Female overweight is not associated with a higher embryo euploidy rate in first trimester miscarriages karyotyped by hysteroembryoscopy

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Overweight women (body mass index $\geq$25 kg/m^2) present an embryo euploidy rate in first trimester miscarriages similar to normoweight controls after a selective biopsy and karyotyping of embryo and/or chorion samples taken by hysteroembryoscopy. (Fertil Steril® 2011;96:931–3. ©2011 by American Society for Reproductive Medicine.)

Key Words: Overweight, first trimester miscarriage, hysteroembryoscopy, karyotype, aneuploidy

Obesity is an increasing health problem in developed countries and has been related to infertility and pregnancy complications in both natural and assisted conceptions (1–5). Several studies have shown an increased risk of first trimester miscarriage in pregnancies achieved spontaneously or by ovulation induction and IVF in women with weight excess (6–11).

Chromosome anomalies are known to be the most common cause of first trimester miscarriage, being more frequent as maternal age advances especially from 35 years old (12–16). An increased embryo aneuploidy rate may also be present in overweight and obese women, even at younger ages, which explains their higher risk of miscarriage. However, this risk has also been described in obese women conceiving through ovum donation (11, 17), pointing to an endometrial and/or environmental disturbance as the main mechanism for pregnancy wastage, such as an association with polycystic ovary syndrome (PCOS), aberrant corpus luteal function induced by hyperinsulinemia, insulin resistance during conception, associated thyroid dysfunction, endometrial dysfunction, and increased prevalence of congenital malformations (8, 18–24).

The aim of the present study was to determine the proportion of aneuploid embryos in first trimester miscarriages in overweight women by using a direct selective biopsy of embryo/chorion through hysteroscopy before dilatation and curettage (D&C) to discard maternal contamination.

We analyzed retrospectively the results of the selective karyotyping of first trimester miscarriages performed by hysteroembryoscopy in our center in the last 10 years in which the body mass index (BMI) of the patient had been recorded (n = 341). In brief, all hysteroembryoscopies and subsequent curettage procedures were carried out under general anesthesia on an outpatient basis. A Hamou examination and contact hysteroscope III with a Hopkins forward-oblique 30° telescope, 2.9 mm in diameter and 30 cm length, and a Bettocchi single-flow operating sheath, size 4.3 mm, provided with a 5-Fr channel for semirigid instruments (Karl Storz GmbH) was used. Normal saline was used as the distending medium. The hysteroscope was gently introduced into the uterine cavity without cervical dilatation. The gestational sac prominence was located. A small hole was made in the gestational sac wall using a 5-Fr biopsy spoon forceps (Karl Storz GmbH). The scope was introduced gradually in the extracelomic and amniotic cavities. Direct chorion and embryo biopsies were taken and placed in normal saline. A suction curettage was performed immediately afterward. A course of oral azitromycin was given postoperatively.

Two hundred fifty-five normoweight (<25 kg/m^2) and 86 overweight ($\geq$25 kg/m^2) women were included. The maternal BMI of the included population was 23.5 (23.0–23.9) kg/m^2. Twenty-two patients presented BMI >30 kg/m^2, representing 6.4% (3.8–9.0) of all patients in the study. BMI was 21.62 (21.4–21.8) kg/m^2 and 28.95 (28.15–29.76) kg/m^2 in the normoweight and overweight groups, respectively. Maternal age was 34.8 (34.2–35.5) years. Only 34 women (9.9%) were older than 40 years. Mean (95% confidence interval) gestational age at miscarriage was 8.2 (7.9–8.4) weeks. PCOS was present in 9.2% (6.1–12.3) of the patients. Sixty-eight pregnancies (19.9% [15.7–24.1]) were from spontaneous conception, while 273 (80% [75.8–84.3]) pregnancies were conceived by assisted reproduction techniques, mostly using intracytoplasmic sperm injection (ICSI; 73.6% [68.3–78.9]). Forty-four women (12.9% [9.3–16.5]) presented with two or more previous miscarriages.

The proportion of abnormal karyotypes was 64.0% in older women ($\geq$35 years of age) and 52.0% in young women (<35), with $P<.05$. The samples analyzed presented 43.7% (38.4–49.0) normal karyotypes, with 43% (n = 64) of them being 46,XY and 57% (n = 85) 46,XX. Trisomy was the most prevalent aneuploidy (36.1% [31.0–41.2] of all women), followed by mosaicism (7.0% [4.3–9.7]), monosomy X (6.5% [3.9–9.1]), triploids (3.5% [1.6–5.5]), tetraploids (2.1% [0.6–3.6]), and other findings representing 1.2% (0–2.3). In normoweight women, abnormal karyotype was detected in 57.6% (51.5–63.7) of samples, and in overweight women in 52.3% (41.7–62.9) of women, with no statistical difference (P=.390). When we compared the type of chromosomal abnormality according to female BMI, no differences were found between normoweight and overweight women (Table 1). In addition, a similar proportion of anatomical defects in

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TABLE 1

Karyotype abnormalities according to female BMI.

Abnormal karyotype	Body mass index, kg/m^2 ≤25	Body mass index, kg/m^2 >25	Total
Monosomy	19, 12.9% (7.5–18.3)	3, 6.7% (0–14.0)	22, 11.5% (7.0–16.0)
Trisomy	91, 61.9% (54.1–69.8)	32, 71.1% (57.9–87.3)	123, 64.1% (6.8–57.3)
Triploidy	9, 6.1% (4.4–13.6)	3, 6.7% (0–14.0)	12, 6.3% (2.9–9.7)
Tetraploidy	7, 4.8% (2.9–11.1)	0, 0%	7, 3.6% (1.0–6.2)
Mosaic	18, 12.2% (6.9–17.5)	6, 13.3% (3.4–23.2)	24, 12.5% (7.8–17.2)
Others	3, 2.0% (0.2–5.8)	1, 2.2% (0–6.5)	4, 2.1% (0–4.0)
Total, n	147	45	192

Note: Data are presented as cases and proportions, with 95% confidence intervals in parentheses. $P>.05$ between groups for all chromosomopathies.

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the embryos analyzed were found in both BMI groups: early intrauterine growth restriction, spina bifida, cord cysts, or abnormal chorion were detected in 44.7%, 0%, 1.6%, and 12.9% of specimens from normoweight women and in 46.6%, 1.1%, 2.3%, and 9.1% of specimens from overweight women ($P=.636$).

Gestational week of miscarriage, maternal age, presence of PCOS, or history of recurrent miscarriage were similar in both BMI groups. When stratified by age (≤ or >35 years), to compare the BMI influence on the risk of having a karyotype abnormality, no differences appeared (Supplemental Table 1). Comparisons of proportions between categories were carried out using the χ^2-test, and logistic regression (either univariate or multivariate, including the most relevant parameters) was also performed to control for potential confounders in the relation between the independent (BMI) and the dependent (karyotype abnormality) variables. Univariate analysis determined no increased risk of having an abnormal karyotype in overweight women, with an odds ratio (OR) of 1.04 (0.99–1.10). The adjusted (Adj) OR obtained after multivariate analysis considering maternal age, history of recurrent miscarriage, presence of PCOS, and mode of conception (assisted reproduction) was also comparable: Adj OR 1.04 (0.98–1.10) and equal to the univariate analysis result.

Two recent retrospective studies have also explored the chromosomal complement of first trimester miscarriages according to the cutoff BMI value of 25 kg/m^2 by analyzing the cytogenetic results of the products of conception obtained by D&C (25, 26). The first study (25) included 204 miscarriages in 153 normoweight (BMI <25 kg/m^2) women and 51 overweight (BMI ≥25 kg/m^2) women; the second study (26) included 352 specimens in 222 and 130 normoweight and overweight women, respectively. In both studies, the embryo aneuploidy rate was higher in women >35 years old and lower in overweight women. The reduction of embryo aneuploidy rate in women with high BMI was only detected in young patients: <35 years in the second study—in which 112 normoweight versus 52 overweight women were compared—and <40 years in the second study. Landres et al. (25) did not show any influence of PCOS, assisted conception, ICSI, or history of recurrent pregnancy loss in the detection of an abnormal karyotype.

However, karyotype was performed from specimens obtained by D&C, with the associated risks of failed result and maternal contamination, as suggested by the authors (25, 26). Landres et al. (25) showed a female-to-male ratio of 1.3:1 in normal karyotypes. In the study by Kroon et al. (26), 70 specimens failed to grow/subculture, and the proportion of normal female and male karyotypes was 62.5% and 37.5%, respectively. Previous studies have determined that no reliable karyotype is achieved in almost 50% of samples obtained after D&C owing to problems in sample taking, culture growth, or maternal contamination (27, 28). In fact, ≥30% of samples obtained by conventional D&C present total or partial maternal contamination, leading to 22% of misdiagnoses (29, 30).

In our center, we perform a hysteroembryoscopic evaluation before D&C in most miscarriages, as described elsewhere (30). This approach is useful to achieve a direct visualization of the embryo and adnexal structures, such as yolk sac, amnion, or chorion, to detect minor abnormalities not easily seen by ultrasound, which can help us to determine the etiology of miscarriage (27, 30). On the other hand, hysteroscopy permits performance of a direct and selective biopsy of the embryo and/or chorion to obtain reliable specimens for cytogenetic analysis (30). This is especially important in women with advanced age, clinical history of recurrent miscarriage, multiple pregnancies, or pregnancies achieved by assisted conception (27, 30, 31). Hysteroembryoscopic biopsies can be taken in 97% of gestational sacs. Eighty percent of samples are successfully karyotyped, and maternal contamination is minimized or avoided (30). The direct in situ visual examination of early gestational structures and the detection of true placental mosaicisms (27, 30) are the main reasons that we prefer this technique of chromosomal analysis to other suggested options such as chorion villus sampling by ultrasound before D&C (32) or DNA-based molecular techniques (29).

The present study suggests that the frequency of embryo chromosomal abnormalities in first trimester miscarriages is not related to BMI in the range studied, yielding similar results when evaluated in the normoweight and overweight women categories. Obviously, the influence of BMI on miscarriage risk may be different at different cutoffs of weight excess and considering other anthropometric parameters (such as central distribution of fat) and associated pathologies (such as diabetes, dyslipidemia, or accompanying male obesity). In the present study and the two previously published ones (25, 26), the BMI cutoff value considered was that of overweight but not of obesity, and patients were mainly healthy except for the sometimes associated PCOS. No data about anthropometric measures were recorded. To determine the real risk of chromosomally abnormal miscarriages in women with high BMI, further studies should be performed using wider ranges of body weight, such as obesity class I (≥30 kg/m^2), II (≥35 kg/m^2), or III (≥40 kg/m^2), and controlling for all possible confounding factors.

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SUPPLEMENTAL TABLE 1

Description of study groups.

	BMI <25 kg/m^2		BMI ≥ 25 kg/m^2	
	Age <35	Age ≥ 35	Age <35	Age ≥ 35
Gestational week of miscarriage	8.0 (7.7–8.3)	8.2 (8.0–8.5)	8.0 (7.5–8.5)	8.8 (7.5–10.2)
Maternal age	31.3 (30.2–32.3)[a,b]	38.7 (38.2–39.1)[a,c]	30.2 (28.1–31.3)[c,d]	38.9 (38.2–39.6)[b,d]
Presence of PCOS, %	12.1 (6.4–17.8)	6.5 (2.2–10.8)	13.3 (3.4–23.2)	5.1 (0–11.9)
History of recurrent miscarriage, %	15.7 (9.3–22.1)	13.7 (7.7–19.7)	5.9 (0–12.8)	8.3 (0–16.9)

Note: Means or proportions (95% confidence interval). Equal superscripts denote statistical differences ($P<.05$) within the same row.

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