Maternal body mass index is not associated with increased rates of maternal embryonic aneuploidy

Lydia M. Hughes, M.D.,[a] Dana B. McQueen, M.D.,[a] Emily S. Jungheim, M.D., M.S.C.I.,[a] Katrina Merrion, M.S.,[b] and Christina E. Boots, M.D., M.S.C.I.[a]

[a] Division of Reproductive Endocrinology and Infertility, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and [b] Natera, Inc., San Carlos, California

Objective: To evaluate the relationship between maternal body mass index (BMI) and embryonic aneuploidy of maternal origin.
Design: Retrospective cohort analysis.
Setting: University hospital-based reproductive center.
Patients: Maternal origin of aneuploidy was available for 453 cycles and 1,717 embryos.
Interventions: Data regarding BMI were collected before egg retrieval. Comparison groups included underweight (BMI, <18.5 kg/m^2), normal weight (BMI, 18.5–24.9 kg/m^2), overweight (BMI, 25–29.9 kg/m^2), and obese (BMI, ≥ 30 kg/m^2). Overall embryonic aneuploidy and maternal aneuploidy rates were compared. The aneuploidy rate was the number of embryos with either maternal or mixed (maternal and paternal) aneuploidy divided by the total number of embryos tested.
Main Outcome Measures: Overall embryonic aneuploidy and maternal aneuploidy rates.
Results: Maternal aneuploidy rate was 51.5% for BMI of ≥ 30 kg/m^2 and 39.3% for BMI of <30 kg/m^2. Female age as well as several in vitro fertilization characteristics were significantly different across groups and were included in the adjusted model. Both the overall embryonic aneuploidy rate (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.11–1.59) and the maternal aneuploidy rate (OR, 1.64; 95% CI, 1.25–2.16) increased with increasing maternal BMI. However, after controlling for significant confounders, BMI did not significantly predict the rate of maternal aneuploidy (OR, 1.16; 95% CI, 0.85–1.59).
Conclusions: Maternal BMI did not correlate with embryonic aneuploidy of maternal origin after adjusting for confounders. (Fertil Steril® 2022;117:783-9. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Embryonic aneuploidy, IVF, maternal BMI, maternal obesity, PGT

The global prevalence of obesity has soared over the past several decades, leading to pervasive maternal, peripartum, fetal, and even childhood complications (1–3). In the United States, obesity affects up to one third of all women of reproductive age and has increased more than threefold since 1980 (2, 4, 5). Obesity has widespread implications for reproductive outcomes, including anovulation, infertility, and poor maternal prognoses, and is associated with an increased risk of miscarriage and stillbirth (1, 5–8). Given the well-studied intimate relationship between metabolism and female fertility, it is not surprising that maternal obesity has been linked to many reproductive sequelae (7). Additionally, multiple studies support a direct correlation between the increasing body mass index (BMI) and the decline in fertility, regardless of the mechanism of conception (6, 9–13).

Previous work has demonstrated that the risk of early miscarriage is increased with maternal obesity (6, 9, 12–15). After in vitro fertilization (IVF), a large retrospective cohort study on assisted reproductive technology outcomes noted a twofold increased risk of miscarriage in obese women compared with a control group with normal BMI (16). This significance persisted even when controlling for other underlying pathologies, namely polycystic ovary syndrome, underscoring the independent influence of obesity on early pregnancy loss (16). The etiology

Received September 1, 2021; revised December 21, 2021; accepted December 29, 2021; published online January 31, 2022.
L.M.H. has nothing to disclose. D.B.M. has nothing to disclose. E.S.J. has nothing to disclose. K.M. is a full-time employee and holds stock of Natera, Inc., San Carlos, California. C.E.B. has nothing to disclose.
Presented, in part, as an oral presentation at the 76th Annual Meeting of the American Society for Reproductive Medicine, Virtual Meeting, October 17–21, 2020.
Reprint requests: Lydia M. Hughes, M.D., Department of Obstetrics and Gynecology, Northwestern Medicine Prentice Women's Hospital, 250 E Superior St., Suite 5-2177, Chicago, Illinois 60611 (E-mail: lhughes@northwestern.edu).

Fertility and Sterility® Vol. 117, No. 4, April 2022 0015-0282

https://doi.org/10.1016/j.fertnstert.2021.12.031

for these findings is postulated to be multifactorial and attributed to obesity's effect on poor oocyte quality (17–19), hypothalamic-pituitary hormonal dysregulation (20, 21), and alterations to the intricate milieu of the endometrial environment during implantation (22). However, an exact mechanism driving these connections between obesity and decreased IVF success is currently unclear.

Maternal obesity has been linked to long-term fetal and childhood consequences, including increasing the offspring's risk of obesity, neurodevelopmental disorders, and comorbidities such as diabetes and asthma (3). This transgenerational impact of obesity may originate preconceptionally—starting with the oocyte (17, 19, 23). For example, in diet-induced obese mouse models, there is mitochondrial dysfunction and higher rates of meiotic aneuploidy due to disorganized spindle formation and subsequent chromosomal misalignment during metaphase (23). Thus, it is biologically plausible that maternal obesity could beget oocyte and embryonic aneuploidy and, therefore, could explain the increased rates of early pregnancy loss in women with higher BMIs.

The aim of our study was to determine whether there was a relationship between maternal BMI and embryonic aneuploidy of maternal origin. Preimplantation genetic testing for aneuploidy (PGT-A) has afforded couples undergoing IVF the ability to detect aneuploidy before embryo implantation and thus has improved IVF outcomes (24). Further advanced technology can also determine whether the aneuploidy origin is maternally or paternally derived. To our knowledge, this study is the first to examine the association between maternal obesity and maternal origin of aneuploidy. Moreover, establishing risk factors for maternal aneuploidy is fundamental to identifying patients who could benefit from PGT-A and can guide physician counseling before patients undergoing IVF. Given the well-established association between maternal obesity and miscarriage, we hypothesized that increasing maternal BMI would be associated with higher rates of embryonic aneuploidy of maternal origin.

MATERIALS AND METHODS

Study Population

Northwestern University institutional review board approval was obtained (STU00211722) for this retrospective cohort study. All IVF cycles that used PGT-A (through one of two reference laboratories) from January 2015 to January 2020 at Northwestern Medicine were included. The data were prospectively collected from an internal IVF database that is used for Society for Assisted Reproductive Technology reporting and routinely inspected for quality control. Northwestern Medicine serves a diverse urban population within Chicago, Illinois, as well as patients from surrounding suburban areas, including Indiana and Wisconsin.

Inclusion and Exclusion Criteria

Demographic data were extracted, including age, BMI, ovarian reserve screening, and IVF stimulation characteristics. Only cycles containing the latter demographic data and those undergoing PGT-A through Natera, Inc., (San Carlos, CA) reference laboratory were included. The IVF cycles without preimplantation genetic testing (PGT) were excluded. Maternal BMI was recorded at the time of oocyte retrieval. The BMI categories were defined according to the World Health Organization guidelines: underweight, BMI of <18.5 kg/m^2; normal, BMI of 18.5 kg/m^2 to <25.0 kg/m^2; overweight, BMI of 25.0 kg/m^2 to <30.0 kg/m^2; and obese, BMI of ≥ 30.0 kg/m^2.

In vitro fertilization cycles were not excluded on the basis of stimulation protocol. Moreover, the stimulation protocol types were not restrictive and included traditional antagonist and down-regulation protocols. The trigger was either human chorionic gonadotropin or a gonadotropin-releasing hormone agonist depending on protocol. The timing of trigger was typically based on physician discretion when at least two follicles were >18 mm in diameter per standard practice.

Outcome Measures

The primary outcome for the study was rate of embryonic aneuploidy of maternal origin and the association with increasing maternal BMI. The secondary outcome was the overall embryonic aneuploidy rate regardless of parental origin.

Laboratory Evaluation

Embryos were cultured to the blastocyst stage in the EmbryoScope time-lapse system (Vitrolife, Gothenburg, Sweden). Individual embryos were placed in 25-mL droplets of Continuous Single Culture-NX Complete (FUJIFILM Irvine Scientific, Santa Ana, CA) and Sage 1-Step (CooperSurgical, Trumbull, CT) with 10% serum protein supplement medium in a 37°C, 6% CO_2, and 5% O_2 environment. The zona pellucida was breached on day 5/6 of embryo development using a LYKOS laser (Hamilton Thorne, Beverly, MA). The laser was subsequently used to remove 5–8 trophectoderm cells from each blastocyst. Embryos were subsequently vitrified and the trophectoderm biopsies and biologic parental samples were shipped to a reference laboratory for analysis (Natera, Inc.). Only one of the two commercial PGT laboratories (Natera, Inc.) uses a platform that allows for the detection of parental origin of aneuploidy, and thus embryos with results from the second laboratory were excluded from the final analysis. Genotyping was performed using Cyto12 (Illumina, San Diego, CA) single nucleotide polymorphism (SNP) microarrays with parental support bioinformatics (25). Parental SNP genotype information was used to predict the possible SNP genotypes for an embryo. Embryo samples were compared with parental samples across multiple SNP loci. For each chromosome, algorithms compared the observed SNP data with each of the predicted allele distributions for each copy number hypothesis and identified one with the maximum likelihood. In addition to evaluating for chromosome copy number, this analysis determines the parental origin of each chromosome and rules out the DNA contamination. Parental support algorithms generate a confidence for each chromosome call, which is an estimate of the probability that the call is correct. In the case of euploid results, the

TABLE 1

Patient characteristics.

Characteristics	Underweight (N = 33 cycles, 137 embryos)	Normal weight (N = 745 cycles, 2,968 embryos)	Overweight (N = 291 cycles, 1,040 embryos)	Obese (N = 174 cycles, 554 embryos)	*P* value
Maternal age, y	35.9 (4.0)	36.1 (3.8)	37.4 (3.6)	37.8 (3.5)	< .01
AMH, ng/mL	4.0 (2.3)	3.1 (2.7)	2.7 (2.4)	2.8 (2.4)	.017
Days of stimulation	10.4 (1.6)	10.5 (1.6)	10.6 (1.5)	10.5 (1.6)	.96
Peak E2, pg/mL	2,744.4 (1,596.2)	2,593.4 (1,563.7)	2,155.7 (1,160.3)	1,988.3 (971.4)	< .01
Oocytes retrieved	17.3 (9.3)	16.3 (9.7)	14.9 (8.0)	14.7 (7.6)	.045
Mature oocytes	11.7 (7.0)	11.1 (7.8)	10.2 (6.3)	9.6 (5.9)	.029
Fertilized oocytes	9.6 (5.7)	9.5 (6.5)	8.4 (5.4)	7.9 (4.8)	.003
Blastocysts biopsied	4.2 (3.1)	4.0 (3.0)	3.6 (2.9)	3.2 (2.0)	< .01
Overall aneuploidy rate per embryo tested (N)	46.7% (64/137)	48.7% (1,445/2,968)	53.3% (554/1,040)	56.9% (315/554)	< .01
Maternal aneuploidy rate per embryo tested (N)	32.3% (21/65)	37.6% (370/983)	44.5% (193/434)	51.5% (121/235)	< .01

Note: Body mass index (BMI) was categorized according to the World Health Organization guidelines as follows: underweight, BMI of <18.5 kg/m^2; normal, BMI of 18.5 kg/m^2 to <25.0 kg/m^2; overweight, BMI of 25.0 kg/m^2 to <30.0 kg/m^2; and obese, BMI of ≥30.0 kg/m^2. Values are presented as mean ± standard deviation with the last two rows displayed as percentage of aneuploidy per embryo tested calculated by N per each group. AMH = antimüllerian hormone; E2 = estradiol.

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confidence denotes the probability that the copy number call is disomic (one copy of a given chromosome from each parent). In the case of aneuploid results, the confidence denotes the probability that the copy number call is anything other than disomic. This methodology does not detect mosaicism. Therefore, embryo results were classified as "euploid" (no chromosome abnormality detected), "aneuploid" (monosomy, tri/polysomy, haploidy, triploidy, large deletions/duplications, and/or uniparental disomy detected), or "No DNA/No Call" for insufficient DNA or inconclusive data. Aneuploid embryos were subcategorized as having maternal aneuploidy, paternal aneuploidy, or mixed (maternal and paternal) aneuploidy.

Statistical Analyses

Statistical analysis was performed using SPSS software (International Business Machines Corporation, Armonk, NY). Continuous variables with normal distribution were compared with Student's *t* test and nonparametric analyses, if not normally distributed. Categorical variables used the χ^2 test. Analysis of variance and Tukey's test were used to compare more than one category. The generalized estimating equation was used to control for multiple embryos (i.e., multiple cycles) from the same couple and to adjust for multiple confounders. The model was built using an exchangeable correlation with the binary dependent variable being embryo maternal aneuploidy (mixed and maternal origin alone). Several predictors were entered into the model, including age, BMI, and IVF characteristics. The following variables were included in preliminary models and were found to be noncontributory: antimüllerian hormone (AMH) level, peak estradiol level, stimulation days, total gonadotropin dose, and the number of mature oocytes. Nonsignificant predictors were removed when each lack of contribution was identified. Ultimately, the final model included only the significant variables of age and maternal BMI.

RESULTS

A total of 1,243 IVF/PGT cycles and 4,699 embryos with known ploidy status were included in the initial evaluation. Of this group, maternal origin of aneuploidy was available for 453 cycles and 1,717 embryos. Baseline patient characteristics and IVF cycle details were compared by stratified BMI as illustrated in Table 1. Maternal age ranged from 28 years to 45 years and BMI from 16 kg/m^2 to 44.5 kg/m^2. In the unadjusted analysis, increasing BMI was associated with older maternal age, lower AMH levels, fewer oocytes retrieved, and fewer blastocysts biopsied (Table 1). Higher BMI was also associated with higher rates of aneuploidy in the unadjusted analysis.

When categorized by obese (BMI ≥ 30 kg/m^2) versus nonobese (BMI < 30 kg/m^2), the mean BMI was 34.4 ± 4.0 kg/m^2 versus 23.2 ± 3.0 kg/m^2, respectively (P<.001; Table 2). Moreover, the mean maternal age was 38.0 ± 2.9 years in the obese group and 36.3 ± 3.5 years in the nonobese group. In this unadjusted analysis, maternal BMI was associated with a significantly increased rate of maternal aneuploidy with a rate of 51.5% in the obese group versus 39.3% in the nonobese group (P<.001). There was a significant

TABLE 2

Relationship between maternal body mass index and embryonic aneuploidy.

	Total aneuploidy rate	Maternal aneuploidy rate
Nonobese, BMI < 30 kg/m^2	49.8% (2,063/4,145)	39.3% (582/1,482)
Obese, BMI ≥ 30 kg/m^2	56.9% (315/554)	51.5% (121/235)
Unadjusted OR	1.3 (95% CI, 1.11–1.59)	1.64 (95% CI, 1.25–2.16)
Adjusted OR	N/A	1.16 (95% CI, 0.85–1.59)

Note: Unadjusted and adjusted values after controlling for confounders are presented as OR with 95% CI. Aneuploidy rates are displayed as the percentage as well as the ratio of embryos with maternal aneuploidy over all embryos tested. BMI = body mass index; CI = confidence interval; N/A = not applicable; OR = odds ratio.

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difference in the rate of overall aneuploidy (both maternally and paternally derived) and BMI: 56.9% in the obese group versus 49.8% in the nonobese group ($P = .002$; Table 2). Given that female age as well as several IVF characteristics were significantly different across groups (displayed in Tables 1 and 2), we performed an adjusted model accounting for these factors. After controlling for age, BMI did not reliably predict the rate of maternal aneuploidy. This nonsignificant association persisted regardless of age or BMI being described as a continuous or categorical variable. Specifically, increasing maternal age was the only significant variable to predict both maternal and overall aneuploidy. None of the other baseline characteristics or IVF parameters such as AMH levels, oocytes retrieved, fertilized oocytes, and peak estradiol levels were significant predictors. Lastly, we examined BMI by class as defined by the World Health Organization (normal, BMI of 18.5 kg/m^2 to <25 kg/m^2; overweight, BMI of 25 kg/m^2 to <30 kg/m^2; class 1, BMI of 30 kg/m^2 to <35 kg/m^2; class 2, BMI of 35 kg/m^2 to <40 kg/m^2; and class 3, BMI of ≥40 kg/m^2), and there was no association with maternal aneuploidy (Table 3).

DISCUSSION

In this large retrospective analysis of embryos with known parental origin of aneuploidy status, maternal BMI was not associated with higher rates of maternally derived embryonic aneuploidy after adjusting for maternal age. Indeed, neither ovarian reserve nor stimulation characteristics predicted embryonic aneuploidy of maternal origin. Maternal age was the sole predictor of aneuploidy, a finding in concert with prior literature (26). Our findings are further supported by Goldman et al. (27) who did not find a relationship between maternal BMI and euploidy when examining overall aneuploidy rates (combined paternal and maternal origin) in couples undergoing IVF. Recently, a large retrospective cohort study further confirmed that maternal BMI was not associated with increased rates of overall aneuploidy, although it did not examine the influence of parental origin (28). Likewise, our results were congruent with prior studies demonstrating increased rates of euploid loss associated with increasing maternal BMI, thereby suggesting that alternative mechanisms are responsible for miscarriage other than aneuploidy (9, 27, 29, 30). Moreover, other studies analyzing products of conception after spontaneous pregnancy support higher rates of euploid embryo loss at <20 weeks of gestation in obese versus nonobese women (31). Tremellen et al. (9) found higher rates of miscarriage after euploid frozen embryo transfers in women with higher BMIs, which is an even more salient finding in the field of reproductive technology. Hence, all these studies underscore that there are adverse factors related to obesity other than genetics that predispose to early pregnancy failure.

Our results support the evidence that the well-described increased rate of miscarriage in obese women compared with women with normal weight is not driven by maternally derived embryonic aneuploidy (10, 12, 14, 15, 32). This theory is corroborated by a large multicenter retrospective study by Bellver et al. (15), which focused only on donor oocytes IVF cycles, thereby directly controlling for maternal age and egg quality confounders. The investigators describe a fourfold increased risk of early pregnancy loss with BMI of ≥30 kg/m^2, which highlights that maternal obesity is an independent

TABLE 3

Body mass index by the World Health Organization class and rate of maternal embryonic aneuploidy.

Obesity by class	Normal BMI of < 25 kg/m^2	Overweight BMI of 25 kg/m^2 to < 30 kg/m^2	Class 1 BMI of 30 kg/m^2 to < 35 kg/m^2	Class 2 BMI of 35 kg/m^2 to < 40 kg/m^2	Class 3 BMI of > 40 kg/m^2
Maternal aneuploidy rate per embryo tested (N = embryos)	37.6% (370/983)	44.0% (191/434)	54.5% (90/165)	50.0% (17/34)	38.9% (14/36)

Note: Body mass index obesity class was defined by World Health Organization criteria. Aneuploidy rates are displayed as the percentage as well as the ratio of embryos with maternal aneuploidy over all embryos tested. BMI = body mass index.

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risk factor for miscarriage (15). Ultimately, this finding is surprising given that the primary cause for miscarriage in both spontaneously conceived and assisted reproductive technology pregnancies has heretofore been attributed to chromosomal aneuploidy (33, 34).

Although embryonic aneuploidy is often responsible for early pregnancy loss, other factors related specifically to maternal obesity have been implicated. For example, obesity-related alterations in hypothalamic-pituitary signaling leads to abnormal and irregular menstrual cycles but may also create hormonal dysregulation surrounding embryo implantation (6, 35). Similar pathophysiology is implicated in polycystic ovary syndrome, a metabolic disorder often related to increased adiposity (36). Obesity has also been shown to disrupt endometrial receptivity due to circulating inflammatory factors (such as interleukin 6 and tumor necrosis factor-α) and, furthermore, alter stromal endometrial decidualization, thereby impairing embryo implantation (22, 35, 37). Lastly, both poor oocyte quality and decreased oocyte production have been linked to obesity due to complex alterations in granulosa cell and overall intrinsic ovarian function (38–40). Taken together, our results support the theory that these alternative mechanisms of obesity-related miscarriage could have a greater impact than just chromosomal aneuploidy.

To our knowledge, this study is the first to examine the association between maternal BMI and embryonic aneuploidy specifically of maternal origin. Limitations of this study include its retrospective nature as well as the general limitations of PGT-A given that parental origin of aneuploidy was not performed on the entire cohort of embryos that underwent PGT at Northwestern Medicine. Although clinically expedient, BMI is an imperfect marker of maternal obesity due to variations in patients' muscle mass, height, and adiposity distribution (central obesity is associated with higher rates of metabolic syndrome compared with peripheral obesity). The strengths of the study include its large sample size and robust data set of advanced SNP microarray test results, which allowed for distinction of maternally derived embryonic aneuploidy. Moreover, the same laboratory was used to perform all SNP microarray analyses for PGT-A, which avoids data variation due to different laboratory equipment and/or methodology. Finally, our data set was comprehensive, affording multiple regression analysis to adjust for confounding factors.

In summary, maternal age remains the sole predictor of maternally derived embryonic aneuploidy. Although embryonic aneuploidy rates were significantly higher among obese women than among women with normal weight, this association was no longer significant after adjusting for maternal age. There was also no association with aneuploidy in the group with the highest BMI (>40 kg/m^2). Although limited by a small sample size in the extreme BMI categories, it was reassuring that we did not see a trend of increased aneuploidy rates even among the very obese women in our study. Our results are clinically relevant insofar as increasing maternal BMI does not predict an increased rate of embryonic aneuploidy of maternal origin. Thus, this study contributes to a deeper understanding of obesity's influence on embryonic potential and could refine physician counseling. Moreover, confirmation that age is more impactful than weight can spark new discussions with patients regarding transfer strategy. These considerations could shift women with obesity toward immediate embryo banking followed by lifestyle changes with weight loss before embryo transfer.

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El índice de masa corporal materno no está asociado con mayores tasas de aneuploidía embrionaria materna.

Objetivo: Evaluar la relación entre índice de masa corporal materno (BMI) y la aneuploidía embrionaria de origen materno.

Diseño: Análisis retrospectivo de cohorte.

Lugar: Centro reproductivo del hospital universitario.

Pacientes: El origen materno de aneuploidía estaba disponible en 453 ciclos y 1,717 embriones.

Intervención(es): Datos con respecto a BMI fueron recolectados antes de la recuperación de ovocitos. Los grupos de comparación incluyeron bajo peso (BMI, <18.5 kg/m^2), peso normal (BMI, 18.5–24.9 kg/m^2), sobrepeso (BMI, 25–29.9 kg/m^2), y obeso (BMI, ≥ 30 kg/m^2). Tasas de aneuploidía embrionaria y aneuploidía materna fueron comparadas en general. La tasa de aneuploidía fue el número de embriones ya sea con aneuploidía materna o mixta (materna y paterna) dividido por el número total de embriones examinados.

Principal(es) medida(s) de resultado(s): Tasas de aneuploidía embrionaria y aneuploidía materna en general.

Resultado(s): La tasa de aneuploidía materna fue 51.5% para BMI de ≥ 30 kg/m^2 y 39.3% para BMI de <30 kg/m^2. La edad femenina así como también varias características de fertilización in vitro fueron significativamente diferentes entre los grupos y fueron incluidos en el modelo ajustado. Ambas tasas en general de aneuploidía embrionaria ([OR], 1.3; 95% intervalo de confianza [CI], 1.11–1.59) y aneuploidía materna (OR, 1.64; 95% CI, 1.25–2.16) aumentaron con el aumento de BMI materno. Sin embargo, luego de controlar factores de confusión significativos, BMI no predijo significativamente la tasa de aneuploidía materna (OR, 1.16; 95% CI, 0.85–1.59).

Conclusión(es): El BMI materno no se correlaciona con la aneuploidía embrionaria de origen materno luego del ajuste de factores de confusión. (Fertil Steril 2021; c 2021 por Sociedad Americana de Medicina Reproductiva.)