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MINI-REVIEW ***Developments in reproductive biology and medicine***

Exploring the causes of semen quality changes post-bariatric surgery: a focus on endocrine-disrupting chemicals

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ABSTRACT: Rapid weight loss promoted by bariatric surgery (BS) can release accumulated lipophilic endocrine-disrupting chemicals (EDCs), making these chemicals systemically available. Men typically have a higher EDC body burden and lose more weight post-BS than women, which may put male BS patients at high risk for testicular toxicity. In this review, we analyze the impacts of BS on semen parameters with a particular focus on the potential effects of EDCs. After BS, serum EDC concentrations progressively increase; and there is evidence that semen parameters deteriorate after BS. Although elevated serum EDC concentrations are associated with inferior sperm parameters, links between semen parameters and EDCs post-BS have not been studied. Understanding these potential associations requires adequately powered studies, particularly within prospective longitudinal cohorts with long-term follow-up for sperm parameters, nutritional status, sex-hormones levels and serum EDC concentrations. Studying BS patients prospectively provides the important opportunity to evaluate dose–response effects of EDC serum concentrations on sperm quality and function. Research is also needed to identify critical chemical exposure periods post-BS to inform reproductive decisions, including consideration of sperm preservation before surgery.

Key words: organochlorines / persistent organic pollutants / lipophilic compounds / weight-loss surgeries / male fertility / sperm aneuploidy / sex hormones / obesogen / metabolic disease / nutritional deficiencies

Introduction

In 2016, 39% of adults worldwide were overweight and 13% were obese (WHO, 2017). In parallel, bariatric surgery (BS) is increasingly performed to avert the impacts of obesity on health. Clinicians worldwide performed 833 687 BS procedures in 2019, most frequently in the USA (335 124 surgeries) and Italy (88 192 surgeries; Ramos *et al.*, 2019). BS is recommended for BMI $\geq$40 or BMI $\geq$35 kg/m^2 with comorbidities aggravated by obesity (Brolin, 1996). The most common BS procedures are sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). Although the benefits include promoting the remission of type II diabetes and hypertension, whether BS confers benefits for male reproductive health remains unclear. While it is recognized that many factors can affect spermatogenesis post-BS, in this review, we explore the hypothesis that endocrine-disrupting chemicals (EDCs) play a role in affecting semen quality.

Obesity can disrupt metabolic pathways in adipose tissue (AT) that affect spermatogenesis (Fig. 1). Mechanistically, an increase in fat mass is followed by an increase in aromatase production, converting androgens into estrogens (Zumoff *et al.*, 2003; Fui *et al.*, 2014). Additionally, elevated insulin caused by insulin resistance reduces hepatic sex hormone-binding globulin (SHBG) secretion, altering the testosterone/estradiol (T:E_2) ratio. These imbalances disrupt testosterone and estrogen levels, impairing the negative feedback loop of the hypothalamic–pituitary–gonadal (HPG) axis, resulting in reduced Sertoli cell activity and leading to persistent secondary hypogonadism (Kahn and Brannigan, 2017). As a consequence, individuals with obesity class 3 (BMI $\geq$ 40 kg/m^2) are more likely to have a low sperm concentration (Ramaraju *et al.*, 2018).

BS-induced weight loss promotes improvements in insulin resistance and in aromatase, leptin and adiponectin secretion, resulting in the normalization of sex hormone levels. Consequently, obesity-associated

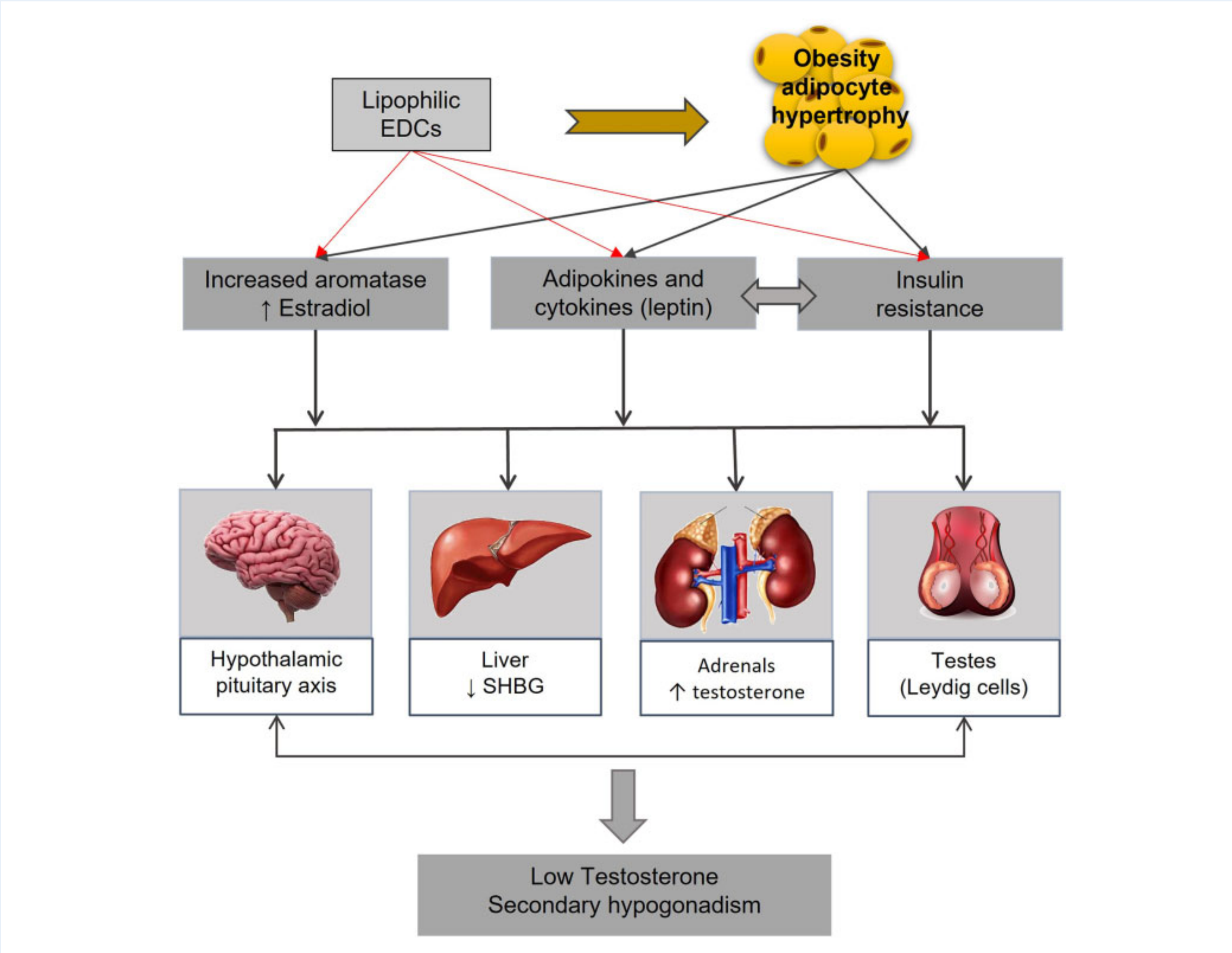

Figure 1. Pathophysiological mechanisms of low testosterone and secondary hypogonadism in obese men caused by fat mass and aggravated by endocrine-disrupting chemicals (EDCs). EDCs aggravate the effect of obesity by promoting insulin resistance and increasing aromatase, adipokines and cytokine production. Endocrine disruption of adipose tissue increases estradiol, leptin and insulin, triggering a cascade reaction that impairs the liver, adrenals and testes, and compromises hypothalamic–pituitary axis feedback regulation, resulting in low testosterone production. SHBG, sex hormone-binding globulin.

secondary hypogonadism may resolve (Lee et al., 2019). However, reported effects on sperm health are contradictory and scarce, with some studies reporting reduced semen quality following BS, even after sex hormone levels have normalized (Lazaros *et al.*, 2012; Calderón *et al.*, 2014; Carette *et al.*, 2019).

Besides hormonal normalization, many factors are postulated to explain the changes in semen parameters post-BS, such as testicular temperature, metabolic changes and nutritional deficiencies. However, the potential links with bioaccumulated EDCs that are released by AT during weight loss have not yet been investigated. EDCs are exogenous chemicals that influence fertility by interfering with normal endocrine function. They can act through many different mechanisms (La Merrill *et al.*, 2020) and exposure occurs primarily through ingestion, particularly intake of fatty foods (La Merrill *et al.*, 2013).

Obese individuals have a higher concentration of lipophilic EDCs in AT per gram of fat than lean individuals, although the concentration in blood is lower (Kim *et al.*, 2011). Inside the AT, they act as obesogens by promoting adipogenesis and lipid accumulation, exacerbating obesity effects on fertility (Fig. 1). Additionally, EDCs act directly or indirectly on multiple AT metabolic signaling pathways related to male reproductive system functionality (Fig. 1). Epidemiological and animals studies have shown that EDCs (e.g. polychlorinated biphenyl, PCB; β-hexachlorocyclohexane, β-HCH; trans-chlordane; trans-nonachlor; dichlorodiphenyldichloroethylene, p,p′-DDE; dichlorodiphenyltrichloroethane, p,p′-DDT; hexachlorocyclohexane, HCB, 2,3,7,8; and tetrachloro-dibenzodioxin, TCDD) cause oxidative stress and activate the synthesis of proinflammatory cytokines, chemokines and other molecules associated with an increased risk of chronic diseases among obese individuals (Arsenescu *et al.*, 2008; Ruzzin *et al.*, 2010; Lee *et al.*, 2014; Evangelou *et al.*, 2016; Mustieles *et al.*, 2017; Gül, 2018; Han *et al.*, 2020). Proinflammatory compounds and metabolic diseases are linked to impaired sex hormone levels and disrupted spermatogenesis (Williams, 2012). EDCs also increase estradiol, leptin and insulin secretion, triggering a cascade reaction that impacts the liver, adrenals and testes, as illustrated in Fig. 1 (Gore et al., 2015; Heindel et al., 2017; Heindel and Blumberg, 2019; Sharma et al., 2020). In summary, general EDC exposures contribute to abnormal sex hormone levels, erectile dysfunction and spermatogenesis disorders, leading to poor semen quality, function and sperm genetic aberrations, and all of which can culminate in subfertility and infertility (Reis and Dias, 2012; Oliveira et al., 2017; Slopien et al., 2019).

Although the storage of EDCs in AT confers some protection against their toxic effects to testis and spermatozoa, for patients undergoing BS, the EDC release is rapid, with sudden onset, resulting in a progressive increase in serum levels. Serum organochlorine concentration rose 388.2% in 1-year post-BS (Hue et al., 2006). Such dramatic and rapid weight loss makes EDCs available to most organs. During weight loss, rodents pretreated with EDCs, such as DDT (Ohmiya and Nakai, 1977), HCB (Jandacek et al., 2005) and TCDD (Joffin et al., 2018), showed a time-dependent increased distribution from AT to several lean organs, including gonads. Few studies have evaluated circulating EDC levels up to 1 year after BS and very few cohort studies have evaluated semen parameters post-surgery. No study has correlated circulating EDCs with semen parameters after BS. Given the increasing use of BS to promote weight loss, there is a crucial need to understand how EDCs released post-BS affect male reproductive functioning.

In this conceptual review, we consider what is known about male reproductive health post-BS, the metabolic changes post-BS that are related to spermatogenesis, the progressive increase of EDCs caused by BS-induced weight loss and EDCs' reproductive effects on animals and humans. This evidence is used to theorize about the effect of BS on male reproductive health and the potential impact of EDCs, among other factors, on male fertility post-surgery and the potential to manage adverse effects. In the section below, we discuss: studies investigating semen parameters post-BS; the possible causes of sperm deterioration or improvement; the chemical mobilization of EDCs from fat during weight loss and risks to male fertility post-surgery (Fig. 2); and current knowledge gaps. We then provide recommendations for future research. This review included case reports and longitudinal cohort studies identified through PubMed, Scopus and Web of Science databases published through 16 September 2021 (Fig. 3). Included studies followed previous World Health Organization (WHO) guidelines (WHO, 1999, 2010) for semen examination and previous WHO lower reference limits (WHO, 2010) were used to define oligozoospermia as a sperm concentration below 15 million/ml and asthenozoospermia as a percentage of progressively motile spermatozoa below 32%.

Semen parameters post-BS

Although BS could present one way to manage obesity-linked male infertility, the effects of BS on semen parameters remain unclear. We identified nine prospective cohort studies and three case reports describing the impact of BS on semen parameters (Table I). From these, two cohort studies reported no differences (n = 14), three reported improvements among men with abnormal sperm parameters (n = 104), one reported improvement among men with normal semen parameters (n = 15) and three cohort studies (n = 84) and all three case reports (n = 11) observed semen quality deterioration. Existing cohort studies are limited by small sample size and vary by postoperative follow-up time and study design. We performed a power calculation for the largest existing cohort, with alpha at 0.05; we found that 25 participants are the minimum needed to achieve 80% power to detect a 1.69-fold difference in sperm concentration and a 1.24-fold difference in sperm motility between pre- and post-BS semen analyses. Only three studies had a sample size higher than 25 participants (El Bardisi et al., 2016; Carette et al., 2019; Velotti et al., 2021). Thus, results must be interpreted with caution.

Of the three largest studies, two cohort studies reported an improvement in sperm parameters post-BS, but only among patients presenting abnormal sperm parameters at baseline (El Bardisi et al., 2016). One study evaluating 46 men (28.9% azoospermic, 41.3% oligozoospermic and 30.4% normal at baseline) observed that at 1-year post-BS, the sperm parameters did not differ from baseline for the whole cohort (El Bardisi et al., 2016). However, stratification by sperm concentration revealed a significant increase in sperm concentration among men classified at baseline as azoospermic (although this difference was extremely small, range: 0–0.3 million/ml, and in 6 of 13 men) and oligozoospermic (sperm concentration increased but remained <15 million/ml in 11 of 19 men, and were ≥15 million/ml in 6 of 19 men) and no changes in men with normal semen parameters at baseline. Velotti et al. (2021) only recruited men with idiopathic infertility (n = 35) attending infertility clinics and observed significant improvements in semen volume, sperm concentration, motility and morphology at 6 months post-surgery. These findings corroborate those of a smaller study (n = 23) in which 73.9% (n = 17) of participants had abnormal semen parameters before RYGB, with an increase in semen volume and viability noted at 6 months post-BS (Samavat et al., 2018). Indeed, three patients had completely normalized sperm parameters (Samavat et al., 2018). In contrast, one small study (n = 15) observed a significant improvement in the percentage of normal sperm morphology at 6 months post-BS, and on semen volume and sperm motility at 12 months post-surgery among men with normal semen parameters (Fariello et al., 2021).

The other largest study (n = 46, 20 undergoing RYGB and 26 undergoing SG) reported a general deterioration in sperm count 1-year post-surgery, despite improvements in total testosterone and SHBG levels (Carette et al., 2019). Most patients had normal sperm parameters at baseline but eight patients (17.4%) were oligozoospermic. Total sperm count (TSC) decreased by 6 months and was significantly lower (>35%) at 12 months for both the RYGB (35%) and SG (40%) groups. Six men with normal baseline TSC became oligozoospermic by the first 12 months post-BS, while five of eight men with oligozoospermia had normalized sperm concentration post-BS, with no significant changes in semen volume, motility or vitality. These findings corroborate the study of Wood et al. (2020; n = 18), which observed a worsening of sperm concentration and total ejaculated sperm count after BS. Two patients became azoospermic at 6 months post-BS. Another smaller (n = 20) but longer study (24-month post-BS) including men with at least one abnormal sperm parameter (Calderón et al., 2019) observed a significant decrease in semen volume and 60% of patients presented low sperm concentration (<15 million/ml) post-BS, compared to 36% at baseline. One patient conceived a child after surgery,

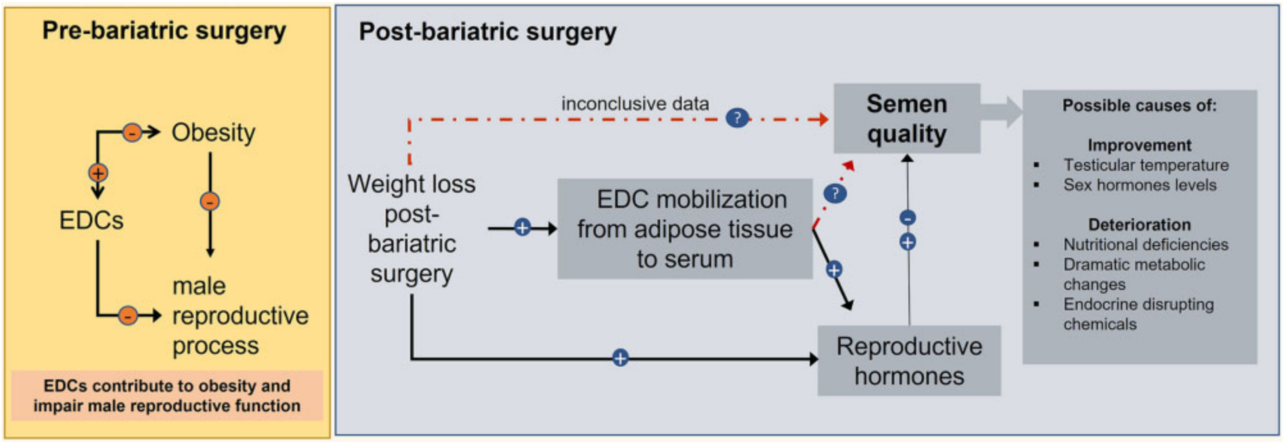

Figure 2. Causal flow diagram showing pre- and post-bariatric surgery (BS) processes involved in male reproductive functioning. Pre-BS, endocrine-disrupting chemicals (EDCs) promote obesity and aggravate male reproductive health outcomes. Post-BS, owing to precipitous weight loss, EDCs are mobilized from adipose tissue into serum. Evidence (25 studies) demonstrates that weight loss post-BS improves reproductive hormone levels despite the large amount of EDCs released; however, the combined effect of weight loss and EDC mobilization on semen quality remains to be determined.

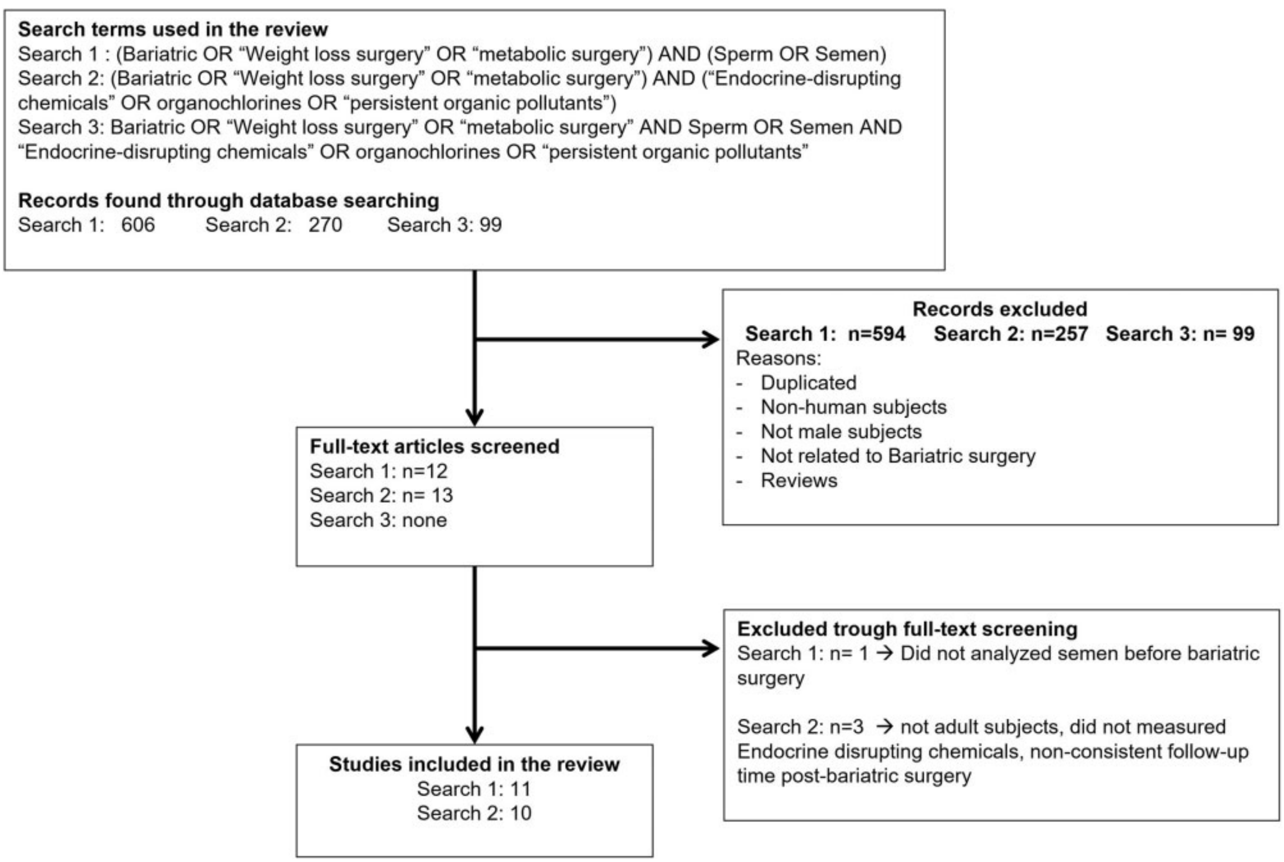

Figure 3. Flowchart showing the literature searches and screening processes. Results included publications until 16 September 2021 on PubMed, Web of Science or Scopus databases.

Table I Cohort studies and case reports analyzing human semen pre- and post-bariatric surgery, sorted in descending order according to sample size.

Study (author, year)	Country	Population	Type of surgery	Time of semen analysis after surgery and method used	Outcomes	Mean of fat mass lost
Prospective cohort and case-control studies						
Carette *et al.* (2019)	France	46 males with no infertility history, but 8 presented oligozoospermia at baseline, 38.9 ± 7.9 years old	RYGB and SG	6 months and 12 months Semen analysis was performed according to WHO guideline (2010). Morphology was assessed according to Auger *et al.* (2000)	6 months of post-surgery: • No significant changes were observed • Six patients with normal baseline sperm count became oligospermic • Normalization of sperm count in four of eight oligozoospermic men 12 months of post-surgery: • ~40% significant decrease in total sperm count • Seven patients with normal baseline sperm count became oligozoospermic • A decrease in partial and total DNA fragmentation • Improvement of sperm count in five of eight oligozoospermic men • Percentage of normal spermatozoa decreased from 15.4% (68.7) at baseline to 12.4% (66.4%) ($P = 0.04$)	6th month—10.9 kg/m^2 or 34.7 kg 12th month—12.7 kg/m^2 or 40.3 kg
El Bardisi *et al.* (2016)	Qatar	46 males: 13 azoospermic, 19 oligozoospermic and 14 with normal sperm concentration; 37 (29–44) years old	SG	12 months Semen analysis was performed according to WHO guideline (2010).	• No significant changes were observed in men with normal sperm analysis • Significant increase in sperm concentration among men with azoospermia and oligozoospermia, but only 6 of 19 oligozoospermic had sperm concentration increased > or = 15 million/ml, and 6 of 13 azoospermic men improved sperm concentration	28.6 kg/m^2
Velotti *et al.* (2021)	Italy	35 males with idiopathic infertility, 36.4 ± 5.17 years old	SG	6 months Semen analysis was performed according to WHO guideline (2010).	• Significant increase in semen volume (from 2.25 to 2.8 ml), sperm concentration (from 6.47 to 10.85 M/ml), total	7.56 kg/m^2

(continued)

Table I Continued

Study (author, year)	Country	Population	Type of surgery	Time of semen analysis after surgery and method used	Outcomes	Mean of fat mass lost
Prospective cohort and case-control studies						
					sperm concentration (from 15.33 to 31.71 million/ml), progressively motile sperm count from 13.84 to 23.29% and normal sperm morphology (from 2.34% to 3.0%)	
Samavat *et al.* (2018)	Italy	31 males: 23 underwent surgery and 8 non-operated men Only six patients had a normal seminal analysis at baseline	RYGB	6 months Semen analysis was performed according to WHO guideline (2010).	• Increase in semen volume of 0.6 ml, and 10% viability • A decrease in Sil-8 levels and sperm DNA fragmentation after bariatric surgery • Three patients had normalized sperm parameters post-surgery • A non-significant increased trend in motility and sperm concentration	11.1 kg/m^2
Calderón *et al.* (2019)	Spain	20 males: 8 presented abnormal morphology, 5 had abnormal sperm motility and 4 low sperm concentration. From these, only 15 patients had seminal analyses repeated at 24 months after surgery, 40 ± 8 years old	RYGB and SG	24 months Semen analysis was performed according to World Health Organization guidelines (2010).	• Significant decrease of 0.2 ml in sperm volume ($P = 0.04$) • 60% of patients presented low sperm concentration (<15 million/ml) post-bariatric surgery, compared to 36% at baseline	18 kg/m^2
Wood *et al.* (2020)	Brazil	18 males, one was impossibility to provide a semen sample post-surgery; 39.0 (IQR: 16.0) years old	RYGB and SG	6 months Semen analysis was performed according to WHO guideline (2010). Morphology was assessed by the Kruger criteria (Kruger *et al.*, 1988)	• Significant reduction in sperm concentration and on total ejaculated sperm count • 2 patients developed azoospermia at the end of the follow-up period. These patients had initial semen concentrations of 0.1 and 82 million/ml. • Higher prevalence of oligozoospermic patients (concentration lower than 15 million/ml) and of severe oligozoospermic patients (concentration lower than 5 million/ml) after surgery.	11.6 kg/m^2

(continued)

Table I Continued

Prospective cohort and case-control studies						
Study (author, year)	**Country**	**Population**	**Type of surgery**	**Time of semen analysis after surgery and method used**	**Outcomes**	**Mean of fat mass lost**
					• Patients experience an increase in TT, FT, FSH and SHBG and reduction in prolactin levels.	
Fariello *et al.* (2021)	Brazil	From 24 men, 15 male participated (3 excluded as azoospermic, 4 changed address, 2 had vasectomy)	RYGB	3, 6, 9 and 12 months Semen analysis was performed according to WHO guideline (2010). Morphology was assessed by the Kruger criteria (Kruger *et al.* 1988)	• Progressive increase in semen volume, sperm concentration, motility and morphology. • Significant increase in semen volume and motility at 12 months post-BS • Significant increase in %normal sperm morphology, and DNA integrity from 6 months post-surgery.	3th month—4.7 kg/m^2 6th month –9.6 kg/m^2 9th month—14.5 kg/m^2 12th month—17.7 kg/m^2
(Reis and Dias, 2012)	Brazil	10 males who underwent surgery compared to 10 control under a weight loss plan; 42.2 ± 11 years old	RYGB	24 months Semen analysis was performed according to WHO guideline (2010).	• No significant improvement or deterioration in sperm parameters, although hormonal and sexual functions significantly improved	24.7 kg/m^2 or 74.1 kg
(Legro et al., 2015)	USA	4 males, 37.5 (30–40) years old	RYGB	1, 3, 6 and 12 months Semen analysis was performed according to WHO guideline (2010). Morphology was assessed by the Kruger criteria (Kruger *et al.*, 1988)	• No significant changes observed, serial semen analysis showed normal ranges for most parameters despite massive weight loss • Sperm concentrations tended to decrease 1 month after surgery ($P = 0.11$), but then returned to preoperative levels by 12 months	1st month—6 kg/m^2 or 19 kg 3rd month—9 kg/m^2 or 32 kg 6th month—12 kg/m^2 or 46 kg 12th month—14 kg/m^2 or 55 kg

(continued)

Table I Continued

Case reports						
Study (author, year)	**Country**	**Population**	**Type of surgery**	**Time of semen analysis after surgery and method used**	**Outcomes**	**Mean of fat mass lost**
Lazaros *et al.* (2012)	Greece	Two patients with low sperm quality from a fertility clinic Patient 1: 41.5 years old Patient 2: 46 years old	RYGB	Patient 1 8 months Patient 2 12 months Semen analysis was performed according to WHO guideline (2010).	Patient 1 • Decrease of 50% in sperm concentration, motility and morphology after surgery • Total sperm aneuploidy rate increased from 25.9% before surgery to 53.3% after surgery • Percentage of mature spermatozoa was reduced from 72% before surgery to 34.6% after surgery Patient 2 • Had 32×10^6 spermatozoa ml^{-1} before surgery and presented with no spermatozoa either in his semen samples or in his testicular biopsy samples after surgery	Patient 1 13.4 kg/m^2 Patient 2 8.8 kg/m^2
Di Frega *et al.* (2005)	Italy	Six patients previously fathered children with normal sex hormones; 38.3 ± 2.4 years old	RYGB	16.8 ± 3.6 months Semen analysis was performed according to WHO guideline (1999)	• 3–4 sperm analyses during 12–15 months • All men became azoospermic, and testis biopsy revealed non-obstructive azoospermia with complete spermatogenic arrest	76.8 ± 12.3 kg
Sermondade *et al.* (2012)	France	Three males from a fertility clinic Patient 1: teratozoospermic with a 4-year history of primary idiopathic infertility, normal sex-hormones levels, 30 years old Patient 2: extreme oligoastheno-teratozoospermic with a 6-year history of primary infertility, 41 years old Patient 3: oligoasthenoterato-zoospermic, 18-month history	Patient 1: SG Patient 2: RYGB Patient 3: RYGB	Patient 1 10 and 13 months Patient 2 6, 15 and 24 months Patient 3 3 and 6 months Semen analysis was performed according to WHO guideline (2010). Morphology was assessed according to Auger *et al.* (2000)	All patients received mineral and vitamin supplementation post-surgery Patient 1 • Drastic worsening, resulting in severe oligoasthenoteratozoospermia, decrease of 80–90% in sperm concentration, and 20–25% in motility • 2 years after surgery showed semen improvement with normalization of both concentration and motility	Patient 1 108 kg in 9 months Patient 2 79 kg in 5 months Patient 3 36 kg in 6 months

(continued)

Table I Continued

Study (author, year)	Country	Population	Type of surgery	Time of semen analysis after surgery and method used	Outcomes	Mean of fat mass lost
				Case reports		
		of primary infertility, 30 years old			Patient 2 • Severe worsening with cryptozoospermia; a presence of 25 non-motile spermatozoa in the centrifugation pellet of the whole ejaculate Patient 3 • Worsening of oligozoospermia	

FT, free testosterone; IQR, interquartile range, RYGB, Roux-en-Y gastric bypass; SHBG, sex hormone-binding globulin; SG, sleeve gastrectomy; TT, total testosterone; BS, bariatric surgery.

but another patient failed to conceive even after ART (Calderón et al., 2019).

Three case reports identified severe effects post-BS, such as increases in sperm aneuploidy, azoospermia and infertility in men seeking ART post-BS (di Frega et al., 2005; Lazaros et al., 2012; Sermondade et al., 2012). Lazaros et al. (2012) described two cases of men who underwent fertility treatment and succeeded in conceiving a child before BS. At 8-month post-BS, one man had a 50% decrease in sperm concentration, motility and morphology; the aneuploidy rate increased from 25.9% before to 53.3% after surgery, and the percentage of mature spermatozoa declined from 72% before to 34.6% after surgery. The second man had no detectable spermatozoa in semen or in testicular biopsy samples at 12 months after surgery. Di Frega et al. (2005) reported a series of six males (all of whom fathered a child before surgery) who developed secondary infertility, identified as non-obstructive azoospermia with complete spermatogenic arrest post-BS. Results were confirmed in semen analyses 12–20 months after RYGB. Sermondade et al. (2012) also performed a repeated measure of semen parameters in three patients who underwent BS, reporting a dramatic worsening of sperm concentration, motility and morphology, as well as cryptozoospermia. In only one patient did the sperm concentration recover to baseline levels 24 months after surgery.

The published studies suffer from a key limitation concerning the number of participants and different study designs. Thus, the long-term effects of BS on semen parameters remain unclear and require further investigation, particularly with respect to causal mediation. We hypothesize that these worsened outcomes may reflect a short follow-up period for spermatogenesis recovery, dramatic metabolic changes, nutritional deficiencies and the release of EDCs or other toxic compounds from AT.

Potential mechanisms underlying BS impact on semen quality

Change in testicular temperature

A decrease in testicular temperature may result from fat mass loss. Spermatogenesis is a temperature-dependent process, and an increase in scrotal temperature can disrupt its progression. The increased scrotal temperature that accompanies obesity is associated with alteration of semen parameters, higher FSH plasma levels and, in some cases, even increased sperm aneuploidies and reduced testicular volume (Garolla et al., 2015). However, no study has investigated testicular temperature changes before and after BS and its effects on sperm parameters.

Recovery of spermatogenesis after hormonal regulation

Normalized semen parameters may reflect the normalization of reproductive hormone levels (a decrease in estradiol and an increase in gonadotrophins, total testosterone, SHBG and T:E_2). Seminal vesicle and prostate secretions are both controlled by androgens, and in the presence of low circulating testosterone ($<$264 ng/dl), ejaculate volume is reduced (Hopps et al., 2004; Di Guardo et al., 2020).

An improvement in sex hormones can occur in the first-month post-surgery (Legro *et al.*, 2012). BS-induced weight loss promotes sex hormone level normalization by decreasing aromatase, proinflammatory cytokines and leptin levels that will re-establish HPG axis function and hypothalamic GnRH and LH secretion (Kim *et al.*, 2011; Terra *et al.*, 2013). Additionally, increasing adiponectin will regulate insulin sensitivity and, consequently, restore circulating hepatic SHBG levels, thereby regulating the balance of testosterone and estradiol levels (Luconi *et al.*, 2013; Samavat *et al.*, 2018). The recovery of testosterone levels post-BS re-establishes LH and FSH feedback on the pituitary as well as LH stimulation of testosterone secretion by Leydig cells in the testis (Palmer *et al.*, 2012). Obesity-associated secondary hypogonadism may resolve (Lee *et al.*, 2019). However, four studies demonstrated a deterioration in semen parameters even after reproductive hormones normalized and the T:E_2 ratio increased, suggesting a perturbation of testis function that is unrelated to the action of sex hormones (di Frega *et al.*, 2005).

Another hypothesis stated by Calderón *et al.* (2019) is that a follow-up period of <2 years may be insufficient to adequately assess the recovery of sperm after BS as a consequence of sex hormone normalization post-surgery. Protocols for the treatment of hypogonadism with GnRH or HCG require an average duration of therapy of 4–5 months before the first sperm appears in the ejaculate, but may require up to 2 years of therapy (Stahl, 2017). Although 2 years post-BS may be sufficient time for patients with previous secondary infertility to improve, this does not explain the worsening sperm concentration and volume. Further, Calderón *et al.* (2019) observed sperm deterioration in patients re-evaluated at 4 years of post-surgery. In contrast, Sermondade *et al.* (2012) described one patient with normalization of both concentration and motility 24 months after surgery. Considering these conflicts, it is uncertain whether the negative effects of BS on semen quality are transitory and, if so, how long the recovery period may be. Longitudinal studies that follow-up sperm parameters for more than 24 months of post-surgery will provide a better understanding of BS impacts.

Dramatic metabolic change

The dramatic metabolic change caused by rapid weight loss is purported to reduce semen quality but should be reversible after weight stabilizes (Carette *et al.*, 2019). Under dietary restriction or starvation, energy for reproduction is allocated toward somatic maintenance (Nalam *et al.*, 2008). One study investigated changes in total daily energy expenditure and resting metabolic rate (RMR) under basal conditions in post-BS patients compared to preoperative baseline (Wolfe *et al.*, 2018). Results indicated that RMR and total daily energy expenditure fall precipitously in the first 6 months, reflecting a metabolic adaptation. However, the metabolic adaptation progressively diminishes between 6 and 24 months, resulting in a rise in energy expenditure after surgery. Thus, metabolism is stabilized around 24 months of post-surgery, when a decrease in sperm volume may still be observed.

Nutritional deficiencies

Mineral and vitamin deficiencies after BS may contribute to sperm deterioration. All studies addressed the type of surgical procedures in patients. While both are restrictive procedures, in SG, the stomach volume is reduced such that food storage capacity is diminished, while RYGB shortens the functional length of the small intestine, which impedes nutrient absorption and can cause undernutrition without adequate supplementation.

Both procedures promote similar weight reduction, but RYGB procedures are associated with more protein–energy malnutrition and deficiencies in micronutrients such as iron, folate, vitamin A, vitamin D, vitamin B1 and vitamin B_{12} (Mechanick *et al.*, 2020). Essential minerals act as enzyme cofactors in biochemical pathways; therefore, their deficiency could harm sperm production and increase sperm aneuploidy frequency (Young *et al.*, 2008). Nutritional deficiencies can affect spermatogenesis and contribute to the sperm deterioration that was observed in some studies post-BS. Nutritional deficiencies are more likely during the initial weight loss phase (up to 12–18 months of post-BS), which may affect spermatogenesis (Calderón *et al.*, 2018; Mechanick *et al.*, 2020). However, deteriorating semen quality is observed after both SG and RYGB at 3, 6 and 24 months of post-surgery (Sermondade *et al.*, 2012; Calderón *et al.*, 2019; Carette *et al.*, 2019). In fact, the lowest sperm counts were in men who underwent SG. To avoid nutritional deficiencies, BS patients must undergo intense nutritional supplementation and monitoring in the first 2 years after surgery (Ziegler *et al.*, 2009). Sermondade *et al.* (2012), however, described three patients who received mineral and vitamin supplementation and still presented worsening sperm parameters from 3 to 24 months after either type of surgery.

Mobilization of lipophilic toxic compounds from adipose tissue

The highest total weight loss occurs in the first year post-BS, when a progressive increase in serum EDC levels is observed (Dirtu *et al.*, 2013; Jansen *et al.*, 2018). From the 10 studies that measured EDC levels post-BS (Table II), six of them followed up for a maximum of 1 year. Minor weight loss still occurs in the second year (van de Laar *et al.*, 2019), likely continuing to increase blood EDC levels. Figure 4 shows the percentage increase in the most studied EDCs for each kg lost after BS, as found in published reports.

Although serum EDC concentrations are significantly higher post-BS, no study has defined the relations between post-BS serum EDCs and semen parameters. The only study available, specifically in French women, reported serum increases of PCB153 by 130%, p,p′-DDE by 120% to and HCB by 120% at 12 months of post-BS compared to baseline (Fénichel *et al.*, 2021). Men have higher levels of EDCs circulating in their blood and greater weight loss after surgery. Thus, men can have a higher concentration of EDCs mobilized to the circulation. Considering that EDCs have a wide range of endocrine actions and are associated with abnormal sperm quality and function, their potential effect on spermatogenesis after BS should not be overlooked.

Potential impact of EDCs on semen parameters

EDCs are disruptive at low doses in animals and humans (La Merrill *et al.*, 2020), and significant dose-dependent responses are observed in semen parameters in men who have not undergone BS but have serum concentrations of EDCs similar to, or lower than, those detected post-BS. Indeed, EDCs have established associations (generally negative and dose-dependent) with sperm parameters in cohort studies of

Table II Cohort studies that monitored endocrine-disrupting chemicals before and after bariatric surgery.

Study	Sample size	Country	Type of surgery	Follow-up time	EDCs measured
Brown et al. (2019)	27 participants, 28–50 years, BMI 39.3–47.8 kg/m^2	USA	N/A	6 months	24 PCBs, 9 OCPs, 11 PBDEs, 2,2′,4,4′,5,5′-hexabromobiphenyl, and 4 PFCs
Jansen et al. (2018)	63 participants (50 females and 13 males), 45 (27–59) years, BMI 38.9 kg/m^2 (SD ± 3.2) and 39.9 kg/m^2 (SD ± 3.9) for females and males, respectively	Norway	N/A	12 months	HCB, β-HCH, p, p′-DDE; 7 PCBs and ΣPCB, 7,5 BDEs and ΣBDE5; and HBCD
Rantakokko et al. (2015)	161 participants, 47.6 ± 8.4 years, BMI 44.6 ± 5.7 kg/m^2	Finland	N/A	12 months	6 PCBs, HCB, β-HCH, trans-non-achlor, *p, p*′-DDE, 4 BDE, 7 PFAAs (PFHxS, PFOS, PFHxA, PFOA, PFNA, PFDA and PFUnA)
Pestana et al. (2014)	189 patients, 42.5 ± 10.9 years (19–65) included 166 females (88.7%)	Portugal	N/A	12 months	aldrin, dieldrin, endrin, HCB, HCH Lindane, ∑HCB (sum of α-HCH, β-HCH and δ-HCH). Endosulfan, methoxychlor, TCDD, *p,p*′-DDD, *o, p*′-DDT and *p,p*′-DDE
Dirinck et al. (2016)	184 (53 male and 131 female) at baseline, 71 (24 male and 47 female) at 6 months, 50 (17 male and 33 female) at 12 months; 40 ± 12 years old, BMI 42.1 ± 3.8 kg/m^2	Belgium	N/A	AT baseline and serum at 6 and 12 months	27 PCBs (IUPAC nos. 28, 74, 95, 99, 101, 105, 118, 149, 146, 153, 138, 187, 183, 128, 167, 174, 177, 171, 172, 156, 180, 170, 199, 196/203, 194, 206, and 209)
Dirtu et al. (2013)	151 participants (46 male and 105 female) and 44 lean controls, 41 (18–84) years old, BMI 38.5 kg/m^2 (26.2–62.3)	Belgium	N/A	3, 6, 12 months	64 OHCs: α-, β- and γ-HCH, DDT and its metabolites, HCB, chlordane metabolites, such as oxychlordane and trans-nonachlor, 22 PCBs and their hydroxylated metabolites (HO-PCBs)—18 compounds, pentachlorophenol (PCP), tribromoanisole and PBDEs—7 trito hepta-BDE congeners
Kim et al. (2011)	18 lean control and 71 obese participants, 44 ± 1.6 years old, BMI 48 ± 0.79 kg/m^2	France	Roux-en-Y gastric bypass (RYGB)	3, 6 and 12 months blood and subcutaneous adipose tissue, at baseline and during follow-up	17 dioxins/furans and 18 PCBs
Hue et al. (2006)	Caucasian male adults: control (n = 15; BMI <25 kg/m^2), obese (n = 14; BMI 30–39.9 kg/m^2) and morbidly obese (n = 13; BMI ≥40 kg/m^2), 45.5 ± 8.1 years old	Canada	Duodenal switch (BPD-DS) procedure	3 and 12 months	14 PCBs and 11 chlorinated pesticides: β-HCH, *p,p*′-DDT, *p,p*′-DDE, HCB, mirex, aldrin, γ-chlordane, α-chlordane, oxychlordane, *cis*-nonachlor and *trans*-nonachlor
Charlier et al. (2002)	30 participants (eight men, 22 women), BMI 37.2 ± 3.5 kg/m^2	Belgium	Gastric by-pass and laparoscopic adjustable gastric banding	6 months	DDT, DDE, HCB and 7 PCBs (no. 28, 52, 101, 118, 138, 153 and 180)
Backman and Kolmodin-Hedman, (1978)	8 participants, 38.5 ± 3.4 years old, bodyweight 137.2 ± 7.7 kg	Sweden	Jejuno-ileostomy	12 months	*p,p*′—DDT and *p,p*′—DDE

BDE, brominated diphenyl ether; DDD, dichloro-diphenyl-dichloroethane; DDE, dichloro-diphenyl-dichloroethylene; DDT, dichloro-diphenyl-trichloroethane; EDCs, endocrine-disrupting chemicals; HBCD, hexabromocyclododecane; HCB, hexachlorocyclohexane; HCH, hexachlorocyclohexane; OCPs, organochlorine pesticides; OHCs, organohalogen contaminants; PBDEs, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; PFAAs, perfluoroalkyl acids; PFCs, perfluorochemicals; PFDA, perfluorodecanoic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFUnA, perfluoroundecanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFUnA, perfluoroundecanoic acid; TCDD, 2,3,7,8-tetrachloro-dibenzodioxin; α-HCH, α-hexachlorocyclohexane; β-HCH, β-hexachlorocyclohexane, δ-HCH, δ – Hexachlorocyclohexane; AT, adipose tissue.

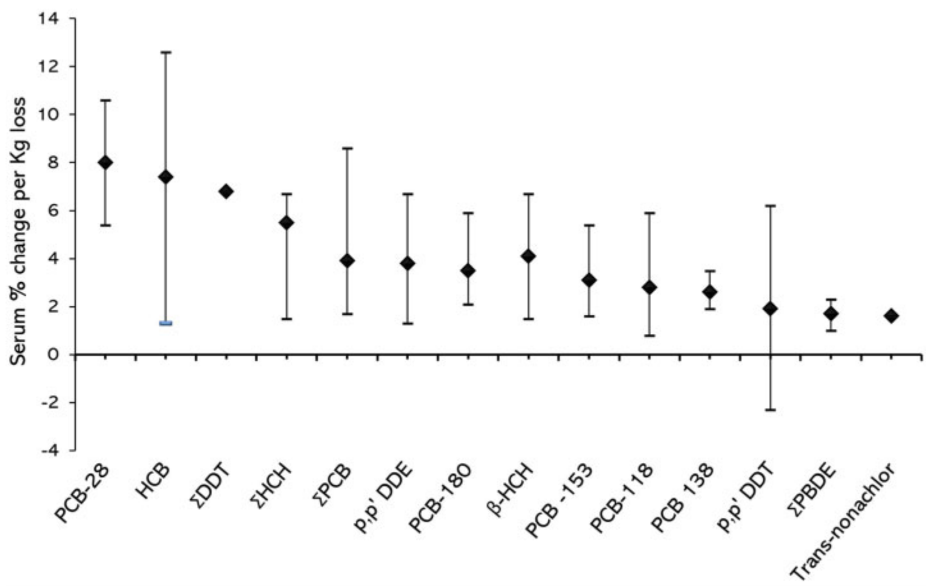

Figure 4. Mean percentage increase in EDCs per 1 kg weight loss after bariatric surgery. The percentage of EDCs increase in serum was calculated using the data from the five studies that provided EDCs in blood before and after bariatric surgery (Charlier *et al.*, 2002; Dirtu *et al.*, 2013; Rantakokko *et al., 2015*; Dirinck *et al.*, 2016; Jansen *et al.*, 2018). The calculated percentages were based on data from one to five studies, and bars show the mean and min–max range. The sample size of existing studies ranged between 151 and 487 patients. EDCs, endocrine-disrupting chemicals; DDE, dichloro-diphenyl-dichloroethylene; DDT, dichloro-diphenyl-trichloroethane; ∑DDT, sum of p,p′-DDT, p,p′-DDE and p,p′DDD; HCB, hexachlorocyclohexane; HCH, hexachlorocyclohexane; ∑HCH, sum of HCH congeners α-, β- and γ-; PBDE, Polybrominated diphenyl ethers; ∑PBDE, sum of BDE congeners -47, -99, -100 and -153; PCB, polychlorinated biphenyls; ∑PCBs, sum of PCB congeners -118, -138, -153 and -180.

non-occupational and occupational exposures (Table III). Adverse effects include impairment of conventional sperm parameters, genotoxicity and genetic instability. Importantly, these reported effects occur at serum EDC concentrations that are commonly found in post-BS patients. Exposure to DDT and its isomers, PCBs and γ-HCH are linked to reduced sperm concentration and count, decreased motility and a higher percentage of morphologically abnormal sperm (Dallinga *et al.*, 2002; Hauser *et al.*, 2003a,b; Khan *et al.*, 2010; Martenies and Perry, 2013; Paul *et al.*, 2017). Some EDCs can exhibit non-monotonic dose–response curves (Vandenberg, 2014), but studies cited in Table III show that elevated EDC concentration is associated with stronger declines in semen parameters. Notably, serum EDC concentrations reported in these non-surgery cohort studies are lower than, or similar to, those found in men at 1-year post-BS (Table III).

Some EDCs and their metabolites generate reactive oxygen species (ROS). ROS create free radicals and damage cell membranes, organelles and DNA (Sidorkiewicz *et al.*, 2017), which are associated with infertility, miscarriage and developmental abnormalities in the offspring (Aitken *et al.*, 2016). Spermatozoa are particularly susceptible to oxidative damage from ROS because their cell membranes largely consist of unsaturated fatty acids that become oxidized, and the sperm cytoplasm has low concentrations of enzymes that neutralize ROS (Aitken *et al.*, 2016). Genotoxicity might result from oxidative damage to nucleobases, induction of membrane lipid peroxidation, DNA methylation and dysfunction of DNA repair. Comet tests measure the degree of sperm DNA damage qualitatively by visualizing single- and double-strand breaks using electrophoresis (Kim, 2018). The higher the level of damage to the DNA, the brighter and longer the comet tail. Concentrations of ΣPCB and HCB similar to those found in post-BS patient sera are associated with an increase in total comet length, in %DNA damage and tail distributed moment in non-surgery cohort studies (Hauser *et al.*, 2003b). Further, PCB-153 was associated with DNA fragmentation in three studies in European populations (Rignell-Hydbom *et al.*, 2005; Spanò *et al.*, 2005; Stronati *et al.*, 2006), and DDT exposure was linked to higher sperm DNA fragmentation measures among men (De Jager *et al.*, 2009). The maximum concentration of PCB-153 in post-BS patients is reported as 550 ng/g lipid (Charlier *et al.*, 2002). One study observed that the percentage sperm DNA fragmentation index (%DFI) was 41% (95% CI, 11–78) higher when PCB-153 serum concentration was above 113 ng/g lipid (Rignell-Hydbom *et al.*, 2005).

Sperm aneuploidy serves as a biomarker for male reproductive toxicity (Mandrioli *et al.*, 2016). Serum concentrations of *p,p*′-DDE and ΣPCB (287 ng/g lipid) similar to those in post-BS patients (Dirtu *et al.*, 2013) are associated with significantly increased rates of sex chromosome disomy in sperm (Table III) in men from the Faroe Islands (Perry *et al.*, 2016) and men from subfertile couples from the Massachusetts General Hospital Fertility Center (McAuliffe *et al.*, 2012). Thus, there is a reason for concern that the precipitous release of EDCs into the blood post-BS could negatively impact sperm chromosome constitution. Only one case study investigated sperm aneuploidy pre- and post-BS, reporting a 27.4% increase in disomic sperm after surgery (Lazaros *et al.*, 2012). Whether the EDC release post-BS is responsible for negative impacts on male reproductive health remains to be

Table III Impact of EDCs on semen parameters reported in non-surgery populations with similar or lower serum EDC concentrations to those reported in post-bariatric surgery studies.

EDC	Reported range concentration after bariatric surgery*	Measured concentration or range in other studies	Study population and country	Outcome definition	The measure of association (95% CI or P-value)	Resume adverse effect	Study (author, year)
p,p'-DDE	**23.3–1570 ng/g lipid**	0.53 (0.23–30.2 ng/g serum)	341 men, 20–54 years old, in the U.S.	Sex chromosome disomy and disomy 18	Significant increase in the rate of XX, XY, and total sex-chromosome disomy for the second (0.23 ng/g), third (0.41 ng/g), and fourth quartiles (0.61 ng/g) of p,p'-DDE compared to the lowest quartile; these results persisted even after adjustment for potential confounders There were no significant relationships between p, p'-DDE and disomy 18	↑ XX, XY disomy ↑Total sex chromosome disomy	McAuliffe *et al.* (2012)
***p,p'*-DDE**	**23.3–1570 ng/g lipid**	40.4–2251 ng/g lipid	149 fishermen from the east and west coast, 47 ± 9.2 years old, in Sweden.	Sex hormones and sperm Y:X chromosome ratio	Participants in the category with the lowest quintile concentration of *p,p'*-DDE (<135 ng/g lipid) had a significantly lower Y chromosome fraction compared to the category with the highest quintile concentration (>472 ng/g lipid) (mean difference 1.6%, 95% CI 0.8, 2.5, *P* = 0.001)	↑ Y chromosome fraction	Tiido *et al.*, (2006)
***p,p'*-DDE**	**23.3–1570 ng/g lipid**	222 ng/g lipid (64.2–8912 ng/g lipid)	212 male partners of a subfertile couple, 35.3 ± 6 years old, in the U.S.	Sperm concentration, motility, morphology	Although not statistically significant, p,p'-DDE showed a weak dose-response trend with below-reference-value sperm motility (1.00, 1.14, 1.51, the *P*-value for trend =0.3)	↓Motility	Hauser *et al.* (2003a)
ΣPCB	**65.8–2310 ng/g lipid**	216 ng/g l (56.0–1733 ng/g lipid)	212 male partners of a subfertile couple, 35.3 ± 6 years old, in the USA	Sperm concentration, motility, morphology	There were inverse, though not significant, relationships between ΣPCBs with sperm motility and sperm morphology (1.00 1.77, 1.88, the *P*-value for trend =0.08), stronger in raw data	↓Motility ↓Morphology	Hauser *et al.* (2003a)
ΣPCB	**65.8–2310 ng/g lipid**	0.55 (0.16–6.14 ng/g serum)	341 men, 20–54 years old, in the USA	Sex chromosome disomy and disomy 18	$\sum_4$PCBs (congeners 118, 138, 153, 180) were associated with a significant increase in the rate of YY, XY, and total sex-chromosome disomy after adjustment for potential confounders XX disomy was significantly decreased above the first quartile of $\sum_4$PCBs There were no significant relationships between PCBs and disomy 18	↑YY and XY chromosome disomy. ↓ XX disomy	McAuliffe *et al.* (2012)

(continued)

Table III Continued

EDC	Reported range concentration after bariatric surgery*	Measured concentration or range in other studies	Study population and country	Outcome definition	The measure of association (95% CI or *P*-value)	Resume adverse effect	Study (author, year)
ΣPCB	**65.8–2310 ng/g lipid**	56–1590 ng/g lipid	212 male partners of a sub-fertile couple in the U.S.	Sperm concentration, motility, morphology, comet extent, %DNA in tail, tail distributed moment	Association with a small increase in comet extent [0.43 mm per IQR increase in ΣPCB; 95% CI: ±3.30, 4.16], tail % (0.43%/IQR increase in ΣPCB; 95% CI: ±0.72, 1.58), and tail distributed moment (0.22 mm/IQR increase in ΣPCB; 95% CI: ±1.26, 1.71)	↑Total comet length ↑%DNA in tail ↑tail distributed moment	Hauser *et al.* (2003b)
ΣPCB	**65.8–2310 ng/g lipid**	2.34 ± 1.2 ng/g lipid	65 men visiting Maastricht University Hospital for fertility treatments, 34.5 ± 5.4 years old, in the Netherlands	Sperm concentration, sperm count, motility and morphology	A significant positive relationship was found between the combined PCB levels in the blood with sperm count (n = 10, $R^2 = 0.79$, $P = 0.0005$), PMSC (n = 10, $R^2 = 0.86$, $P = 0.0001$) and sperm morphology (n = 9, $R^2 = 0.40$, $P = 0.05$) PCB metabolites were negatively associated with sperm count and PMSC in a group of men with normal sperm quality	↑Sperm count ↑Morphology ↑PMSC	Dallinga *et al.* (2002)
PCB 118	**4.82–690 ng/g lipid**	2.7 ± 1.3 ng/g lipid Men with low semen quality 1.9±1.13 ng/g lipid Men with normal semen quality	50 men, 24 of which had low semen quality and 26 had high semen quality, 38.04±5.01 years old, in Spain	Semen volume, sperm concentration, motility, morphology	Serum PCB-118 levels were negatively correlated with sperm volume ($r = -0.539$; $P = 0.031$) in those participants with normal sperm parameters	↓Volume	Paul *et al.* (2017)
PCB 138	**65.8-12 310 ng/g lipid**	7.3–295.4 ng/g lipid	212 male partners of a subfertile couple, 35.3 ± 6 years old, in the U.S.	Sperm concentration, motility, morphology	There was a statistically significant inverse relationship between log-transformed sperm concentration and PCB-138 (*P*, 0.08) There was a dose–response relationship between PCB-138 and below-reference values of sperm motility (1.00, 1.68, 2.35), and sperm morphology (1.00, 1.36, 2.53, *P*-value for trend = 0.04) There was a non-significant dose–response relationship for PCB-138 and below-reference value sperm concentration (1.00, 1.72, 1.62, *P*-value for trend = 0.3)	↓Concentration ↓Motility ↓Morphology	Hauser *et al.* (2003a)

(continued)

Table III Continued

EDC	Reported range concentration after bariatric surgery*	Measured concentration or range in other studies	Study population and country	Outcome definition	The measure of association (95% CI or *P*-value)	Resume adverse effect	Study (author, year)
PCB 153	**17.3–550 ng/g lipid**	40.5–1460 ng/g lipid	149 fishermen from the Swedish, east and west coast, 47 ± 9.2 years old, in Sweden	Sex hormones and sperm Y: X chromosome ratio	PCB-153 showed a tendency of a lower fraction of Y chromosomes among participants within the lowest quintile (<112 ng/g) compared to participants in the category with the highest quintile (>328 ng/g lipid) exposure (mean difference 0.8%, 95% CI 0.1–1.7, $P = 0.07$)	↑ Y chromosome fraction	Tiido *et al.* (2006)
PCB 153	**17.3–550 ng/g lipid**	39–1460 ng/g lipid First quintile <113 ng/g Second	176 fishermen with low and high consumption of fatty fish, 48 years old (29–67), in Sweden	Sperm chromatin structure assay (SCSA) to assess sperm DNA/chromatin integrity	PCB-153 was categorized into five equally sized quintiles, the quintile with the lowest exposure had significantly lower levels of %DFI compared with the other quintiles ($P < 0.001$). This effect remained when age was included in the model ($P = 0.006$). The four highest exposed quintiles (>113 ng/g lipid) had 41% (95% CI, 11–78) higher %DFI compared with the lowest exposed quintile	Increase in 41% the %DFI	Rignell-Hydbom *et al.* (2005)
HCB	**7.31–1200 ng/g lipid**	6.6–68.1 ng/g lipid	212 male partners of a sub-fertile couple, 35.3 ± 6 years old, in the USA	%DNA in tail, total comet length, TDM	HCB was associated, though not significantly, with a small increase in comet extent (0.32 mm/IQR increase in sum of PCB; 95% CI: ±3.69, 4.32), tail % (0.47 %/IQR in sum of PCB; 95% CI: ±0.75, 1.69), and TDM (0.19 mm/IQR in sum of PCB; 95% CI: ±1.40, 1.79)	↑Total comet length ↑%DNA tail ↑Tail distributed moment	Hauser *et al.* (2003b)
ΣPBDE	**0.9–75.6 ng/g lipid**	12.7 ng/g (BDE-47) and 11.7 ng/g (BDE-99)	153 men, 18–41 years old, Canada	Sperm concentration, motility and quality	Computer-assisted semen analysis was completed using SpermVision software (12 520/7000). A clinical assumption was that the motile portion of sperm is more indicative of the fertility potential in a semen sample than the total sperm population	N/A	Albert *et al.*, (2018)

*Endocrine-disrupting chemical (EDC) range concentrations after surgery were based on the measured serum levels in the studies described in Table II. BDE, brominated diphenyl ether; DDE, dichloro-diphenyl-dichloroethylene; DFI, sperm DNA fragmentation index; HCB, hexachlorocyclohexane; IQR, interquartile range; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; ∑PCBs, sum of PCB congeners 118, 138, 153, 180; PMSC, progressive motile sperm concentration; TDM, tail distributed moment.

determined. Knowledge on the impact of EDCs on spermatogenesis post-BS is necessary to develop strategies to protect patient fertility, including storing sperm before surgery.

Recommendations for future studies

The effect of weight loss after BS on semen parameters is still inconclusive as only a few studies, often with small sample sizes, have been performed. The impact of BS on male reproduction is not well investigated, which is surprising considering the known effects of obesity on male fertility. Several gaps in our knowledge emerge from the findings of this review that would benefit from further research, which must be advanced with improvements in study design to adequately test the hypotheses we have developed here.

BS-induced weight loss brings dramatic metabolic changes in the first 1–2 years of post-surgery, and BS patients commonly experience nutrient deficiencies. Nutritional supplementation and monitoring of nutritional status are mandatory post-BS to prevent such deficiencies. Because malnutrition is associated with poor sperm quality, future studies evaluating semen parameters post-BS should consider nutritional status and metabolic changes as an important confounding variable.

Indeed, while the physiological environment post-BS is complex, the potential for EDC mobilization after BS to exert endocrine-disrupting effects should not be overlooked. There is little information on temporal changes in circulating EDCs following BS. We recommend at least three serum samples post-surgery to build a curve of exposure. Also, it is likely that high serum EDC levels are temporary and will stabilize as bodyweight stabilizes, at around 24 months of post-surgery. Determining whether there are critical periods of EDC exposure post-BS is important for understanding reproductive outcomes and to discuss the risks with patients. Information about the risk of semen parameter deterioration post-surgery, if or when sperm parameters might recover, and which patients are most affected, will inform couples seeking to become pregnant post-BS.

It is therefore necessary to undertake prospective, long-term longitudinal studies that recruit patients at their first BS consult and follow them for 24 months, or preferably longer, post-BS. Additionally, studies should control for type of surgery, nutritional status and sex hormone levels, as well as factors related to semen quality, such as age, chemical exposure and smoking. To do this, using multivariate longitudinal mixed models that include random coefficients is recommended because relations over time can be evaluated rather than at individual time points, and because mixed models can capture increases in responses (EDCs progression in serum) in relation to the other random-effects variables. Multicenter recruitment is recommended to achieve satisfactory sample sizes ($n > 25$ to achieve 80% of power), because males typically represent only 20% of BS patients. Critically, the requirements for reliable semen examination must be carefully followed to identify post-BS EDC impacts more accurately. Poor-quality assessments of semen parameters can cause random errors to influence results so that true relations or differences cannot be detected. New standards for basic semen examination are now available (International Standards Organization, 2021; WHO, 2021).

Importantly, patients undergoing BS offer a unique population in which to evaluate how serum EDC concentrations influence male reproductive health. Toxicology studies alone will be of limited information without determining the extent to which animal findings can be extrapolated to humans. Longitudinal epidemiological studies may provide robust evidence to understand EDC toxicodynamics and the role of AT in EDC exposure.

Conclusion

Only relatively few studies with small sample sizes have addressed semen parameters after BS, and the findings are inconsistent. Indeed, most studies focus on sex hormones and attest that secondary hypogonadism improves post-BS. However, even with improved sex hormone levels and general reproductive function, a deterioration in semen parameters has been reported post-surgery. There is a multitude of explanations that can be provided for spermatogenesis disturbance post-BS, as discussed in this paper, but the progressive release of EDCs from AT during weight loss should receive special attention. It is important to determine if EDC release triggers a general worsening in semen quality and an increase in the risk of genetic instability, in at least a subset of men. This information is necessary to guide clinical management, such as including a fertility evaluation before surgery and discussing the possibility of sperm preservation. Filling these gaps requires adequately powered long-term prospective cohort studies of BS patients, with continuous follow-up of sperm parameters, nutritional status, sex hormone levels and EDC serum concentrations. Identifying these many dynamics will help ensure that men undergoing surgical treatment for obesity can preserve their fertility.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

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The authors declare no actual or potential competing financial interest or benefit and that their freedom to design, conduct, interpret and publish research is not compromised by any controlling sponsor as a condition of review or publication.

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