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## **64<sup>th</sup> International Days of Clinical Endocrinology - Henri-Pierre Klotz : Hormones & Fertility**

### **Bariatric surgery and human fertility**

#### **Chirurgie bariatrique et fertilité humaine**

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**Key words** : obesity, metabolic syndrome, infertility, bariatric surgery, polycystic ovary syndrome

**Mots-clés**: obésité, syndrome métabolique, infertilité, chirurgie bariatrique, syndrome des ovaires polykystiques

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Worldwide, human fertility is decreasing while obesity is spreading. Several studies tend to confirm that obesity plays a major role in fertility lowering in both men and women. Ramlau-Hansen et al.(1) showed a decrease in fertility when **man's** Body Mass Index (BMI) exceeded 30 kg/m<sup>2</sup> with an odds-ratio (OR) of 1.53 (1.32-1.77) if **the woman partner's** BMI was within the normal range (18.5 to 25 kg/m<sup>2</sup>); OR increased to 2.74 (2.27-3.30) after multiple adjustments, when both man and woman had a BMI > 30 kg/m<sup>2</sup>. Numerous studies tried to identify the mechanisms by which obesity alters fertility in both genders.

### Obesity and male fertility

The impact of paternal obesity on sperm has been explored in the context of assisted reproductive technology (ART). Despite some older studies showing conflicting results (2–4), a recent meta-analysis confirm that elevated BMI could be an important factor influencing the outcome of in vitro fertilization by intracytoplasmic sperm injection (IVF-ICSI) (5). Sermondade et al. published two studies showing a higher risk of oligospermia and azospermia associated with **male** obesity. A meta-analysis of 21 studies looking for association between sperm concentration and BMI included 13 077 men from the general population and fertility clinics and demonstrated that higher BMI **was** associated with lower sperm concentration (OR 1.28 (1.06-1.55) for BMI > 30 kg/m<sup>2</sup> and 2.04 (1.59-2.62) for BMI > 35 kg/m<sup>2</sup>) (6).

The mechanism most often reported is hypogonadotrophic hypogonadism, which is present in men with metabolic syndrome as in those with obesity (7). Knowing that hypotestosteronism leads to weight gain, the issue is a spinning vicious circle (8–10). Obesity is also associated with increased oxidative stress which **has** a deleterious effect on reproductive functions and may be associated to an increase in sperm DNA fragmentation (11,12). Chronic inflammation, epigenetic changes, erectile dysfunction and increased scrotal temperature are other hypotheses that have been suggested before.

### Obesity and female fertility

The negative impact of obesity occurs at several points in a woman's life (13–15). It can be the result of **a** hypogonadotrophic hypogonadism state, as for men, but **most often** is the consequence of a polycystic ovary syndrome (PCOS) that is associated with anovulation and hyperandrogenism. Hyperandrogenism and metabolic abnormalities are more frequent in PCOS women with obesity (16,17).

In the literature, it is also reported that the fertility rate is inversely proportional to the BMI, even for women with normal menstrual cycles (18–20). Moreover, the risk of miscarriage during the first trimester is increased in obese women with a spontaneous pregnancy (21). Finally, female obesity is negatively associated with live birth rate following IVF (22). These elements led to the hypothesis that the uterine environment could also be unfavorable in case of obesity. But, the literature is contradictory regarding the effects of obesity on the implantation rate after egg donation (23,24). Increased oxidative stress, chronic inflammation and epigenetic changes have also been suggested to explain obesity consequences on women reproductive functions.

### Nutritional interventions and fertility

Several mechanisms are discussed in the literature to explain the lower fertility rate associated with obesity in both gender. In mice, an increase in physical activity and food restriction lead to an improved fertility (25). A few studies highlighted improved reproductive functions after weight loss in men with an increase in testosterone and sex hormone binding globulin (SHBG) blood levels, as well as in total sperm count (TSC) (26,27). Several studies demonstrated the efficacy of lifestyle modifications in women with PCOS. A moderate weight loss (5-10%) is sufficient to obtain an improvement in menstrual cycles, a reduction in hyperandrogenism and a better ovulation rate. This phenomenon could be the result of physical activity benefits more than diet (28). Moreover, a meta-analysis of 15 randomized clinical trials showed that a weight intervention for women with BMI  $\geq 25$  kg/m<sup>2</sup> increases the rates of spontaneous or ART pregnancies (RR 1.87 (1.20, 2.93)) and live births (RR 2.20 (1.23, 3.94)), but there was no statistical difference compared to those receiving access to ART without weight intervention (29).

### Bariatric surgery and fertility

Bariatric surgery induces a long term weight reduction with a decrease in mortality and comorbidities (30–32). In France, more than 50 000 procedures are performed each year (33). In 2016, the median age of patients was 41 years and the sex ratio was 1 man to 4 women. Different types of surgery exist: gastric banding, sleeve gastrectomy (SG) and Roux-en-Y gastric by-pass (RYGBP). The latter is known to lead to the most important weight loss, up to 30% over the long term (30), while causing more vitamin and mineral deficiencies than sleeve gastrectomy.

Data are conflicting about the outcome of male fertility after bariatric surgery. Some studies confirmed an increase in testosteroneemia after BS but they did not evaluate sperm count or did not investigate changes in sperm parameters (34,35). Other authors reported an

improvement in both hormonal profile and seminal parameters 12 months after BS (n=15) (36). For men with pre-existing spermatogenic quality defects, like in the specific context of ART, BS seems to improve the sperm parameters (37,38). Indeed, El Bardisi et al. showed a higher testosterone in 46 men one year after sleeve gastrectomy. However, only those with azoospermia or oligospermia before surgery had an improvement in their sperm concentration, whereas mobility and morphology remained stable. Other studies reported an unexpected lower sperm quality. Di Frega et al. described azoospermia for 6 patients at 13 to 20 months after GBP (39). These men had already had children before surgery. Sermondade et al. also reported 3 cases of altered TSC at one year after surgery, however, one patient had a normal TSC two years after surgery (40). It is important to note that these men already presented abnormal semen parameters before surgery. A prospective study from Samavat et al. comparing 23 men with GBP versus 8 controls showed that 6 months after surgery, sperm volume and vitality were improved. However, there was no statistical difference on TSC and sperm concentration, compared to the control group (41). Finally, in France, the national study "Bariasperm" prospectively evaluated TSC one year after SG or GBP in 46 men with obesity. One of the main inclusion criteria was the absence of known sperm defects. The authors reported a decrease in TSC ( $-69.5.10^6$  ( $-42.2.10^6$ ;  $-65.8.10^6$ ),  $p = 0.03$ ) despite a better metabolic profile, a higher testosterone and a lower DNA fragmentation (42). Bariatric surgery can be considered as a solution for hypogonadotropic hypogonadism induced by obesity. But, side effects of this surgery like chronic nutritional deficiencies, oxidative stress, lipophilic endocrine disruptor release or altered gonadotropin-releasing hormone pulsatility can alter the spermatogenesis and raise the question of its indication for young men without fertility disorders (43). More studies with longer follow-up are needed to assess the benefits of bariatric surgery on male fertility.

Regarding female fertility, it has been described that BS improves PCOS with recovery of regular cycles and spontaneous fertility. It is estimated that PCOS incidence can be decreased from 45% to 6.8% after BS (44,45). Mechanisms of this fertility recovery are still unclear. A meta-analysis of 8 studies in 589 infertile women aged 29-44 yrs showed that 58% of these women had a spontaneous pregnancy after surgery. Some information was lacking like the infertility cause and the time to get pregnant. The authors did not evaluate the association with weight loss (46).

A few studies explored the impact of bariatric surgery in the context of ART. One study compared the results of IVF performed in 29 patients who had undergone bariatric surgery, 57 women with obesity without surgery and 94 women with a normal weight but whose partner was infertile. The number of pregnancies was not different between the three groups but the doses of gonadotropins used were not specified as well as the number of punctured and

matured oocytes (47). Another study showed that the doses of gonadotropins used to obtain the same level of estradiol was lower after surgery (n=7) than before surgery, without difference between the number of punctured oocytes and percentage of matured oocytes (48). However, a retrospective cohort study evaluated cumulative live birth rate (CLBR) after IVF in women having had a bariatric surgery. CLBR was higher in operated women compared to non-operated women having a higher BMI, but without reaching statistical significance (22.9% vs 12.0%). Results showed that CLBR in the surgery group was similar to that of non-operated women having the same BMI (22.9% vs 25.9%) (49).

Data about a direct impact of obesity on ovarian follicular reserve are inconsistent. Few studies have evaluated the relationship between a marker of ovarian reserve, anti-Müllerian hormone (AMH) and BMI. Some of these studies reported that the higher the BMI the lower the AMH levels (50,51) whereas this relationship was not confirmed in other works (52–56). Currently, the larger study in this domain analyzed AMH levels from 32 women who had had a SG or GBP, aged 27-33 yrs, with a BMI of  $45 \pm 7$  kg/m<sup>2</sup>. The AMH levels decreased one year after surgery in women with PCOS ( $5.44 \pm 3.74$  ng/ml to  $4.25 \pm 3.65$  ng/ml, p= 0.02) or without PCOS ( $1.83 \pm 1.04$  ng/ml to  $1.36 \pm 1.04$  ng/ml, p= 0.04) (57). If BS would favor the women with PCOS in short-term studies, it could also alter the ovarian reserve of women without this syndrome. Data are lacking about AMH levels more than one year after surgery. It could be a transitory consequence of the important weight loss and/or the possible impact of nutritional deficiencies. This information is crucial since pregnancy is not recommended during the 12 months following BS. In conclusion, the literature is reassuring about female fertility after BS, especially in case of PCOS, but its indication must be challenged according to age and the ovarian reserve of women without fertility disorders.

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