Journal of Assisted Reproduction and Genetics (2021) 38:343–345
https://doi.org/10.1007/s10815-021-02068-6

COMMENTARY

Obesity and IVF: weighing in on the evidence

Begum Aydogan Mathyk[1] · Alexander M. Quaas[2,3]

Received: 6 January 2021 / Accepted: 7 January 2021 / Published online: 14 January 2021

Abstract

Obesity is associated with serious health risks, and its rising prevalence represents a growing public health emergency. Ongoing research into the association of obesity and assisted reproductive technology (ART) outcomes aims to disentangle selective detrimental effects of obesity on the oocyte and the endometrium. More translational studies involving women with severe obesity and in the third-party reproduction setting will help improve the standard of care in the provision of ART services for obese patients.

Keywords Obesity · In vitro fertilization · Assisted reproductive technology

In this month's issue, Romanski et al. highlight the effects of class III and IV obesity on pregnancy rates and live birth outcomes after fresh embryo transfer cycles [1].

According to the CDC, the age-adjusted prevalence of obesity in US adults in 2017/2018 was a staggering 42.4% [2]. Childhood obesity is increasing at an alarming rate, with 20.6% of 12-19 years old classified as obese (BMI ≥ 30 kg/m^2) [3]. And overweight adolescents are more likely to be obese by the age of 35 than their normal-weight counterparts [4]. Longitudinal studies show that 56% of children with obesity and 80% of children with severe obesity progress to class II (BMI 35-39.9 kg/m^2) and III (BMI 40-49.9 kg/m^2) obesity as adults [5].

The deleterious impact of obesity on reproduction has increasingly been recognized. According to a recent meta-analysis, the live birth rate in obese women undergoing IVF is statistically significantly decreased (RR = 0.85) compared to normal-weight women [6]. In the latest data brief from the National Center for Health Statistics (NCHS), the prevalence of severe obesity (BMI > 40 kg/m^2) was substantially higher in women (11.5%) than men (6.9%) [2].

A large part of the literature on obesity and ART has focused on patients in the overweight (BMI 25.0-29.9 kg/m^2), class I (BMI 30.0-34.9 kg/m^2), and class II (BMI 35-39.9 kg/m^2) categories. The focus of the study by Romanski et al. is on pregnancy outcomes of women with class III (BMI 40-49.9 kg/m^2) and class IV (BMI > 50 kg/m^2) obesity in fresh cycles.

This work did not demonstrate significant differences in pregnancy rates across BMI categories. However, increasing BMI was associated with decreased live birth rate due to an increased rate of miscarriage (12.6% in normal-weight women versus 22.2% in those with a BMI ≥ 40 kg/m^2) in women who conceived by IVF/ICSI. Moreover, women with severe obesity were more likely to experience fresh transfer cancelation, and showed a tendency to give birth via cesarean section in the setting of singleton gestations.

Might the observed increase in the miscarriage rate be due to impaired endometrial receptivity, decreased oocyte quality, or both?

With increasing BMI, the authors noticed a gradual decline in the number of retrieved oocytes, mature oocytes, zygotes, and cryopreserved blastocysts.

Adverse effects of obesity on ovarian hemostasis, function, and oocyte quality have been widely discussed in the literature [7]. In the ovary, cytokines play different roles throughout folliculogenesis, and display an intertwined relationship with obesity and inflammation. At the cellular level, obesity causes lipotoxicity leading to increased levels of proinflammatory cytokines in the systemic circulation. These cytokines and

✉ Alexander M. Quaas
aquaas@health.ucsd.edu

[1] Department of Obstetrics and Gynecology, HCA Healthcare / University of South Florida Morsani College of Medicine GME, Brandon Regional Hospital, Brandon, FL, USA

[2] Division of Reproductive Endocrinology and Infertility, University of California, San Diego, CA, USA

[3] Reproductive Partners San Diego, 9850 Genesee Avenue, Suite # 800, La Jolla, San Diego, CA 92037, USA

adipokines elicit inflammatory responses in target tissues. Ovaries are well-vascularized undergoing dynamic tissue remodeling, with follicular fluid providing an essential milieu microenvironment supporting oocyte development. In obese women, follicular fluid metabolomics are altered in a variety of pathways [8, 9].

Molecular alterations in the oocytes of obese patients have been observed in RNA-seq studies as shown by Ruebel et al. [10]. When analyzing the single-cell transcriptome of germinal vesicle (GV) oocytes in a cohort of obese patients, a correlation was observed between serum C-reactive protein (CRP) concentrations and proinflammatory CXCL2 expression.

There is also emerging evidence for impaired endometrial receptivity in obese patients undergoing IVF. Using techniques of functional genomics analysis to study endometrial gene expression patterns, Comstock et al. demonstrated dysregulation of genes encoding cytokines and immune cells during the window of implantation in obese women [11]. At the organelle level, obesity is associated with endoplasmic reticulum stress and mitochondrial dysfunction [12, 13].

One way to begin to untangle the differential effects of obesity on the egg and the endometrium is research involving third-party reproduction. For example, Fuchs Weizman et al. reported that clinical pregnancy, live birth, and miscarriage rates were not significantly different across BMI categories in gestational carriers [14]. Similar findings regarding pregnancy and live birth rates were described with oocyte donor cycles involving normal weight and obese cohorts [15]. While this approach holds promise, the above findings are preliminary and need to be interpreted with caution, as the studies were limited by the small number of participants with severe obesity.

More research is therefore needed, including on a molecular level, given the often low sample size of published metabolomic and genetic studies in this area. Other pitfalls of research in this realm include inconsistent or heterogenous definitions of obesity (such as using a lower cutoff to define obesity in Asian patients, ≥ 25 kg/m^2), and limitations of using BMI rather than body fat composition as a measure of adiposity.

Perhaps the most important area of ongoing investigation in this context consists of ways to improve live birth outcomes in obese patients. Conflicting data on the effects of bariatric surgery on reproductive outcomes have been published. While Milone et al. reported improved IVF outcomes following bariatric surgery in a pilot study without control group of women with prior failed ART [16], another retrospective European study concluded that bariatric surgery had no significant impact on IVF success [17].

The great fifteenth-century philosopher Erasmus is famously quoted saying “prevention is better than cure”. An increasing spotlight has been put on the dangers and the rising prevalence of obesity. Attempts to effect societal change in this context include lifestyle modification involving dietary changes and increased physical activity, and modifications at the workplace.

When counseling couples in ART, obesity categories and their potential impacts on cycle outcomes need to be considered, and data including those reported by Romanski et al. assist with the counseling process. The effects of obesity beyond the ART process should also be considered, with the goal of optimizing the safety of the pregnancy and the health of the mother after delivery. Future translational studies in this area, including those in the third-party setting, can be expected, and will guide the standards of care in the provision of ART services to obese women.

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