The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study

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Objective: To investigate the independent and combined associations between female and male body mass index (BMI) on the probability of achieving a live birth after treatments with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) under adjustment for relevant covariates.
Design: Population-based cohort study.
Setting: Danish national registers.
Patient(s): Patients with permanent residence in Denmark receiving IVF or ICSI treatment with use of autologous oocytes from January 1, 2006, to September 30, 2010.
Intervention(s): None.
Main Outcome Measure(s): Live birth. Analyses were adjusted for age and smoking at treatment initiation and results stratified by BMI groups and presented by IVF/ICSI treatment.
Result(s): In total, 12,566 women and their partners went through 25,191 IVF/ICSI cycles with 23.7% ending in a live birth. Overweight and obese women with regular ovulation had reduced odds of live birth (adjusted OR 0.88, 95% CI 0.79–0.99 and adjusted OR 0.75, 95% CI 0.63–0.90, respectively) compared with normal-weight women. IVF-treated couples with both partners having BMI ≥ 25 kg/m^2 had the lowest odds of live birth (adjusted OR 0.73, 95% CI 0.48–1.11) compared with couples with BMI <25 kg/m^2. BMI showed no significant effect on chance of live birth after ICSI.
Conclusion(s): Increased female and male BMI, both independently and combined, negatively influenced live birth after IVF treatments. With ICSI, the association with BMI was less clear. (Fertil Steril® 2013;99:1654–62. ©2013 by American Society for Reproductive Medicine.)
Key Words: Body mass index, in vitro fertilization, intracytoplasmic sperm injection, live birth, multilevel analysis

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The prevalence of obesity is increasing and constitutes a major worldwide epidemic affecting more than one billion people worldwide (1, 2). In Denmark, the proportion of overweight and obese individuals constituted 32.5%–39.8% among women and 46.2%–57.6% among men aged 25–44 years in 2010. The prevalence tends to increase during reproductive age in both sexes (3). Overweight and obesity is known to be associated with a number of comorbidities, such as type 2 diabetes, hypertension, certain cancers, and stroke (4). Over the past decades, attention has been directed toward the effect of obesity on fertility.

In women, adipose tissue affects the gonad hormonal balance, leading to increased levels of leptin and decreased levels of adiponectin, which is negatively associated with plasma

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insulin levels. The altered hormone levels may result in hyperandrogenism (1), and in adipose women contribute to anovulation. However, even in ovulating women, increased body mass index (BMI) reduces conception rates. Increased BMI may thus detrimentally affect the oocytes and/or embryo quality (5).

In men, increased scrotal temperatures with increased BMI can adversely influence spermatogenesis (6). Moreover, leptin and E_2 levels correlate with the amount of fat tissue, and higher levels of E_2 may cause shifts in levels of gonadotropins and in the LH/FSH ratio, disturbing the spermatogenesis (7). However, a prospective study of 1,466 men did not find any negative effect of increased BMI on semen quality (8). Nor did a systematic review with meta-analysis find any overall relationship between levels of E_2 and BMI in men (9).

Female obesity has been associated with lower chance of conception, regardless of menstrual cycle pattern (2, 10), and Ramlau-Hansen et al. found a dose-response relationship between increasing female BMI and prolonged time to pregnancy (TTP) in a Danish cohort study (11). Reportedly, TTP increased by 2.84 days per 1 kg increase in body weight, and increased risk of TTP >12 months was observed among couples with both partners being obese (11).

Among men, the odds of taking >12 months to conceive has been detected to increase by 12% with each 3-unit increase in BMI, compared with BMI 20–22 kg/m^2 (6). Another study found 20% and 36% higher risks of TTP ≥12 months among men with BMIs 25.0–29.9 kg/m^2 and 30.0–34.9 kg/m^2, respectively, compared with men with BMI 20.0–22.4 kg/m^2. Contrasts may even be underestimated, because couples without conception were not included (12).

Also, studies of outcome from assisted reproductive technology (ART) treatments have detected negative effects of increased female BMI (13–15). In recent reviews, the probability of live birth after ART was found to be 9%–10% lower among overweight/obese women compared with normal-weight women (16, 17). Obesity affects the outcome even more than overweight (16, 18, 19), with suggestions of a dose-response relationship (16). However, other studies found no effect of increased female BMI on pregnancy rate after IVF (20) or on deliveries after IVF/ICSI (21).

Knowledge about effects of male BMI on ART outcome is scarce, but increased male BMI has been found to reduce the chance of live birth (22). However, the effect may be possible to overcome by the use of ICSI (intracytoplasmic sperm injection) rather than IVF (23).

In Denmark, the cumulative proportion of infertility is 16%–26% in women who tried conceiving for ≥12 months (24, 25). Approximately 10% of all Danish children were born after medically assisted reproduction (MAR) treatment in 2010, and >15,000 ART treatments are initiated each year (26). The Danish health care system offers infertile couples and single women up to three fully reimbursed IVF or ICSI treatment cycles with fresh embryos and an unlimited number of frozen embryo transfer and insemination cycles (in practice, 3–6 cycles) if the woman's age does not exceeds 40 years. According to Danish law, women can be treated in a private setting until their 46th birthday. In Denmark, information on all MAR treatments, including characteristics of both partners, is recorded in publicly administrated registries. The objective of the present study was to investigate the independent and combined associations between female and male BMI and the probability of achieving a live birth following treatment with IVF or ICSI.

MATERIALS AND METHODS

Study Population

This study was based on nationwide Danish register data. Information on ART treatments was collected from the IVF registry and linked to information on all births and abortions obtained from the Danish Medical Birth Registry (MBR) and the Danish National Patient Registry (NPR). Linkage was done by use of the central personal registry (CPR) number, which is a unique identity allocated to all citizens with permanent residence in Denmark. The CPR number allows linkage of Danish registries with little or no error.

Women with permanent residence in Denmark were eligible for inclusion if they had at least one IVF or ICSI treatment cycle with the use of autologous oocytes from January 1, 2006, to September 30, 2010. Information on treatment-specific conditions was registered at first visit to the fertility clinic. Height and weight information was routinely registered from 2006 for women and from 2009 for men. For women with one or more registered live births from January 1, 2006, to June 30, 2011, we calculated the number of days between treatment cycle and live birth. A live birth was considered to be the result of the particular ART treatment if the difference was 140–308 days (20–44 weeks). The calculated difference was compared with the reported gestational age (in days) from the MBR by subtracting the gestational age from the calculated difference. Births with differences of 0–29 days were included. If the difference was >29 days, the birth was considered to be the outcome of another cycle. Because women and men could have several treatments, the observation unit was treatment cycle.

Figure 1 shows exclusions from the baseline dataset and numbers in the final cohort. The majority of the exclusions were due to missing female BMI information. We excluded couples if their first treatment cycle was a frozen embryo transfer cycle, because this indicates a treatment cycle before the inclusion period, during which information was not available.

This study was approved by the Danish Data Protecting Agency (2011-41-6052). According to Danish law, no approval is required from the National Committee for Health Research Ethics for registry-based research.

Body Mass Index

BMI was calculated as body weight (kg) divided by height squared (m^2) and categorized according to the World Health Organization classifications as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).

Live Births

We obtained information on live births from the MBR, which contains information on all births in Denmark.