Obesity and Reproduction

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Abstract

Objective: To provide a comprehensive review and evidence-based recommendations for the delivery of fertility care to women with obesity.

Outcomes: The impact of obesity on fertility, fertility treatments, and both short and long-term maternal fetal outcomes was carefully considered.

Evidence: Published literature was reviewed through searches of MEDLINE and CINAHL using appropriate vocabulary and key words. Results included systematic reviews, clinical trials, observational studies, clinical practice guidelines, and expert opinions.

Values: The Canadian Fertility & Andrology Society (CFAS) is a multidisciplinary, national non-profit society that serves as the voice of reproductive specialists, scientists, and allied health professionals working in the field of assisted reproduction in Canada. The evidence obtained for this guideline was reviewed and evaluated by the Clinical Practice Guideline (CPG) Committee of the CFAS under the leadership of the principal authors.

Benefits, Harms, and Costs: The implementation of these recommendations should assist clinicians and other health care providers in counselling and providing reproductive care to women with obesity.

Validation: This guideline and its recommendations have been reviewed and approved by the membership, the CPG Committee and the Board of Directors of the CFAS.

Sponsors: Canadian Fertility & Andrology Society.

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Recommendations: Twenty-one evidence based recommendations are provided. These recommendations specifically evaluate the impact of obesity on natural fertility, fertility treatments, and maternal-fetal outcomes. Strategies to lose weight and BMI cut-offs are also addressed.

Résumé

Objectif : Présenter une revue exhaustive ainsi que des recommandations fondées sur des données probantes en matière de soins de fertilité offerts aux femmes présentant une obésité.

Résultats : L'incidence de l'obésité sur la fertilité, les traitements de fertilité et les issues maternelles et fœtales à court et à long terme a été analysée avec soin.

Données : Des études publiées récupérées au moyen de recherches dans MEDLINE et CINAHL à l'aide d'une terminologie appropriée et de mots-clés ont été évaluées. Les documents retenus comprenaient des revues systématiques, des essais cliniques, des études observationnelles, des directives cliniques et des opinions d'experts.

Valeurs : La Société canadienne de fertilité et d'andrologie est une organisation multidisciplinaire nationale à but non lucratif qui se veut la voix des spécialistes de la procréation, des scientifiques et des professionnels de la santé alliés qui travaillent dans le domaine de la procréation assistée au Canada. Les résultats obtenus ont été évalués par le Comité des lignes directrices de pratique clinique de la Société canadienne de fertilité et d'andrologie, sous la direction des auteurs principaux.

Avantages, inconvénients, coûts : La mise en œuvre de ces recommandations devrait aider les cliniciens et les autres fournisseurs de soins de santé à offrir du counseling et des soins de fertilité aux femmes qui présentent une obésité.

Validation : Cette directive clinique et les recommandations qu'elle contient ont été révisées et approuvées par les membres de la Société canadienne de fertilité et d'andrologie, ainsi que par son Comité des lignes directrices de pratique clinique et son conseil d'administration.

Commanditaire : Canadian Fertility & Andrology Society.

Recommandations : Vingt et une recommandations fondées sur des données probantes sont proposées. Plus précisément, ces recommandations décrivent les conséquences de l'obésité sur la fertilité naturelle, les traitements de fertilité et les issues maternelles et fœtales. Des stratégies pour la perte de poids et les seuils d'IMC sont aussi abordés.

This document is based on available evidence to date, often in a rapidly advancing field of study. Recommendations may not reflect emerging evidence and are subject to change. Clinical guidelines are intended as an aid to clinical judgement, and not to replace it. Clinical guidelines do not prevent clinicians from exercising freedom in their good clinical practice, nor relieve them of their responsibility to make appropriate decisions based on their own knowledge and experience.

Table 1. Internationally recognized BMI cut-off values for underweight, normal weight, overweight and obese[3]

BMI	Category
<18.5	Underweight
18.5–24.9	Normal Weight
25–29.9	Overweight
30–34.9	Obesity Class I
35–39.9	Obesity Class II
≥40	Obesity Class III

BMI: body mass index.

INTRODUCTION

The purpose of this guideline is to provide a framework for the delivery of fertility care to women with obesity. In Canada, as in many other countries, the prevalence of obesity in adults is increasing. More than half of Canadian men and women are overweight, and from 1978 to 2011 the rate of obesity increased from 14 to 26%.[1] Furthermore, the proportion of Canadians who are obese now exceeds the proportion of Canadians who regularly smoke (11%) or drink alcohol to excess (16%).[2]

The World Health Organization (WHO) defines obesity as abnormal or excessive fat accumulation that impairs health.[3] Obesity is most commonly defined using body mass index (BMI). BMI is the weight in kilograms divided by the square of height in metres (kg/M^2). The international cut-off values for defining underweight, normal weight, overweight and obese using BMI are listed in Table 1. It should be noted that other measures of obesity such as waist circumference, waist-to-hip ratio and the Edmonton obesity scoring system have merit,[4,5] but that this guideline focuses primarily on BMI as this is the measure most commonly used in the obesity and reproductive medicine literature.

Excessive caloric intake is the fundamental cause of obesity. Globally we are seeing an increase in the consumption of energy-dense foods, and a reduction in physical activity.[2] The health consequences of this imbalance include cardiovascular disease, diabetes, musculoskeletal disorders, sleep apnea and an increased risk of certain malignancies, such as breast, endometrial and colon cancer.[6,7] It has been estimated that in young adults a BMI >45 reduces life expectancy by as much as 5 to 20 years.[8]

Obesity also has a profound impact on reproductive health. Women who have obesity are at increased risk for menstrual dysfunction, anovulatory infertility and pregnancy-related complications.[9] In this guideline we will highlight the current literature related to obesity and reproduction, and present evidence-based recommendations using GRADE (Table 2).

WHAT IS THE IMPACT OF OBESITY ON FEMALE FERTILITY?

The impact of obesity on fecundity is complex.[10,11] Perhaps the best understood association is that between obesity and anovulation. Obesity induces a hormonal milieu consisting of insulin resistance, hyperinsulinemia, low sex hormone-binding globulin, elevated androgens, increased peripheral conversion of androgens to estrogens, increased free insulin-like growth factor 1 and high leptin.[12,13] The combined effect of these changes causes hypothalamic dysfunction, aberrant gonadotropin secretion, reduced folliculogenesis and lower luteal progesterone levels.[14–16]

Table 2. GRADE

Recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE offers two strengths of recommendation: strong and week. The strength of the recommendation is based on the quality of supporting evidence, degree of uncertainty about the balance between desirable and undesirable effects, degree of uncertainty or variability in patient values and preferences and degree of uncertainty about whether the intervention represents a wise use of resources.

Strong recommendations are those for which the Canadian Task Force on Preventive Health Care is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most individuals will be best served by the recommended course of action.

Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention), but appreciable uncertainty exists. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, or there is more variability in the values and preferences of patients. A weak recommendation implies that most people would want the recommended course of action but that many would not. Clinicians must recognize that different choices will be appropriate for each individual, and they must help each person arrive at a management decision that is consistent with his or her values and preferences. Policy-making will require substantial debate and involvement of various stakeholders.

Quality of evidence is graded as high, moderate, low or very low, based on how likely further research is to change the task force's confidence in the estimate of effect.

As a result, menstrual irregularity is more common in women with obesity, and increases in frequency with the level of obesity.[17,18] Several cohort studies have shown that the incidence of anovulatory infertility is more than twice as likely in women with obesity compared to normal BMI controls.[19–21] Interestingly, the distribution of body fat is also important. It has been shown that women with higher waist circumference (excess abdominal fat) are more likely to suffer from anovulation than obese women with the same BMI who have less abdominal fat.[22,23]

However, even in ovulatory women, obesity appears to inhibit natural fecundity and prolong the time to conception.[18,24–27] A study of 3029 Dutch women with ovulatory cycles, at least one patent fallopian tube and whose partner had normal semen parametres revealed that the likelihood of pregnancy within a 12 month period was reduced by 4% for each kg/M^2 increase in BMI over 29.[28] In that study, women with a BMI of 35 had a 26% lower likelihood of spontaneous pregnancy, and women with a BMI of 40 had a 43% lower likelihood of spontaneous pregnancy than women with a BMI between 21 and 29. The authors commented that frequency of intercourse may be one potential cofounder. Obesity has been associated with decreased sexual desire, erectile dysfunction and decreased frequency of sexual intercourse.[29] However, a Danish study of 1651 women that controlled for frequency of sexual intercourse, cycle regularity and waist circumference confirmed a progressive increase in the time to pregnancy among both nulliparous and parous women as the BMI increased from 25 to 30 to over 35.[30]

Obesity may also alter the endometrium.[31] There is evidence of altered endometrial gene expression during the implantation window of natural cycles in obese women.[32] Similarly, there is evidence of lower implantation and clinical pregnancy rates in obese donor egg recipients.[33,34]

Recommendations

1. Women with obesity should be advised that their risk of anovulatory infertility is more than twice that of non-obese women (strong recommendation, moderate quality evidence).
2. Women with obesity should be advised that even when ovulatory, their natural fecundity rates are reduced (strong recommendation, moderate quality evidence).

WHAT IS THE IMPACT OF OBESITY ON MALE FERTILITY?

Obesity often affects both partners in a relationship.[35,36] For men with obesity the average temperature of the scrotum may be higher due to closer contact with surrounding tissues.[37,38] Moreover, the combination of insulin resistance, reduced sex hormone binding globulin and increased peripheral conversion of androgens to estrogens may also disrupt gonadotropin release.[39–41] Consequently, men with obesity have decreased testosterone levels, that correlate negatively with both their fasting insulin and leptin levels.[42,43]

Despite these changes research regarding the relationship between male obesity and semen parametres has yielded conflicting results.[44] Some cohort studies have reported an association between male obesity and oligospermia,[41,45–47] while others have found no such association.[48–54] Likewise, meta-analyses have reported conflicting results with one reporting an increased risk of oligospermia and azoospermia,[55] while two others reported no impact of male obesity on semen parametres.[56,57] Similarly, data regarding the impact of obesity on sperm DNA fragmentation has been mixed, with some studies suggesting a negative effect,[57-59] while others report no differences.[60–62] Thus, although it is clear that obese couples have a higher incidence of infertility,[63] it remains unclear to what extent changes in sperm quality contribute to this association.

In contrast the literature clearly shows that obese men have a higher incidence of erectile dysfunction.[29,64,65] Several randomized controlled trials have demonstrated that lifestyle changes associated with weight loss may improve erectile dysfunction in obese men.[66,67] Similarly, improvement in erectile function have been documented after bariatric surgery.[68–72]

Recommendation

3. Men with obesity should be advised that they have increased risk of erectile dysfunction, and that this may be improved with weight loss (strong recommendation, high quality evidence).

WHAT IS THE IMPACT OF FEMALE OBESITY ON FERTILITY TREATMENTS?

Obesity has been associated with a reduced response to gonadotropins.[73,74] In a large retrospective cohort study of 1189 gonadotropin/intrauterine insemination (IUI) cycles, BMI over 30 was associated with significantly higher gonadotropin requirements, prolonged gonadotropin stimulation, lower peak estradiol levels, and fewer large and medium size follicles.[75] The reduced responsiveness of obese women to gonadotropins is likely due to the increased volume of distribution. A randomized, crossover study showed that there was no difference in gonadotropin absorption between subcutaneous and intramuscular routes, but that a decline in area under the curve

Table 3. The impact of female obesity on IVF Outcomes

	BMI 18.5–24.9	BMI 25–29.9	BMI 30–34.9	BMI 35–39.9	BMI 40–44.9	BMI 45–49.9	BMI >50
Number of IVF cycles	134 588	54 822	24 922	11 747	4084	1292	463
Oocytes retrieved	12.4	12.3	12.3	12.1	11.6	11.2	10.5
Cancellation rate	10.3%	11.3%	11.3%	12.2%	13.3%	14.2%	11.7%
Embryos transferred	2.4	2.4	2.4	2.4	2.4	2.5	2.3
Implantation rate	29.5%	28.3%	26.9%	25.8%	23.6%	22.9%	20.3%
Clinical pregnancy rate	37.9%	36.8%	35.7%	33.7%	32%	30.6%	30%
Pregnancy loss rate	11.3%	12.7%	14.6%	15.3%	14.8%	17.6%	20.3%
Live birth rate	31.4%	29.8%	28%	26.3%	24.3%	22.8%	21.2%

Adapted from Provost et al.[101]

BMI: body mass index.

occurred in women with elevated BMI.[76] The same decline in area under the curve is true for injections of HCG, but in this case two separate cross-over studies have reported better serum levels if HCG is given intramuscularly compared to subcutaneously.[77,78]

With regard to clinical pregnancy rates in women with obesity undergoing gonadotropin IUI study findings are mixed. Some studies report no difference[73,74,79] in the clinical pregnancy rates in obese patients compared to non-obese controls, while several other report a paradoxical increase.[75,80–82] Possible reasons for an increased effectiveness of gonadotropin/IUI in women with obesity include correction of anovulation, and compensation for erectile dysfunction and decreased frequency of intercourse.

In IVF patients, female obesity is associated with increased gonadotropin requirements (both increases starting dose and duration of gonadotropins), higher cycle cancellation rates, decreased peak estradiol levels and decreased oocyte yield.[83–91] However, there has been little consensus regarding the impact of female obesity on IVF success rates. Some studies have reported reductions of clinical pregnancy and live birth rates on the order of 15% to 30% in obese women undergoing IVF compared to non-obese controls.[83,85,86,90,92,93] Other studies have reported reductions in clinical pregnancy and live birth rates of more than 50%.[94,95] In contrast, at least nine studies have reported no discernable impact of female obesity on IVF pregnancy rates.[87–89,91,96–100]

The most comprehensive study to date regarding the impact of female obesity on IVF outcomes is from the Society for Assisted Reproductive Technology (SART) registry.[101] This analysis involved 239 127 fresh IVF cycles from 2008 to 2010 and included over 6000 cycles in women with a BMI 30 to 40 and almost 1000 cycles in women with a BMI over 40. The results of this study are summarized in Table 3. In brief, there is a slight decline in the number of oocytes retrieved and the number of high quality embryos as the BMI rises over 40. Implantation, clinical pregnancy and live birth rates all decline gradually with increasing severity of obesity. However, the absolute decline in pregnancy rates is small. Based on the data reported, implantation rates declined by approximately 0.2% to 0.25% and live birth rates declined by approximately 0.3% to 0.4% for each 1 kg/M^2 increase in BMI over 25. Thus the overall likelihood of a live birth per cycle start declined from 31.4% in women with a normal BMI, to 28% in women with BMI 30 to 34.9, to 24.3% in women with a BMI 40 to 44.5, and down to 21.2% in women with a BMI >50.

The exact mechanism by which obesity lowers IVF success rates is unclear. Some studies have demonstrated alterations in embryo development[102,103] and day-3 spent culture media metabolomics[104] while others have not detected any changes of indicators of embryo quality between obese women and non-obese controls.[90,105–107] Alternatively, obesity may alter endometrial receptivity.[32,108]

Perhaps the best model to help elucidate the impact of obesity on reproduction is oocyte donation. Several studies have suggested that obesity does not impact donor egg recipient implantation or live birth rates[109–111]; while other studies have found a negative association.[112–114]

Again, the most comprehensive data comes from the SART registry.[34] In an analysis of 22 317 fresh donor/recipient cycles performed between 2008 and 2010 the implantation rate (49%) and live birth rate (51%) in normal BMI recipients declined to 41% in women with a BMI over 40. Moreover, the pregnancy loss rate before 24 weeks gestation increased from 8.6% in normal BMI recipients to 13.5% in recipients with a BMI over 40.This finding is

consistent with that of a meta-analysis of miscarriage risk after oocyte donation in obese recipients.[115] Since the embryos came primarily from young, healthy donors there is no reason to suspect that the differences were related to an embryo factor. Indeed, an observational cohort study of 372 women with recurrent pregnancy loss showed that euploid miscarriages were significantly more common in women with obesity (58%) compared to non-obese controls (37%).[116]

This increase in pregnancy loss rate (8.6% with normal BMI to 13.5% with BMI over 40) in oocyte recipients is comparable to the change in pregnancy loss reported by SART in women using their own eggs: 11.3% with normal BMI to 14.8% with BMI 40 to 45, 17.6% with BMI 45–50 and 20.3% with BMI over 50[101] suggesting that changes in embryo quality are probably not the primary driver for the BMI related increase in pregnancy loss rates after IVF. Obesity clearly increases miscarriage risk. However, the absolute risk of pregnancy loss in women with obesity undergoing IVF is still lower than the reported risk of spontaneous pregnancy loss in women with 2 or more prior pregnancy losses (25%) or women age over 40 (≥35%).[117]

Aside from IVF outcomes, it is important to also recognize that obesity complicates the delivery of assisted reproductive technologies. In obese women undergoing controlled ovarian hyperstimulation, the ovaries may shift to a higher position in the pelvis, making them more difficult to visualize with transvaginal scanning and increasing the risk of complications with oocyte retrieval such as bleeding, infection, and injury to surrounding tissue. In addition, the risks of providing anesthesia to obese patients is well described, and makes management of these patients through non-hospital centres a challenge. In a recent survey of obesity policies at IVF facilities in the United States, 62% of respondents cited anesthesia concerns as the primary reason for their BMI cut-off.[118]

Recommendations

4. Women with severe obesity should be advised of a lower oocyte yield with IVF (strong recommendation, moderate quality evidence).
5. Women with an elevated BMI should be advised that implantation rates, clinical pregnancy rates and live birth rates decline with increasing severity of obesity. The best available evidence regarding live birth rates suggests a decline of approximately 0.3% to 0.4% for each 1 kg/M^2 increase in BMI over 25 (strong recommendation, moderate quality evidence).
6. Women with obesity should be advised that pregnancy loss rates prior to 24 weeks gestation increase as BMI increases (strong recommendation, moderate quality evidence).
7. Women with obesity using an egg donor should be advised that the live birth rate per cycle start is lower compared to non-obese recipients (strong recommendation, moderate quality evidence).
8. Women should be advised that obesity can compromise pelvic ultrasound imaging and the safety of oocyte retrieval (strong recommendation, low quality evidence).

WHAT IS THE IMPACT OF OBESITY ON MATERNAL RISKS OF PREGNANCY?

The risk of miscarriage is increased in women with obesity who conceive with IVF, irrespective of whether they use their own eggs or donor eggs. Miscarriage risks are also increased for women with obesity who conceive spontaneously. A recent Danish cohort study involving over 5000 women reported a hazard ratio for miscarriage of 1.23 in obese women compared to non-obese controls.[119] Similar results were reported in a British population study involving 1644 women with obesity and 3288 controls (odds ratio 1.2 for miscarriage if obese).[120] Among women with recurrent miscarriages the association with obesity may be even greater. Two studies have suggested that among women with recurrent miscarriages the odds of the next pregnancy resulting in miscarriage is elevated 3- to 4-fold in obese patients.[120,121]

Women with obesity who conceive are also at greater risk for gestational diabetes. The baseline risk of gestational diabetes in over one million pregnancies in Ontario from 1996 to 2010 was documented as 4.1%.[122] Similarly, a study of over 400 000 pregnancies in Alberta found that the incidence of gestational diabetes increased from 3.1% in 2000 to 4.6% in 2009.[123] In British Columbia, a study of 226 000 singleton pregnancies from 2004 to 2012 reported the incidence of gestational diabetes as 7.9%.[124] In that study the risk of gestational diabetes increased steadily with increasing BMI (Table 4). The risk of gestational diabetes was doubled with a BMI over 30 and more than tripled with a BMI over 40.

The risk of preeclampsia is doubled in women that are overweight, and tripled in those that are obese.[124,125] The risk further increases with the severity of obesity (Table 4). It has been suggested that increasing physical activity in pregnancy may reduce the incidence of both gestational diabetes and pre-eclampsia.[126] However, a recent multicentre randomized control trial in over 1500 women with obesity found no difference in the incidence of gestational diabetes or mac-

Table 4. Risk of adverse maternal and perinatal outcomes with increasing BMI in a population cohort study of over 226 000 pregnancies in British Columbia

	BMI 18.5–24.9 n = 144 502	BMI 25–29.9 n = 46 317	BMI 30–34.9 n = 17 210	BMI 35–39.9 n = 6695	BMI ≥40 n = 3380	*P* value
Gestational diabetes	6.1%	9.7%	13.7%	16.6%	20.8%	<0.001
Preeclampsia	3.4%	6.4%	10%	12.8%	16.3%	<0.001
Macrosomia	1.4%	2.8%	3.8%	4.5%	6.1%	<0.001
Shoulder dystocia	3.5%	4.1%	4.1%	4.4%	4.1%	<0.001
Birth injury from shoulder dystocia	0.1%	0.1%	0.1%	0.2%	0.3%	<0.001
Cesarean delivery	26.5%	33.1%	38.2%	43.1%	49.7%	<0.001
Indicated birth <37 weeks	1.6%	2%	2.5%	3.4%	4.1%	<0.001
Stillbirth	0.3%	0.3%	0.4%	0.4%	0.6%	<0.001
Birth <32 weeks	0.6%	0.6%	0.6%	0.6%	0.5%	NS
Maternal mortality	0.6%	0.6%	0.6%	0.5%	0.6%	NS

Adapted from Schummers et al.[124]

BMI: body mass index.

rosomia in women randomized to behavioural intervention in pregnancy, versus routine care.[127]

A recent Canadian meta-analysis revealed that there is a 31% increased risk of delivery prior to 37 weeks in obese women.[125,128] This may be related to the higher incidence of preterm premature rupture of membranes (PPROM) and need for medical induction of labour. PPROM might be more common in obese patients with increased circulating adipokines and inflammatory proteins. Increased rates of sleep apnea and antenatal depression have also been reported.[125,128]

A systematic review of the risks associated with obesity in pregnancy demonstrated that pregnant women with obesity have a longer duration of labour, particularly the first stage (4.7 hours compared with 4.1 hours in non-obese women).[129–131] Women who with obesity have less successful trials of labour and vaginal birth after Caesarean section (VBAC): 54% to 68% success if BMI >29, 13% if weight >136 kg/300 lbs. There is increased fetal distress, instrumental delivery, and shoulder dystocia in women with obesity going through labour (Table 4).[125,128] The Caesarean section rate increases significantly with increasing BMI (Table 4).[125,132–133] There are also increases in wound infection and dehiscence, post-partum hemorrhage and DVT.[125,132,134]

Recommendations

9. Women with obesity should be advised that they have increased prenatal risk of having gestational diabetes and preeclampsia (strong recommendation, moderate quality evidence).
10. Women with obesity should be advised of increased peri-partum risks such as a prolonged first stage of labour, less success with VBAC, increased instrumental deliveries, shoulder dystocia and cesarean section rates (strong recommendation, moderate quality evidence).
11. Women with obesity should be aware that these obstetrical risks are increased with higher BMI (strong recommendation, moderate quality evidence).

WHAT IS THE IMPACT OF OBESITY ON FETAL/NEONATAL RISKS OF PREGNANCY?

Women with obesity are also at an increased risk of fetal macrosomia (Table 4), an association compounded by the presence of gestational diabetes. A recent Swedish population-based cohort study involving 1 249 908 singleton births between 1998 and 2012 documented an incidence of macrosomia of 7.7% for non-obese women without gestational diabetes, compared to 14% in gestational diabetics.[135] The odds ratio for macrosomia in women with obesity was 2.55 (95% CI 2.51–2.59) without gestational diabetes compared to 6.50 (95% CI 6.10–6.92) with. Macrosomia increases the need for obstetrical interventions like induction of labour and Caesarean section, and increases the incidence of a number of complications such as shoulder dystocia, nerve palsy, and NICU admission. Maternal obesity also increases the risk of obesity in the child, with a higher risk of diabetes and cardiovascular disease later in life.[135–139]

The National Birth Defect Prevention Study found that the mothers of offspring with anomalies were more likely

to have obesity, with an odds ratio of 1.3 to 2.1, suggesting that maternal adiposity alters development in the embryonic period.[140] In the 10 249 cases compared to the 4065 controls, there was a 39% increase in neural tube defects,[141] with 50% increase in spina bifida, and 20% increase in oral clefts. Hydrocephaly (OR 1.68), anorectal atresia (OR 1.48), limb reduction anomalies (OR 1.34) and cardiovascular anomalies were also increased. The metabolic basis for those anomalies is not known, but poor glycemic control may play a role. Some have advocated for increased folic acid supplementation but evidence to support this practice is unclear.[142] Obesity can also prevent visualization of congenital defects on ultrasound possibly leading to their discovery later in pregnancy or lack of prenatal detection. A large retrospective study demonstrated 20% less detection of anomalous fetuses in women with high BMI compared to normal BMI.[143]

Recommendation

12. Women with obesity should be advised that their risk of having a baby with macrosomia or a congenital anomaly is increased (strong recommendation, moderate quality evidence).

WHAT SCREENING TESTS ARE APPROPRIATE FOR WOMEN WITH OBESITY SEEKING FERTILITY CARE?

The 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children contain recommendations for assessment of obesity and its complications.[144] Obesity induces insulin resistance and a baseline inflammatory state and increases the risk of diabetes, hypertension, dyslipidemia and cardiovascular disease.[145–149] The prevalence of diabetes in the United States general population increases with BMI (8% risk if normal BMI, 43% risk if BMI ≥40 kg/m^2) and obesity is the most important modifiable risk factor for the prevention of type 2 diabetes.[150,151] An analysis of the United States National Health and Nutrition Examination Survey (NHANES) found the prevalence of diabetes in 2011–2012 among adults aged 22 to 44 years was 5.0% (95% CI 3.8–6.7), and when stratified by BMI, the increase in prevalence of diabetes from 1988 to 2012 was seen only among those with BMI ≥30, regardless of age.[152] NHANES also found that regardless of age, ethnicity, education or smoking habits, lipid profile worsened and the risk of hypertension increased with increasing BMI.[153] In this study, woman age 20–39 with a BMI ≥30 were 7 times more likely to have high blood pressure, 3.4 times more likely to have high cholesterol, and 13.2 times more likely to have low HDL cholesterol than women with a BMI <25. Not surprisingly obesity, and particularly central obesity, is associated with increased risk of cardiovascular disease.[153–155]

Abundant literature demonstrates that elevated BMI is associated with an increased risk for complex endometrial hyperplasia and endometrial cancer in premenopausal women.[156–160] In a recent review the pooled odds ratio for endometrial cancer was 5.3 in women with a BMI >30 and 19.8 in women with a BMI >40.[31] Similarly, a prospective cohort study followed 495 477 women in the United States for 16 years showed a significant increase in risk of mortality from cancers according to BMI.[7] Compared to non-obese controls, women with a BMI of 40 or more had a relative risk of 2.1 for dying from breast cancer and a relative risk of 6.3 of dying from endometrial cancer.

Women with obesity are also at risk for obstructive sleep apnea: periodic, partial or complete obstruction of the upper airway during sleep which leads to repetitive arousal from sleep.[161] The airway obstruction may also cause episodic sleep-associated oxygen desaturation, episodic hypercapnia, significant negative intrathoracic pressure and cardiovascular dysfunction.[162] Approximately 35% of women with a BMI ≥35 report symptoms compatible with obstructive sleep apnea.[163,164] Sleep apnea exacerbates the cardio-metabolic risk attributed to obesity and metabolic syndrome.[165] Self-reported sleep apnea appears to be an independent prognostic marker of all-cause mortality.[166]

Recommendations

13. Women with obesity should be informed that they are at increased risk of metabolic abnormalities (diabetes, dyslipidemia, hypertension), cardiovascular disease, breast and endometrial cancer (strong recommendation, moderate quality evidence).
14. Prior to starting fertility treatment, women with obesity should be advised to have screening for and appropriate management of comorbidities such as diabetes, hypertension and dyslipidemia (strong recommendation, moderate quality evidence).

WHAT ARE THE MOST EFFECTIVE TREATMENTS TO HELP INFERTILE WOMEN WITH OBESITY LOSE WEIGHT?

Canadian guidelines on managing obesity have focused primarily on eating habits and exercise.[167] The 2015 Canadian Task Force on Preventive Health Care recommended structural behavioural interventions focused on diet and exercise as first-line treatment for patients with a BMI 30 to 39.9.[1] Pharmacotherapy and surgery are options for more severe cases of obesity (BMI ≥40). It should be noted that body

weight is tightly regulated by a complex homeostatic system and that powerful neuroendocrine mechanisms defend the body against weight loss, thus accounting for the over 95% recidivism (weight regain) generally associated with behavioural obesity management.[168,169] The same is seen when pharmacologic treatments are discontinued or bariatric surgery is reversed.

LIFESTYLE MODIFICATION

Obesity has been associated with poor body image, low self-esteem, depression and anxiety, all of which may influence binge eating.[170,171] One of the challenges of lifestyle modification is breaking this pattern and introducing behavioural strategies that facilitate weight loss and prevent weight regain.[172]

Lifestyle modification with diet and exercise yields modest weight loss. Dietary interventions typically focus on reduced energy uptake from fat and carbohydrates, and increased uptake of fruits, vegetables, whole grains and nuts. The Diabetes Prevention Program (DPP, 3234 participants)[173,174] and Diabetes Prevention Study (DPS, 522 participants)[175] showed that weight loss of approximately 4 to6 kg could be achieved following an intensive program of lifestyle changes (counselling, education, support, changes in exercise and diet) and that this was sufficient to reduce the incidence of type 2 diabetes, metabolic syndrome and dyslipidemia in individuals at risk. Unfortunately, weight lost in the first year of lifestyle intervention is gradually gained back, and in the DPP study, total weight loss in the intervention group was 2 kg after 10 years, which was only 1 kg more than in the control group.[176] Indeed, the meta-analysis on which the current Canadian weight loss guidelines are based noted an average weight loss of only 3.1 kg (95% CI 2.4–3.9) with behavioural interventions.[177]

PHARMACOTHERAPY

Current Canadian guidelines recommend adding pharmacological treatment only when lifestyle modification is not sufficient to achieve or maintain clinically significant weight loss.[1] The rationale for this approach is that behavioural modification has better benefit-to-harm ratio than pharmacotherapy. In Canada, two drugs are currently approved by Heath Canada for the treatment of obesity-Orlistat and Liragutide. Orlistat (Xenical®) is a selective absorption fat inhibitor.[178–180] It exerts an effect in the digestive tract by binding to gastric and pancreatic lipases and prevents absorption of at least 30% of dietary fat. However, side effects include flatulence, greasy stool, fecal urgency and abdominal cramps. Liragutide (Saxenda®) is an analogue of human glucagon-like-peptide-1.[181,182] Liragutide leads to weight loss by decreasing appetite. The most common side effects are nausea, diarrhea and hypoglycaemia by stimulating insulin secretion and inhibiting glucagon. Liragutide 1.2 to 3 mg subcutaneously per day may lead to greater weight loss (4.8–7.2 kg after 20 weeks) than Orlistat 120 mg by mouth 3 times per day (4.1 kg after 20 weeks).[181] The safety of both of these drugs in pregnancy is unknown. Although metformin is not specifically approved by Health Canada for weight loss, its properties in this regard have been well studied.[1,183–190] Current data suggests that metformin induces weight loss of an average of 1.9 kg, while Orlistat on average 3.1 kg.[177] Unfortunately, even in controlled trials with fixed timelines, drop-out rates with weight loss medications typically exceed 30%.[191]

BARIATRIC SURGERY

Bariatric surgery is considered when the BMI is over 40, or if BMI exceeds 35 with comorbidities, and if other weight loss attempts have failed.[167] Bariatric surgery modifies the architecture of the digestive tract in order to limit caloric intake. There are restrictive procedures such as vertical banded gastroplasty, laparoscopic adjustable gastric banding or sleeve gastrectomy designed to accelerate the feeling of "being full," and there are malabsorptive procedures such as biliopancreatic diversion with or without duodenal switch that are designed to reduced nutrient absorption. Bariatric surgery may also be a mixed restrictive/malabsorptive procedure as Roux en Y gastric bypass. In malabsorptive or mixed procedures, the greater the excluded intestinal portion, the greater the decrease in caloric intake.[192,193]

Bariatric surgery typically induces significant weight loss. The Swedish Obese Subjects (SOS) study included over 2000 bariatric surgery patients and showed that maximal weight loss was achieved after 1 year (gastric bypass 45 kg, vertical banded gastroplasty 30.8 kg and gastric banding 24.9 kg) but that significant weight reduction was maintained even after 10 years of follow-up (gastric bypass 29.6 kg, vertical banded gastroplasty 19.5 kg and gastric banding 15.6 kg).[194] Other studies have confirmed profound weight loss 1 to 2 years after gastric bypass surgery (29–45 kg), biliopancreatic diversion (48 kg) and sleeve-gastrectomy (25.1 kg).[195,196]

Furthermore, bariatric surgery improves metabolic profile and significantly reduces all-cause mortality.[164,197] In fact, bariatric surgery has been shown to be more effective than usual care in the prevention of type 2 diabetes,[198] and more effective than medical therapy in the treatment of type 2 diabetes in obese patients.[196] Finally, among obese patients with uncontrolled type 2 diabetes, three years of intensive medical therapy plus bariatric surgery results in

significantly better glycemic control and weight reduction than medical therapy alone.[195]

Mortality associated with bariatric surgery is less than 1%.[199] The most common postoperative complications in the SOS study were pulmonary complications (6.1%). Other complications (<5%) are bleeding, venous thrombosis, wound infections, anastomotic leaks.[164] Long term complications include vitamin deficiencies in 20% to 50% of cases. Surgical complications (internal bowel herniation) related to the previous bariatric procedure may also impact 1% of pregnancies.[200] Depending on the procedure, complications may lead to health problems: anemia (iron, B12 and folate deficiencies), osteopenia (loss in calcium and vitamin D), alopecia (zinc deficiency), muscle weakness (magnesium deficiency), visual disorders, neuropathy, and hemorrhagic disease (Vitamins A, C, E and K deficiencies).[201,202] For these reasons bariatric surgery requires long-term monitoring.

DELAY OF CONCEPTION AFTER BARIATRIC SURGERY

There are no prospective randomized trials addressing time to conception after bariatric surgery. Nevertheless, concerns over the impact of rapid weight loss and vitamins deficiencies on the mother and fetus, delaying pregnancy for one to two years after bariatric surgery has been recommended.[203–205] A retrospective study comparing 104 pregnancies conceived less than one year after bariatric surgery to 385 pregnancies conceived more than year after bariatric surgery found no differences between the two groups regarding bariatric complications, pregnancy related complications or perinatal outcomes.[206] Similarly, a Danish cohort study involving 158 women who conceived within the first year of Roux en Y gastric bypass surgery to 128 women who conceived after one year found no difference obstetric or neonatal outcomes between the two groups.[207] Thus, particularly in the late reproductive years, the possible benefits of postponing pregnancy must be balanced against the risk of declining reproductive potential with advancing age.

ADVERSE OBSTETRIC AND NEONATAL OUTCOMES AFTER BARIATRIC SURGERY

Bariatric surgery significantly reduces the risk of gestational diabetes, fetal macrosomia and hypertensive disorders of pregnancy.[208–211] Unfortunately, bariatric surgery also increases the risk of maternal anemia[212] and the risk of small-for-gestational age (SGA) infants.[210,213,214] In nationwide Danish registry-based cohort study obese women who conceived following bariatric surgery were 3.3 times less likely to have a large-for-gestational age (LGA) infant but 2.3 times more likely to have a SGA infant compared to BMI matched controls.[214] Similarly, a nationwide Swedish registry-based cohort study that matched 670 pregnancies in women who had previously undergone bariatric surgery to five controls matched for pre-surgery BMI reported reduced risks for gestational diabetes (1.9% vs. 6.8%) and LGA infants (8.6% vs. 22.4%) but a higher risk for SGA infants (15.6% vs. 7.6%).[210] In that study, the median time from surgery to conception was 1.1 years and, of concern, the risk of still birth or neonatal death (1.7% vs. 0.7%; OR 2.39; 95% CI 0.98–5.85; $P = 0.06$) was slightly higher in the bariatric surgery group.

To date there does not appear to be a difference in obstetrical or neonatal outcomes based on the type of bariatric surgery performed. A study that compared laparoscopic gastric banding, ring vertical gastroplasty and vertical banded gastroplasty reported no significant differences in subsequent obstetric or perinatal outcomes between the three procedures.[215] Similarly, another study reported comparable neonatal outcomes between women conceiving after laparoscopic adjustable gastric banding and Roux en Y gastric bypass.[216]

Recommendations

15. Women with obesity should be advised that modest reductions in weight combined with lifestyle modification will improve their metabolic profile (strong recommendation, moderate quality evidence).
16. Women with obesity should be offered or referred for lifestyle modifications (diet + exercise) as a first-line effort to help them lose weight (strong recommendation, low quality evidence).
17. Women with obesity who fail to lose weight with lifestyle modification may be offered a referral to other practitioners/specialists who can appropriately counsel them regarding alternative therapies such as pharmacotherapy and bariatric surgery (strong recommendation, moderate quality evidence).
18. Women who have undergone bariatric surgery should be advised that the possible benefits of waiting for 1–2 years after surgery before attempting conception should be balanced against the decline in fertility related to advancing age (strong recommendation, low quality evidence).
19. Women who have undergone bariatric surgery should be advised that they are at lower risk for fetal macrosomia, gestational diabetes and hypertension, but at higher risk for small-for-gestational age infants (strong recommendation, good quality evidence).

IS THERE DATA DEMONSTRATING A DIFFERENCE IN OUTCOMES FOR WOMEN WITH OBESITY WHO LOSE WEIGHT COMPARED TO WOMEN WITH OBESITY WHO PROCEED DIRECTLY TO TREATMENT?

In anovulatory women with obesity, weight loss of 5% to 10% can induce ovulation and increase the chance of pregnancy.[217–221] One weight loss intervention study randomized 49 women to either an intensive 12-week dietary intervention (n = 27) or simply written instructions on how to lose weight (n = 22).[222] The 22 women who completed the intensive intervention lost an average of 6.6 kg while the controls lost an average of 1.6 kg. Despite just a 5 kg difference in weight loss the authors reported significantly more pregnancies (48% vs. 14%; $P = 0.007$) and live births (44% vs. 14%) in the intervention group. Similarly, striking results (live birth rates of 71% vs. 37%; n = 52) have been reported for women with a BMI >25 who succeed in achieving meaningful weight loss (≥10% of their weight).[223]

Following bariatric surgery, it has been estimated that 58% of previously infertile women with obesity may conceive spontaneously.[224] Bariatric surgery may also increase the number and quality of oocytes obtained at the time of IVF treatment[225]; however, it is unclear if this increase actually improves clinical outcomes.[226]

Recommendation

20. Women with obesity should be advised that weight loss improves spontaneous fecundity rates (strong recommendation, low quality evidence).

SHOULD THERE BE A NATIONAL BMI CUT-OFF FOR ACCESS TO FERTILITY CARE?

Concerns regarding poor clinical outcomes and maternal/fetal risks have led to calls to restrict access to fertility treatments in women with elevated BMI.[227,228] A 2014 survey of Canadian IVF medical directors found that 50% of respondents imposed a BMI cut-off.[229] The median upper permitted BMI was 38 and the interquartile range was between 35 and 40. The National Institute of Clinical Excellence (NICE) guideline states that it is desirable to achieve a BMI below 30 prior to commencing fertility treatment.[230] In 2000, clinical priority criteria in New Zealand restricted women with a BMI >32 from accessing fertility treatment.[231] In 2007, the British Fertility Society recommended deferring fertility treatment until a woman's BMI was below 35,[232] and most IVF units in the United Kingdom impose BMI cut-offs between 30 and 35.[233]

Thus far the American Society for Reproductive Medicine has resisted calling for a national BMI cut-off.[40] However, many providers believe that BMI cut-offs should exist.[234] In a 2014 survey of 349 clinics, 35% (n = 120) reported using a BMI or body weight cut-off to determine IVF eligibility.[235] In that study the mean BMI cut-off was 38.4 and the mean weight cut-off was 130 kg. Among the clinics with a BMI cut-off, only 54% provided weight loss instructions for their patients. Another survey that involved 77 responding clinics reported that 65% had a BMI cut-off (50% between 35–40, 24% between 40–45).[117] Most cited anesthesia requirements as the primary reason for having a cut-off, and only 38% of respondents had a BMI cut-off for intrauterine insemination.

Clearly, there is no consensus in clinical practice. Furthermore, we must recognize that any specific cut-off value is arbitrary, and that for many patients, weight loss is difficult to achieve. Most weight loss interventions result in less than 7 kg of weight reduction. For a woman of average height (163.5 cm) this results in 3 kg/M^2 or less change in BMI. Although it might improve their metabolic profile, it is unclear that this amount of weight reduction substantially changes the maternal/fetal risks of pregnancy.

The situation is further complicated by the increasing number of women who are obese. From an ethics perspective, clinician's duty to respect their patients' decision-making autonomy is counterbalanced by their duty to do no harm. This duty extends not only to the patient with obesity, who may suffer irreversible health complications as a consequence of pregnancy, but also to the child-not-yet-born whose health may be significantly compromised as a consequence of the mother's obesity. Clearly, weight loss should be encouraged. However, the risk, benefits and limitations of weight loss interventions prior to fertility treatment should be balanced against the risks, benefits and limitations of proceeding directly to fertility treatments.

It is important to recognize that denying fertility care leads to stigmatization, may be perceived as discriminatory; and can exacerbate feelings of low self-esteem, social isolation, anxiety and depression.[236–238] Moreover, denying fertility treatment to older obese women or women with diminished ovarian reserve until they have lost a specific amount of weight may cost them valuable time and any chance of pregnancy.[239]

In other areas of healthcare, the risk of complications does not necessarily prevent obese patients from receiving elective medical care. Although obese women face a higher chance of obstetric complications their absolute risks remain low. Moreover, their risk of complications does not clearly

exceed the risk of complications encountered with other pre-existing medical conditions such as diabetes, hypertension and epilepsy. Thus, in the absence of simple, safe effective strategies that reliably help patients with obesity lose weight in a timely fashion, it is difficult to advocate for a universal BMI cut-off in place of careful counselling, screening for metabolic abnormalities and informed consent.

Recommendation

21. Programs that impose BMI cut-offs should offer resources for patients to help them lose weight and should inform patients about both the risks and benefits of delaying fertility treatment (strong recommendation, low quality evidence).

CONCLUSION

The prevalence of obesity is steadily increasing and affects a substantial number of reproductive age women in Canada. Obesity reduces natural fertility rates and those from fertility treatments. Women with obesity have a reduced response to fertility medications, reduced likelihood of success with assisted reproductive technologies, increased risk of miscarriage and increased risk of maternal/fetal complications in pregnancy. Weight loss is the mainstay of treatment and is important for optimizing the safety and success of natural and treatment-related conception. Unfortunately, it is not easy for patients with obesity to lose weight and, aside from bariatric surgery, most interventions result in only modest weight reductions that are difficult to maintain. Therefore, patients with obesity should be assessed carefully in the preconception period and comorbid conditions addressed. A careful balance should then be sought between the principle to do no harm and the responsibility to respect patient autonomy.

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