrent abortion." Exclusion criteria included those with products of conception that were not associated with a spontaneous pregnancy loss and those patients without BMI data available at the time of specimen collection. When patients had multiple specimens from repeat pregnancy loss only the earliest pregnancy loss was included. Demographic data for each patient also was collected and included age, BMI from the day of specimen collection, and race. Gestational age at time of pregnancy loss also was collected as available, however, only 31.5% of patients had a gestational age reported. Hemoglobin A1c and thyroid-stimulating hormone (TSH) were collected for each subject to assess underlying thyroid dysfunction or poor glycemic control. Beta-2 glycoprotein 1 antibody, lupus anticoagulant antibodies, and anticardiolipin antibodies also were gathered to assess for concurrent antiphospholipid antibody syndrome (APLS), a clinical autoimmune syndrome that is associated with poor pregnancy outcomes including pregnancy loss. Finally, anti-Mullerian hormone, follicle-stimulating hormone, and estrogen levels were collected in an attempt to further define the study population in regard to ovarian reserve. All of these values were collected within 1 year of initial specimen collection (before or after). These data were not incorporated into primary analysis but were explored in a supplemental analysis (Supplemental Table 1, available online). When more than one value was available, the value closest to the date of specimen collection was used. All data from the EDW database were transferred to an Excel (Microsoft) spreadsheet for analysis. Chart review was performed for missing data.

At our institution, products of conception can be sent for karyotype analysis at the provider's discretion in line with the patient's wishes. Specimen collection occurred at multiple clinical settings including the operating room, the emergency department, labor and delivery and triage, outpatient procedure rooms, and clinics. BMI data were either measured by clinical staff or were patient reported. Race was patient reported. Gestational age was reported by the ordering physician. It is important to note that the reported gestational age was not standardized to reflect the gestational age at time of loss or time of procedure and is an estimated date. All gestational age values were rounded up or down to the nearest week.

A total of 3,307 pregnancy losses results were derived from the initial database query. Two hundred thirty-nine results (7.2%) were excluded because the analysis of products of conception was unable to be obtained, most commonly because no culture was grown or no products of conception were identified in the submitted sample. Additionally, 96 (2.9%) patients were excluded because BMI data was not available. Finally, 352 (10.6%) results reflected repeat pregnancies and only the earliest pregnancy loss results were included in final analysis (Fig. 1). The decision to exclude

FIGURE 1

Number of Products of Conception Specimens
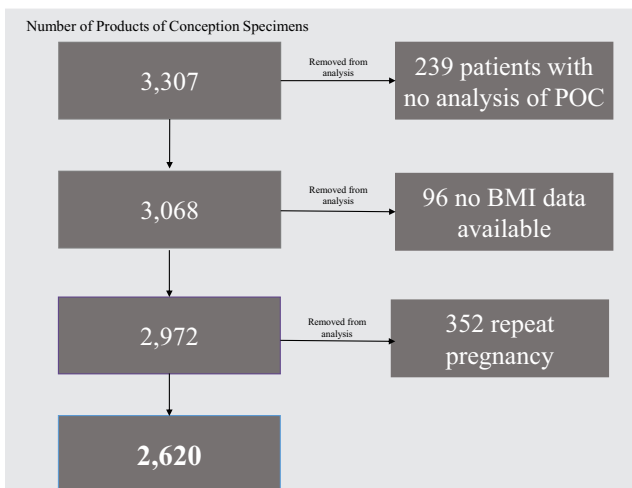
Removal of subjects after initial database query for "Products of Conception" results with associated diagnosis codes signifying spontaneous abortion. BMI = body mass index; POC = products of conception.

Lee. Obesity and euploid miscarriage. Fertil Steril Rep 2020.

TABLE 1

Characteristics of included women and genetic results of products of conception.

Characteristic	n	Mean (± SD)	Obese	Nonobese	*P* value
Age (y)	2,620	34.9 (± 4.9)	34.6 (± 5.5)	34.9 ± 4.7	NS
BMI (kg/m²)	2,620	25.3 (± 5.5)			
Underweight	69 (2.6)				
Normal	1,487 (56.8)				
Overweight	642 (24.5)				
Obese I	257 (9.8)				
Obese II	101 (3.9)				
Obese III	64 (2.4)				
Race					
White	1,691 (64.5)		213 (50)	1,478 (67)	<.001
Black	198 (7.6)		95 (23)	103 (5)	<.001
Hispanic	150 (5.7)		47 (11)	103 (5)	<.001
Asian	176 (6.7)		10 (2)	166 (8)	.009
Other	405 (15.5)		57 (14)	348 (15)	NS
Euploid	935 (35.7)				
46, XX	468 (17.9)		101 (24)	367 (17)	NS
46, XY	467 (17.8)		93 (22)	374 (17)	NS
Aneuploid	1,685 (64.3)				
Trisomy	1,068 (40.8)		148 (35)	920 (42)	NS
Trisomy 16	257 (24.1)				
Trisomy 22	175 (16.4)				
Trisomy 15	134 (12.5)				
Trisomy 21	123 (11.5)				
Monosomy	207 (7.9)		29 (6.9)	178 (8.1)	NS
Monosomy X	197 (95.2)				
Monosomy 21	10 (4.8)				
Polyploidy	185 (7.1)		20 (4.7)	165 (7.5)	NS
Multiple[a]	132 (5)		19 (4.5)	115 (5.1)	NS
Mosaic	52 (2)		6 (1.4)	46 (2.1)	NS
Duplication	14 (0.5)		1 (0.2)	13 (0.6)	NS
Inversion	7 (0.3)		2 (0.5)	5 (0.2)	NS
Deletion	5 (0.2)		0 (0)	5 (0.2)	NS
Other	15 (0.6)		3 (0.7)	12 (0.5)	NS

Note: Data presented as n (%), unless stated otherwise. BMI = body mass index; Deletion = mutation in which a part of a chromosome or a sequence of DNA is left out during DNA replication; Duplication = segment of chromosome is repeated and exists as extra genetic material; Inversion = rearrangement in which a segment of a chromosome is reversed end to end; Mosaic = 2 or more cell populations with distinct karyotypes existing within one specimen; NS = not significant; SD = standard deviation.
[a] Multiple ≥1 abnormality (i.e., trisomy + polyploidy).

Lee. Obesity and euploid miscarriage. Fertil Steril Rep 2020.

multiple pregnancies from the same woman was done to avoid bias given that two pregnancies from the same woman are not independent outcomes. Ultimately, 2,620 results met the inclusion criteria for final analysis.

Statistical analysis was performed using SPSS software (IBM). Means with standard deviations and frequencies were computed for demographic results. Logistic regression was performed to compare the rates of aneuploidy between obese and nonobese women, allowing adjustment for both age and race.

RESULTS

Of the 3,307 pregnancy losses results derived from the initial database query, 2,620 unique patients with karyotype results from products of conception were used in the final analysis (Fig. 1). As described in Table 1, mean age at time of pregnancy loss was 34.9 years (± 4.9) with a range of 18–48 years old. Mean BMI was 25.3 kg/m² (±5.5) with a range of 15–57 kg/m². Due to the small representation of each minority, race was analyzed categorically as white and nonwhite. Table 1 shows that the percentage of black and Hispanic patients

was higher in the obese group compared with the nonobese group. Conversely, the percentage of White and Asian patients was higher in the nonobese group. All karyotype results were derived from conventional cytogenetics.

Within the cohort, 64.8% of the losses were aneuploid, of which 41% were trisomies, 8% were monosomies, and 7% were polyploidies. Two types of monosomies were identified in our cohort, monosomy X (95.2%) and monosomy 21 (4.8%). Of trisomy results, trisomy 16, 22, 15, and 21 were the most common making up 24.1%, 16.4%, 12.5%, and 11.5% of trisomies, respectively. The minority of genetic results displayed mosaicism, deletions, duplications and inversions, or multiple abnormalities (Table 1). Of note, for the purposes of primary analysis, all noneuploid results were grouped together as abnormal regardless of the type of mutation. Of the euploid losses, 50.1% were 46,XX and 49.9% were 46,XY. When analyzed separately, obese women also had a ratio of 1:1 female-to-male euploid results.

As shown in Table 2, obesity was associated significantly with euploid pregnancy losses. In addition, younger age and nonwhite race also were associated significantly with lower rates of chromosomal abnormalities. After adjusting for age

TABLE 2

Characteristics of women with euploid losses.

Characteristic	Euploid (%)	Aneuploid (%)	Unadjusted			Adjusted		
			OR	95% CI	P value	OR	95% CI	P value
Age (y), mean	33.4	35.7	1.1	1.11–1.13	<.001	1.1	1.08–1.12	<.001
BMI (kg/m²)								
Nonobese (<30)	741 (33.7)	1,457 (66.3)						
Obese (≥30)	194 (46)	228 (54)	1.67	1.36–2.1	<.001	1.56[a]	1.25–1.95	<.001
Underweight (<18.5)	16 (23.2)	53 (76.8)	0.62	0.35–1.1	.104			
Normal (18.5–24.9)	485 (32.6)	1,002 (67.4)						
Overweight (25–29.9)	240 (37.4)	402 (62.6)	1.23	1.02–1.5	.033			
Obese I (30–34.9)	113 (44)	144 (56)	1.62	1.24–2.12	<.001			
Obese II (35–39.9)	46 (45.5)	55 (54.5)	1.72	1.15–2.59	.008			
Obese III (≥40)	35 (54.7)	29 (45.3)	2.49	1.51–4.13	<.001			
Race								
White	537 (31.8)	1,154 (68.2)						
Nonwhite	398 (42.8)	531 (57.2)	1.61	1.37–1.9	<.001	1.4[b]	1.18–1.67	<.001

Note: Data presented as n (%), unless stated otherwise. BMI = body mass index; CI = confidence interval; OR = odds ratio.
[a] OR calculated using number of nonobese vs. obese patients with euploid loss.
[b] OR calculated using number of white vs. nonwhite patients with euploid loss.

Lee. Obesity and euploid miscarriage. Fertil Steril Rep 2020.

and race, obese women were 56% more likely to have a euploid pregnancy loss compared with nonobese women (P<.001; odds ratio [OR] 1.56; 95% confidence interval [CI] 1.25–1.95). Based on the result of karyotype analysis in obese patients, we showed that increased BMI does not seem to contribute to pregnancy loss due to an increase in aneuploidy.

As previously mentioned, 352 results were repeat pregnancies from women who were already included in the study from another loss. These results were not included in the final analysis to avoid bias; however, a separate analysis was performed to further evaluate this cohort. Of these 352 results, 66.5% were aneuploid with similar rates of euploid male and euploid female results, 17.9% and 15.6%, respectively. This is comparable with those pregnancies included in primary analysis.

Finally, the database was queried for other known risk factors for miscarriage (Supplemental Table 1, available online). Only 132 women had a recent hemoglobin A1c (5.7%–6.4%, n = 23; >6.5%, n = 5). Few women had a complete evaluation for anti-phospholipid syndrome (lupus anticoagulant n = 396, anticardiolipin n = 216, and beta 2-glycoprotein n = 15). Gestational age was only available for 824 of the women and was analyzed as ≤10 weeks (n = 615; 74.6%) or >10 weeks (n = 209; 25.4%). Losses <10 weeks were significantly less likely to be euploid (OR 0.14; 95% CI 0.1–0.2; P<.001) and obese women were more likely to have a loss after 10 weeks' gestation (OR 2.01; 95% CI 1.46–2.97). Anti-Mullerian hormone level was only available for 99 women. Follicle-stimulating hormone level was available for 229 women and could not be chronologically correlated with estradiol levels. Lastly, TSH level was available in 594 women, of whom 461 were within normal range. An additional 75 subjects had results between 2.5 and 4.5 mIU/L, consistent with subclinical hypothyroidism. Only 13 TSH results were consistent with a hypothyroid state (TSH >4.5 mIU/L), and 45 were consistent with a

hyperthyroid state (<0.4 mIU/L). Given the lack of data available for these factors, we were unable to assess association with these factors and they were not included in the final analysis.

DISCUSSION
Principal Findings and Context

In this study, obese women were 56% more likely to have a euploid pregnancy loss compared with nonobese women after adjusting for age and race, suggesting that the cause of an early pregnancy loss may be different for women with a BMI >30 kg/m². Obesity is linked to a wide range of negative reproductive health outcomes, including miscarriage. In an era of rapidly increasing obesity worldwide, it is imperative that we continue to explore and understand how BMI may be impacting reproduction.

In a meta-analysis of data exploring the relationship between obesity and miscarriage, Metwally et al. (5) showed that patients with a BMI ≥ 25 kg/m² were significantly more likely to experience a spontaneous miscarriage <20 weeks of gestation (OR 1.67; 95% CI 1.25–2.25). Of note, similar to our study population, this analysis included women who experienced both assisted and spontaneous pregnancy conception.

Likewise, in a nested case-control study, Lashen et al. (4) explored the relationship between obesity and miscarriage in obese primiparous women. In this study, women with an obese BMI defined as ≥30 kg/m² were significantly more likely to experience early miscarriage or recurrent early miscarriage (OR 1.2 and 3.5; 95% CI 1.01–1.46 and 1.03–12.01, respectively) when compared with their normal weight–matched counterparts. Of note, neither of the studies described stratified miscarriages by the results of chromosomal analysis.

Furthermore, in a retrospective cohort study of women with recurrent pregnant loss, Boots et al. showed that obese

women with more than two pregnancy losses had an increased frequency of euploid miscarriage when compared with their normal weight counterparts (13). Primary analysis included 117 miscarriages. The frequency of euploid miscarriage among obese women was 58% compared with 37% of nonobese women (relative risk 1.63; 95% CI 1.08–2.47).

Clinical and Research Implications

These findings are relevant for the increasing obese population because the percent of losses secondary to chromosomal abnormalities may be overestimated, and thus miscarriages in this population may have other pathophysiologic etiologies that have yet to be clearly elucidated. In clinical practice, this may change how women are counseled and alter the evaluation performed both preconception and following a pregnancy loss. This retrospective study cannot state causation or suggest that weight loss will decrease miscarriage rates; it emphasizes that lifestyle and weight counseling may be beneficial, especially if implemented prior to conception. Additionally, although post-miscarriage counselling often centers on discussions of high rate aneuploidy in pregnancy loss, it is also a critical opportunity to do screening and make lifestyle recommendations, especially for the obese population. This has the potential to help patients navigate their health prior to conception that is either spontaneous or through assisted reproductive technology.

There are many hypothesized mechanisms by which obesity can influence pregnancy failure, including via hormonal dysregulation, changes in the endometrium, or direct effect on an early embryo. Obesity is a state of low-grade inflammation and increased secretion of cytokines including leptin is well described (14). It is known that circulating levels of the cell-signaling protein leptin, which is produced in adipose tissue, is higher in obese women. Increased leptin levels lead to down-regulation of the leptin receptor at the hypothalamus and, therefore, a relative leptin deficiency, which is thought to effect reproduction through increased rates of anovulation and dysregulation of the hypothalamic-pituitary-ovarian axis (15, 16). Furthermore, dysregulation of leptin has been found to influence reproductive function including embryo development, implantation, and placental function (17). Abnormal leptin signaling has even been suggested as a potential contributor to recurrent early pregnancy loss (18). Mahany et al. (19) studied the effect of leptin receptor deficiency in mice. These mice displayed a morbidly obese phenotype and had a high rate, >80%, of embryo resorptions. The placentas of these resorbed embryos displayed increased necrosis and inflammatory changes, suggesting that the obese environment could have a negative effect on the integrity of a developing early pregnancy.

Another possible mediator of the negative effect of obesity on early pregnancy is the effect on the endometrium. If the obese environment alters the receptivity or readiness of the endometrium for embryonic implantation, this could influence implantation and miscarriage rates in these women. The oocyte donation model reported by Bellver et al. (20) showed a significant decrease in pregnancy implantation, clinical pregnancy, and live birth rates for obese donor oocyte

recipients, suggesting reduced receptivity of the endometrium in obese patients. Furthermore, in a multicenter, prospective, case-control study, Comstock et al. (21) analyzed the endometrial gene expression from endometrial biopsy specimens during the window of implantation in infertile patients stratified based on BMI. They found that obese women with receptive endometria by endometrial receptivity assays had altered endometrial gene expression despite uniform endometrial preparation with a hormone replacement cycle. The molecular function of the genes that were differentially expressed is involved in functions including extracellular matrix organization and immune response. This change in gene expression could contribute to lower implantation rates, increased miscarriages, and poor pregnancy outcomes in the obese population.

Limitations and Strengths

Importantly, obstetric histories, mode of conception, and rate of preimplantation genetic testing (PGT) were not available for these results. Many practitioners in our clinical setting use hospital facilities for operative procedures, such and dilation and curettage, but do not share an electronic medical record with our institution, thus limiting collection of this data. Obstetric histories would provide additional information to counsel women on the risk of subsequent losses; however, this would not change the results of our study. Although data on modes of conception also would be interesting, miscarriage rates have not been shown to vary by mode of conception. Lastly, although the use of PGT has increased in the last several years, the number of pregnancy losses after PGT likely still represents a very small minority of samples in our cohort that spans from 2006–2018.

Obesity also is associated with endocrine disorders including thyroid disease and diabetes, which are known risk factors for pregnancy loss. We attempted to identify these confounders, however, these data were not universally available. Only 5% of the women had a hemoglobin A1c drawn within the year of pregnancy loss and <25% of the women had a recent TSH. Thus, sample sizes were too small to control conclusively for these confounders. However, this study emphasizes the importance of preconception counseling and evaluation. Obese women should be screened for both insulin resistance and thyroid dysfunction prior to conception.

Another limitation to this study is its retrospective nature. The data available was restricted to values recorded by staff at the time of the encounter. BMI, gestational age, and race data were often reported by the patient, which can be inaccurate. Additionally, only 824 subjects included in the final analysis had recorded gestational age data available for the miscarriage that was analyzed. Even when this value was recorded, there is inherent variation among providers on reporting of estimated gestational age based on the suspected gestational age at the time of pregnancy loss or the dating on the day of specimen collection.

As with all retrospective studies, it is not possible to control for all confounding factors. In particular, the dataset held minimal information on known miscarriage confounders, such as endocrine disorders as described, antiphospholipid

syndrome, and uterine cavity anatomy (i.e., fibroids and septum). The limited data that is available regarding these factors can be found in Supplemental Table 1 (available online). Notably, very few patients had comprehensive testing for APLS as evidenced by only 15 patients with a beta-2-glycoprotein result. Per the American Society for Reproductive Medicine, testing for APLS is not indicated until a woman has three or more unexplained, consecutive spontaneous losses at <10 weeks' gestation after other causes are excluded (6). Therefore, women who had an aneuploid loss (64.3% in our study) would be less likely to receive additional testing. These limitations also emphasize the importance of using our electronic health records in an accurate and meaningful way so that we can learn from clinical experience.

Although cytogenetic analysis of products of conception is a test available to all patients at our institution, the role of socioeconomic inequalities in a patient's access to this test was not evaluated. It has been shown that patients that undergo surgical evacuation for miscarriage management are more likely to be of elevated socioeconomic status and that patients who present to the emergency department for miscarriage care are more likely to be uninsured or publically insured (22, 23). Although not directly addressed in either of the above studies, one could hypothesize that patients without insurance or of low socioeconomic status are less likely to get karyotype analysis either because their pregnancy loss is managed medically or expectantly and procedures are not in place for efficient chromosome collection as is available in the operating room or they defer this test due to an inability to pay. If patients who could not pay or did not have access to cytogenetic analysis were excluded, it reduces the generalizability of our findings.

A final limitation is that all tissue was analyzed using conventional cytogenetics. Because only conventional cytogenetic analysis was performed, the way to minimize maternal cell contamination is to clearly identify, isolate, and culture chorionic villi. However, our results show a 1:1 ratio of euploid male–to–euploid female, suggesting that maternal cell contamination was likely minimal. Current technology, such as single nucleotide polpmorphism microarray or array comparative genomic hybridization, does not require cell growth in culture and thereby reduces the number of analyses that yield a "no result." These arrays also can more definitely exclude maternal cell contamination, having a higher resolution to detect smaller deletions and duplications, and some can provide parental origin of the aneuploidy, both of which can be incredibly useful in counseling and management recommendations.

Strengths of this study include its large number of study subjects (2,620 vs. 117 women in the most similar study). These samples were collected in the emergency department, in general gynecology clinics, in the labor and delivery department, and in the operating room by general obstetrician gynecologists, emergency department physicians, reproductive endocrinologists, and family planning providers. This heterogeneity increases the generalizability of these results and adds to the only other study on this topic, which previously reported association between obesity and euploid pregnancy loss only in the recurrent early pregnancy loss population. Of the cohort studied, only 93 of the 2,620 samples were collected in the department of endocrinology and infertility. Thus, it is more likely that the majority of these early losses followed spontaneous conception. Additionally, there is likely a low level of maternal cell contamination given equal number of euploid female (46, XX) and male (46, XY) karyotype results.

CONCLUSIONS

Given that miscarriage can be a psychologically challenging experience, both patients and physicians seek ways to prevent pregnancy loss. These data add to the growing knowledge about the mechanism for pregnancy loss in the obese population, further supporting that the maternal environment contributes to pregnancy loss via factors other than chromosomal aberrations. Lifestyle modifications, such as improved nutrition and increased physical activity prior to conception may have a meaningful effect in decreasing pregnancy loss in the obese population, but further data are needed to determine if there is true therapeutic benefit. At a minimum, obese women need preconception counseling and screening for the known comorbidities, such as insulin resistance and thyroid dysfunction.

Importantly, these data should not be used to imply blame or shame. We, as providers, must approach all of these conversations with empathy, sensitivity, and an opportunity to motivate patients and equip patients with the information we have regarding early pregnancy loss, specifically for the obese population. Ultimately, more research is needed both to understand the mechanism for pregnancy loss in the obese population and to identify possible interventions.

REFERENCES

1. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011-2014. NCHS Data Brief; 2015.
2. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril 2017;107:840–7.
3. Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. Fertil Steril 2010;94: 290–5.
4. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Hum Reprod 2004;19:1644–6.
5. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril 2008;90:714–26.
6. American Society for Reproductive Medecine. Practice Committee of American Society for Reproductive Medicine evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103–11.
7. Eiben B, Bartels I, Bahr-Porsch S, Borgmann S, Gatz G, Gellert G, et al. Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. Am J Hum Genet 1990;47:656.
8. Nikčević AV, Kuczmierczyk AR, Nicolaides KH. The influence of medical and psychological interventions on women's distress after miscarriage. J Psychosom Res 2007;63:283–90.
9. Pylyp LY, Spynenko LO, Verhoglyad NV, Mishenko AO, Mykytenko DO, Zukin VD. Chromosomal abnormalities in products of conception of first-trimester miscarriages detected by conventional cytogenetic analysis: a review of 1000 cases. J Assist Reprod Genet 2018;35:265–71.
10. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Hum Reprod Update 2003;9:359–72.

11. Halvorson LM. Chapter 6: First-trimester abortion. In: Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM, editors. Williams gynecology. 3rd ed. New York: McGraw-Hill Education LLC.; 2016.

12. Luzzo KM, Wang Q, Purcell SH, Chi M, Jimenez PT, Grindler N, et al. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. PLoS One 2012;7: e49217.

13. Boots CE, Bernardi LA, Stephenson MD. Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. Fertil Steril 2014;102:455–9.

14. McGown C, Birerdinc A, Younossi ZM. Adipose tissue as an endocrine organ. Clin Liver Dis 2014;18:41–58.

15. Tortoriello DV, McMinn JE, Chua SC. Increased expression of hypothalamic leptin receptor and adiponectin accompany resistance to dietary-induced obesity and infertility in female C57BL/6J mice. Int J Obes 2007;31:395–402.

16. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. Endocrinology 2004;154:1238–47.

17. Pérez-Pérez A, Toro A, Vilariño-García T, Maymó J, Guadix P, Dueñas JL, et al. Leptin action in normal and pathological pregnancies. J Cell Mol Med 2018;22:716–27.

18. Laird SM, Quinton ND, Anstie B, Li TC, Blakemore AIF. Leptin and leptin-binding activity in women with recurrent miscarriage: correlation with pregnancy outcome. Hum Reprod 2001;16:2008–13.

19. Mahany EB, Han X, Borges BC, Da Silveira Cruz-Machado S, Allen SJ, Garcia-Galiano D, et al. Obesity and high-fat diet induce distinct changes in placental gene expression and pregnancy outcome. Endocrinology 2018; 159:1718–33.

20. Bellver J, Pellicer A, García-Velasco JA, Ballesteros A, Remohí J, Meseguer M. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. Fertil Steril 2013; 100:1050–8.

21. Comstock IA, Diaz-Gimeno P, Cabanillas S, Bellver J, Sebastian-Leon P, Shah M, et al. Does an increased body mass index affect endometrial gene expression patterns in infertile patients? A functional genomics analysis. Fertil Steril 2017;107:740–8.e2.

22. Schreiber CA, Chavez V, Whittaker PG, Ratcliffe SJ, Easley EBF. Treatment decisions at the time of miscarriage Diagnosis Obstet. Gynecol 2016;128: 1347–56.

23. Miller CA, Roe AH, Mcallister A, Koelper N, Schreiber CA. Management in the emergency and ambulatory settings. 2019;134:1285–92.