

REVIEW

Obesity and Reproductive Performance in Women

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Abstract

Obesity and overweight are not only problem of developed nations but also an increasing problem in developing countries with health consequences. Studies have highlighted the link between obesity, infertility and adverse reproductive health outcome. Obesity contributes majorly to two most common medical risks in pregnancy: diabetes and hypertension. It is associated with increased risk of large-for-gestational age and hypertensive disorders, including pre-eclampsia, which may be associated with low birth weight. Combination of factors viz individual lifestyle, environmental and genetic play role in obesity. Weight loss has demonstrated to improve fertility in obese women through recovery of spontaneous ovulation, and improved response to ovarian stimulation in infertility treatment. Therefore, weight management interventions, should be considered for overweight and obese infertile women (*Afr. J. Reprod. Health* 2010; 14[3]: 143-151).

Résumé

Obésité et la performance de reproduction chez la femme. L'obésité et la surcharge pondérale sont non seulement des problèmes qui se posent aux pays avancés, mais aussi aux pays en développement avec des conséquences pour la santé. Des études ont souligné les liens entre l'obésité, la stérilité et les conséquences défavorables pour la santé de reproduction. L'obésité contribue de manière significative à deux risques médicaux les plus communs pendant la grossesse: le diabète et l'hypertension. Elle est associée au risque accru d'avoir une grossesse qui est plus grande que l'âge gestationnel et des désordres hypertensifs, y compris la pré-éclampsie qui peut être liée à un faible poids de naissance. Une combinaison de facteurs, c'est à dire le mode de vie individuel, l'environnement et les facteurs génétiques jouent un rôle dans l'obésité. On a démontré que la perte de poids améliore la fécondité chez les femmes obèses à travers le rétablissement spontané de l'ovulation et la réponse améliorée à la stimulation de l'ovaire dans le traitement de la stérilité. En conséquence, les interventions des modalités du traitement du poids doivent être considérées à l'égard des femmes stériles obèses et qui ont une surcharge pondérales (*Afr. J. Reprod. Health* 2010; 14[3]: 143-151).

Key words: Obesity, reproductive health, fertility.

Introduction

Obesity has become a global health issue because of its negative impact on health and contribution to morbidity and mortality. It is estimated that 1.3 billion people are overweight or obese globally¹. Evidences abound of its association with adverse reproductive health outcome especially among women of child bearing age. Obesity is defined as having a body mass index (BMI: the weight in kilograms divided by the square of height in metres) greater than 30 kg/m². In the Western developed countries, it is a growing significant problem³. According to the Centres for Disease Control, it causes 112,000 deaths a year - nearly three times more than the toll from drugs and alcohol. The direct healthcare costs of obesity increased from \$52 billion in 1995 to \$75 billion in 2003². In the United

States, between 2005–2006, data from the National Centre for Health Statistics show that 34% of U.S. adults 20 years of age and older -over 72 million people are obese. In 2003–2006, 16.3% of children and adolescents aged 2–19 years had a body mass index greater than or equal to the 95th percentile for age and sex on the CDC growth charts⁴. Obesity was estimated to contribute 8% of all illness costs (around £40 billion a year)⁴. In Britain, the Food Standards Agency reported that a quarter of men and one fifth of women are now classified as obese. In addition, 41% of men and 33% of women are officially overweight⁵. The consequence on annual healthcare budget is over 2 billion pounds³. In Finnish population-based study, the prevalence of obesity and central obesity among women were found to be 23.5% and 28.0% respectively, while in an Australia survey, overweight and obesity was noted

in 67% of men and 52% of women⁶⁻⁷. The cost of obesity to national health systems is high due to the increased morbidity and mortality, including the risk of several cancers associated with obesity^{8,9}.

In pregnancy, the cost of prenatal care is 5 times higher for overweight women. An Australian study reported that 34% of the total samples of pregnant women in that study were overweight or obese and they had increased adverse maternal and neonatal outcomes, resulting in increased costs of obstetric care¹⁰. Reports of obesity among pregnant women in the USA range from 18.5% to 38.3%, making it one of the most frequent high-risk obstetric situations⁵. However, obesity is not only a problem of developed countries, but is becoming an increasing problem in the developing countries as well¹¹⁻¹³.

Compared with normal-weight patients, obese women patients have a higher prevalence of infertility. They have higher rate of early miscarriage and congenital anomalies, including neural tube defects. Besides the coexistence of pre-existing diabetes mellitus and chronic hypertension, obese women are more likely to have pregnancy-induced hypertension, gestational diabetes, thrombo-embolism, macrosomia, and spontaneous intrauterine death in the latter half of pregnancy¹⁴. Obesity increases the risk of preeclampsia and fetal macrosomia and operative deliveries.

Many research studies have been conducted in developing countries and the findings showed that obesity is not only a problem of developed nations but is becoming an increasing problem in developing countries as well. In Nigeria, although both under-nutrition and over-nutrition are common problems, obesity and its associated problems have been identified as a public health problem among rural women, men and children¹⁵. In a study conducted in the south east of Nigeria, of the 2860 deliveries that took place within the study period, 220 out of this 2860 women were obese and had obesity associated problems¹⁶. The incidence of hypertension, obstructed labour, perineal tear and postpartum haemorrhage was higher in the obese than in the control. There was also statistically significant difference in the mean duration of hospital stay of the obese.

The 2008 study by Alebiosu et al of the Olabisi Onabanjo University Teaching Hospital (OOUTH), Shagamu, showed that the number of overweight Nigerians is growing at geometric proportion. The OOUTH team screened 512 volunteers and found that about two-thirds were either overweight or obese¹⁷. Similarly, in a study conducted in 1995 – 2005 on “rapid increases in obesity in Jamaica, compared to Nigeria and the United States”, women in Nigeria and the US had higher weight gains than men, with the converse observed among Jamaicans¹⁸.

The prevalence of obesity was surveyed among members of staff of Adamawa State College of Agriculture, Mubi. Out of the sampled populations, it was observed that risk of co-morbidities in females was 3.9% while in males was 2.6%. Moderate risk was higher in males (16.6%) than in females (4.3%). Similarly, severe risk was higher in males (19.2%) than females (9.6%) and very severe risk was higher among males (24.5%) than in females (18.8%). Severe and very severe risk of co-morbidity was higher in males than females within the age group of 30 – 39 years and 40 – 49 years respectively. Although these findings could be attributed to the fact that majority of the male staff was engaged in sedentary work as compared to their female. It showed that obesity with its associated problems is a growing problem in Nigeria^{19,20}. The prevalence of overweight and obesity in 270 children studied in Nigeria were 13.7% and 5.2% respectively¹⁸.

Obesity is a major contributing factor to the two most common medical risks in pregnancy: diabetes and hypertension^{21,22}. Although obesity is associated with an increased risk of large-for-gestational age, it is also associated with increased risk of hypertensive disorders, including preeclampsia, which may be associated with low birth weight (LBW)²³. Obesity has also been shown to be an independent risk factor for a longer, more difficult delivery and for a cesarean delivery^{24,25}. In a study in the South West Nigeria, outcome of pregnancy in the 205 obese patients identified (using a weight of 90 kg and above as cut-off) was compared with 206 controls. Obesity increased the risk of preeclampsia and fetal macrosomia and operative deliveries²⁶.

Factors Contributing to Obesity

There are varieties of factors that play role in obesity. Overweight and obesity result from an energy imbalance that involves eating too many calories without corresponding energy expenditure or not getting enough physical activity. This imbalance can be as a result of combination of several factors which include individual behaviors, environmental and genetic factors.

Individual Behaviour

Individual's behavior in terms of personal choices concerning calorie consumption and physical activity can contribute to overweight and obesity. Preference of pre-packaged foods, fast food restaurants, and soft drinks contribute to increase in weight. While such foods are fast and convenient, they also tend to be high in fat, sugar, and calories. Some foods are marketed as healthy, low fat, or fat-free, but may contain more calories than the fat containing food they are designed to replace. Also, the quantity of these fast foods contributes largely to the

amount of calorie an individual will get from them. Frequent and increased quantity of a meal or snack results in increased calorie consumption. If the body does not burn off the extra calories consumed from larger portions of meals, fast food, or soft drinks, weight gain can occur. Transition to lipid rich diets and reduction in physical exercise as a result of improvement in socioeconomic status has been observed to have contributed significantly to increase in weight gain²⁷.

Our bodies need calories for daily functions such as breathing, digestion, and daily activities, however, weight gain occurs when calories consumed exceed this need. Physical activities such as bodily movement produced by skeletal muscles that result in an expenditure of energy play a key role in energy balance. These could include: Walking, biking, swimming, dancing, gardening, farming, washing, and running, playing of tennis, football, skating and other aerobics. These Physical activities do not have to be strenuous to be beneficial. They help to control weight, contributes to healthy bones, muscles, and joints.

Genetics

Science showed that genetics plays a role in obesity. Genes can directly cause obesity in disorders such as Bardet-Biedl syndrome and Prader-Willi syndrome. A commonly quoted genetic explanation for the rapid rise in obesity is the mismatch between today's environment and "energy-thrifty genes" that multiplied in the past under rather different environmental conditions. In other words, according to the "thrifty genotype" hypothesis, the same genes that helped our ancestors survive occasional famines are now being challenged by environments in which food is plentiful all year round¹¹. The findings relate to the genetics of modern Pima Indians who have an unusually high rate of obesity but could be extrapolated to all people. Their obesity is thought to be linked to a thrifty metabolism that allowed them to metabolize food more efficiently in times when little was available but causes problems when food is in abundance. Mark Rowe, David McClellan, and colleagues at Brigham Young University in Provo, Utah, USA, have studied the effect of evolutionary selection on Pima Indians, a people indigenous to the present-day Sonora desert of Arizona and New Mexico. The researchers anticipated an effect consistent with higher metabolic efficiency among these people and focused specifically on recently discovered variations in their mitochondrial DNA or single nucleotide polymorphism (SNPs).

The metabolic rates of 200 obese Pima individuals were measured and revealed that two of the three known SNPs influence metabolic efficiency. The researchers then used the genetics software TreeSAAP, to analyze the biochemical changes caused by these SNPs and then tracked the evolu-

tionary selection of these genetic variations in 107 different types of mammals. This allowed them to propose a mechanism by which these SNPs affect the mitochondrial respiratory chain and consequently increase metabolic efficiency in the Pima people.

The team suggests that an increased metabolic efficiency could have been an evolutionary advantage. The SNPs may have persisted because they helped the Pima survive the harsh dietary environment of the Sonora desert throughout the history of the people. In the current environment of caloric over-consumption an increased efficiency is unfavourable and may contribute to the high rates of obesity among the Pimas²⁸.

While the Pima Indians are an extreme case, the entire human population may also have evolved in a restricted caloric environment, say the researchers. Many populations may exhibit similar SNPs that were advantageous to our ancestors but may now be detrimental. The presence of these SNPs may thus provide one explanation as to why obesity is so widespread in the 21st century. An explanation of the genetic role in obesity epidemic therefore has to include both the role of genetics as well as that of the environment. However genes do not always predict future health. Genes and behavior may both be needed for a person to be overweight. In some cases genes may increase one's susceptibility for obesity but require outside factors such as abundant food supply or little physical activity.

Environment

Despite all the benefits of being physically active, improvement in modern technology has enhanced sedentary life style of individuals. For examples the use of cars, elevators, computers, dishwashers etc have made most individuals sedentary. Cars are used to run short distance errands instead of people walking or riding a bicycle. As a result, these recent lifestyle changes have reduced the overall amount of energy expended daily. Environmental influences can affect people's decisions. An individual may choose not to walk to the store or to work because of the location of these centers which may not be of close proximity to the individual's residence or a lack of pedestrian sidewalks especially in busy towns. Jobs that involve sitting down in one place for a very long time without facilities for physical activities can enhance weight gain and influence people's health. Because of this influence, it is important to create environments in these locations that make it easier to engage in physical activity and to eat healthy diet.

Other Factors

Diseases and Drugs

Some illnesses may lead to obesity or weight gain. These may include Cushing's disease and polycys-

tic ovary syndrome. Drugs such as steroids and some antidepressants may also cause weight gain.

Health Consequences of Obesity

Overweight and obese individuals are at increased risk for many diseases and health conditions, including the following:

- Hypertension (high blood pressure)
- Type 2 diabetes
- Coronary heart disease
- Stroke
- Osteoarthritis (a degeneration of cartilage and its underlying bone within a joint)
- Dyslipidemia (for example, high total cholesterol or high levels of triglycerides)
- Gallbladder disease
- Sleep apnea and respiratory problems
- Some cancers (endometrial, breast, and colon)

Obesity and Fertility:

Obesity has been known to be associated with several abnormalities of sex steroid balance. It alters important homeostatic factors such as pancreatic secretion of insulin. Hyperinsulinemia and insulin resistance are widely accepted to be involved in the underlying mechanisms linking obesity to multiple metabolic abnormalities. Such alterations involve androgens and oestrogens and their carrier protein, sex-hormone-binding-globulin (SHBG)²⁹.

Body fat distribution has been shown to substantially affect SHBG concentrations. Fat accumulation in the abdominal viscera (visceral fat) has been described as a possible cause of insulin resistance and the resulting metabolic syndrome. Women with central obesity and with higher proportion of visceral fat usually have high insulin resistance leading to lower SHBG concentrations in comparison with those with peripheral obesity.

In insulin resistance syndrome, excess insulin is capable of stimulating steroidogenesis, excessive androgen production from the theca cells and excessive oestrogen production from the granulosa cells of the ovaries. In addition, by directly inhibiting SHBG synthesis, excess insulin may further increase the delivery of free androgens to target tissues. The excess in local ovarian steroidogenesis induced by excess circulating of insulin may cause premature follicular atresia and then favour anovulation.

Accumulating data conclude that insulin resistance and hyperinsulinemia resulting in hyperandrogenemia are the hormonal abnormalities, which disturb ovarian function in women with excess adipose tissue. However these abnormalities seem not to be associated with total fat mass *per se* but more so with visceral fat accumulation.

Fertility processes involve a complex of factors and mechanisms of both ovarian and extra ovarian origin. Obesity may interfere with many neuroendocrine and ovarian functions, thereby reducing both ovulatory and fertility rates in otherwise healthy women. Oligoovulation, anovulation and sub fertility are present in obese females with a relative risk of anovulatory infertility of 3.1 for women with a BMI >27 compared with women of BMI 20-25. Polycystic ovary syndrome (PCOS), a condition characterized by hyper-androgenism and menstrual disturbances, further complicates the issue³⁰. Many obese women have normal ovulatory menstrual cycles, remain fertile and have no apparent hyperandrogenism. However, currently, there is substantial evidence to support the relationship between obesity and anovulatory infertility³¹. Obesity, particularly in women with PCOS, can result in many reproductive disorders. This is due to the complex interaction between the pituitary gland, pancreas and ovary resulting in a changed hormonal secretion pattern:

Hormonal mechanisms that link nutrition/diet and female fertility:

(a) Normal ovarian function resulting in normal puberty and reproductive competence is controlled primarily by the gonadotrophins LH and FSH from the pituitary gland, the secretion of which is regulated by the brain hormone, GnRH. Nutrition is linked to the female reproductive system through the effects of a hormone emanating from fat cells (leptin) and by insulin from the pancreas, which alters the bio-availability of estradiol and testosterone by affecting production of SHBG (sex hormone-binding globulin) from the liver. Insulin can also function directly on the ovary.

(b) In overweight women and/or those with polycystic ovary syndrome (PCOS), an increase in the number of fat cells results in a cascade of changes involving increased leptin and insulin levels and a preferential increase in LH, but not FSH levels. The net effect of these changes is to stimulate the partial development of follicles that secrete supranormal levels of testosterone, but which rarely ovulate (hence low progesterone). These changes are exacerbated by insulin-induced reduction in SHBG which amplifies ovarian testosterone production / action. In addition, there is a genetic predisposition to PCOS. It should be noted that impaired fetal growth can also result in an increase in the number / size of fat cells and an increase in insulin resistance in adulthood, although the relationship to fertility and PCOS is still unclear³².

The use of hormone measurement and ultrasound led to a realization that not all patients with PCOS suffered from being over-weight. Over a third to 50% of PCOS subjects are overweight or obese^{33,34}. Variation in body weight between PCOS

populations in USA and Europe, attributed to genetic and lifestyle factors has also been reported recently³⁵. In PCOS women of Caucasian origin, the severity of both metabolic and clinical symptoms is positively correlated with the body mass index (BMI)³⁶. There is also evidence showing that even normal weight PCOS subjects have increased intra-abdominal fat³⁷.

Obesity and leptin

Leptin plays a potentially important role in human infertility given the discovery of its regulatory effect on fertility in the mouse³⁸. There is a strong correlation between serum leptin concentrations and body fat and BMI in humans³⁹⁻⁴². Leptin levels have also been reported to be increased in women with PCOS^{41,43} although this was not supported by many other studies^{42, 44, 45}. Given the well-established effect of leptin on ovarian steroidogenesis and ovulation in rodents⁴⁶⁻⁴⁸ and in humans⁴⁹⁻⁵¹, it can be speculated that the high concentration of leptin might have a role in the pathogenesis of PCOS and reproductive disorders influenced by obesity.

Obesity and menstrual disorder

Anovulation was strongly associated with obesity. Grossly obese women had a rate of menstrual disturbance 3.1-fold more frequent than women in the normal weight range (BMI 18.5–25.0 kg/m²). Teenage obesity was positively correlated with menstrual irregularity later in life and obesity was correlated with abnormal and long cycles, heavy menstrual flow and hirsutism. Lake et al studied women at ages 7, 11, 16, 23 and 33 years and found obesity in childhood and at the early 20s increased the risk of menstrual problems⁵². Women who were overweight (BMI 23.9–28.6 kg/m²) and obese (>28.6 kg/m²) at 23 years of age were respectively 1.32 and 1.75 times more likely to have menstrual difficulties. Girls with menarche at 9, 10 or 11 years were more likely to have menstrual problems at 16.5 years (OR 1.45 for mild and 1.94 for severe menstrual abnormality), as confirmed by Ibanez et al. (1998)⁵³.

The presence of PCOS may further aggravate the effect of obesity on menstrual functions. Of 1741 UK subjects with PCOS, 70% had menstrual disturbances and only 22% had normal menstrual function if their BMI was >30 kg/m²^{33,54}. Furthermore, obese subjects with PCOS had an 88% chance of menstrual disturbance compared to 72% in non-obese subjects with PCOS.

Obesity, miscarriage and other adverse pregnancy outcomes

Weight excess is associated with an increased risk of miscarriage. In a study of primiparous women, miscarriage was found in 11% of women with a

BMI 19–24.9 kg/m², 14% of women with BMI 25–27.9 kg/m² and 15% of those weighing >28 kg/m^{2,55}. Women weighing >82 kg are more likely to have miscarriage than thinner women⁵⁶. Another recent study in women receiving donated oocytes also observed obesity as an independent risk factor for miscarriage⁵⁷⁻⁵⁸, although it was found unrelated to preclinical pregnancy loss⁵⁹.

The adverse effect of overweight and obesity on pregnancy and obstetric outcome is well known. High pre-pregnancy weight is associated with an increased risk of pregnancy-induced hypertension, toxemia, gestational diabetes, urinary infection, macrosomia, caesarean section, and increased hospitalization^{60,61}.

Obesity and response to infertility treatment

Most studies show conclusive evidence that increasing BMI is associated with an increased requirement for clomiphene citrate. In several of these, large doses of clomiphene (up to 200 mg per day) were required to ensure ovulation in the heaviest women⁶²⁻⁶⁵. Doses of gonadotrophins required to induce ovulation are also increased in anovulatory women and those requiring ovarian stimulation for any reason⁶⁶. Increased weight and BMI in PCOS lead to impaired response to standard doses of clomiphene citrate, although most obese women with this condition will respond to larger doses⁶⁷. Fedorcsak et al (2001)⁶⁸ showed that obesity, independent from hyperinsulinaemia, was related to lower oocyte recovery on IVF and increased total FSH requirements for stimulation. A similar observation has been made with gonado-trophin ovulation induction in non-PCOS women⁶⁹.

Thus, excess weight appears to have a major impact on reproductive performance and obesity can compromise reproductive outcome in a variety of ways:

- 1) *Menstruation*: increased risk for amenorrhea, oligomenorrhea, and menorrhagia due to ovulatory dysfunction.
- 2) *Infertility*: increased risk for infertility and anovulation; poor response to fertility drugs.
- 3) *Miscarriage*: increased risk for miscarriage, both spontaneously and after infertility treatment.
- 4) *Pregnancy and labour*: increased prevalence of pregnancy-induced hypertension, gestational diabetes, thromboembolism, urinary tract infections, induction of labour, instrumental delivery, caesarean section, anaesthetic and postoperative complications including uterine infections.
- 5) *Neonatal morbidity/mortality*: increased risk to the fetus of macrosomia, potentially leading to birth trauma; increased risk of neonatal admission to the intensive care unit; increased risk of neonatal death.

- 6) *Congenital anomalies*: increased risk for the fetus of neural tube defects and heart defects.

Improving reproductive performance through weight management

Many advances have been made in recent years on the effect of weight reduction in improving reproductive function in overweight and obese infertile women. It has been documented that weight reduction through dieting /exercising leads to improved reproductive performance. Available studies indicate that weight loss is associated with significant improvement in reproductive function with reduction in hyperandrogenism, hyperinsulinaemia, and altered gonadotrophin pulsatile secretion⁷⁰. Weight loss results in increase in SHBG, reduction in testosterone and androgenicity, improved menstrual function, improved conception rates and reduction in miscarriage rates.

Short-term weight loss has been achieved in overweight PCOS subjects with very low calorie diets (VLCD) (330–421 kcal / day)⁷¹⁻⁷⁵ and moderate caloric restriction (1000 –1500 kcal/day for 3–6 months)^{54,73,76-81}. In a cross-sectional study, Shick et al (1998)⁸² assessed the dietary patterns of 438 subjects from the National Weight Control Registry who maintained a weight loss of 30 kg for 5.1 years. Subjects who successfully maintained weight reported continued consumption of a low energy and low fat diet. A systematic evaluation of six randomized controlled trials using partial meal replacement plans for weight management suggests that these types of interventions can safely and effectively produce significant sustainable weight loss and improve weight-related risk factors of disease⁸³. In addition to physical activity, behaviour modification and healthy eating practices are essential. Clark et al (1995)⁸⁴ conducted a prospective study including a weight loss component to determine whether it could help infertile, overweight, anovulatory women. A weekly programme of behavioural change in relation to exercise and diet for 6 months resulted in an average weight loss of 6.3 kg, a restoration of ovulation in 12 of the 13 subjects and pregnancy in 11 women. Fasting insulin and testosterone concentrations dropped significantly. A further study⁸⁵ using the same protocol involved 67 anovulatory women in an exercise and dietary intervention for 6 months. Women in the study lost an average of 10.2 kg or 3.7 kg/m² (10% reduction of BMI) with 60 of the 67 anovulatory subjects resuming spontaneous ovulation. Of these women, 52 achieved a pregnancy, 45 of which resulted in a live birth. A low fat (~30% of energy and saturated fat ~10% of energy), moderate protein and moderate carbohydrate intake and increased consumption of fibre, whole-grain breads and cereals and fruit and vegetables in conjunction with moderate regular exercise (30–60 mins/day) is pro-

posed to aid in weight loss and maintenance both in the general population and in obese infertile women with PCOS⁸⁶.

Conclusion

The increase incidence of obesity reflects the profound changes in society and in behavioural patterns of individuals over recent decades. Although genes are important in determining a person's susceptibility to weight gain, the actual energy balance is determined by calorie intake and physical activity. Obesity causes abnormalities of sex hormones in women of reproductive age leading to oligo-ovulation, anovulation and subfertility. Furthermore, it is associated with increased risk of miscarriage, congenital malformations, labour complications, neonatal morbidity and mortality. Treatments aimed at reducing weight should represent the primary interventional strategy in obese women with anovulation and infertility. There is long-standing clinical evidence concerning the efficacy of weight reduction in endocrinological features of obese infertile women. Weight reduction is associated with better success rates in infertility treatment programmes, including ovulation induction and various assisted reproductive techniques. Therefore weight reduction is the appropriate treatment for obese women with endocrine derangement, menstrual irregularities and infertility.

Furthermore, lifestyle modification programmes in form of engaging in physical exercise and healthy eating patterns can lead to improved reproductive function and should be recommended especially for the young people and women of reproductive age. Nutritional education to mothers to encourage and counsel their children on healthy dietary habit and exercise is also important. Short-term (weeks or months) treatment with drugs is not warranted nor is it probably appropriate. Treatment with medication is likely to be necessary for years, and perhaps for a lifetime in order to sustain weight loss and improve health. To date, there have been few published studies where patients have received anorexiant for more than 1 year. In addition, data on the long-term safety and efficacy of anorectic drug combinations is also very limited. The lack of long-term safety and efficacy data is disappointing, given that most of these anorexiant have been available for more than 20 years⁸⁷. Pharmacotherapy is not recommended for treatment of obesity⁸⁸. There is need for further studies in developing countries to guide policy formulation on nutritional education.

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