

CHAPTER

71

Women and Obesity : One Decade of Experience with Sibutramine

M. V. Muraleedharan

Obesity is a common disorder. Overweight persons (BMI 25-29) form 60% and obesity (BMI >30) is noted 42% of American population. The situation is not far different in other parts of the world. With changing economic scenario, India also host a substantial percentage of obese and overweight population. Medical profession, health care providers and the population at large still do not consider overweight and obesity as a disease entity. Consequently, it is not a subject of intense research and therapeutic intervention. Until the subject reaches morbid obesity with its associated mechanical, metabolic and psychosocial problem, medical assistance is rarely requested for.

However, in the past two decades, there is better awareness about obesity among the medical profession, healthcare providers and population. It is considered as a disease entity and early intervention is sought. Substantial interest is seen in study of the disease entity in the form of epidemiological studies, evaluation of pathophysiology and relation between major clinical diseases like diabetes, coronary artery disease, cancers and obesity.

Both men and women are afflicted with the disease but incidence of obesity in women is higher than in men (NHANES data). Even though there are common problems affecting both sexes when obese, some of the problems of obesity are gender

dependant and seen in women only. Women who have abdominal obesity have a metabolic risk profile similar to that of men^{1,2} Women have more fat as a per cent of body weight than men from puberty onward, and tend to gain more fat during adult life than men. In addition, women experience modest but adverse increases in body weight and fat distribution after a first pregnancy that appear to be persist.³ The trend for increased incidence of obesity is first observed during adolescence and persist into adulthood. This is attributed to the change in body composition between two sexes. When body fat decreases in boys during this period, it increases in girls. However, it is difficult to predict which obese child would become obese adult.

Pregnancy is an important milestone in the weight gain history of women. Most of the women gain 2 to 3 Kg in postpartum period. Weight gain with oral contraceptives is not supported by scientific evidence. However, most of the women gain weight during menopause. Decrease in estrogen and progesterone with menopause cause central fat deposition and enhanced cardiovascular risk. Estrogen therapy does not prevent weight gain but minimize fat distribution in the central abdomen.

Obesity in women can be classified as those associated with polycystic ovary disease and those which are independent. Pathogenesis, clinical

course and management are different in polycystic ovaries when compared to women with simple obesity. There are some similarities between the two group however.

Obesity (Not associated with polycystic ovaries)

Fertility

Decreased fertility in obese women is supported by available data. This often result from anovulation with or without polycystic ovary syndrome. In many obese women, weight reduction is associated with return of ovulation and conception. It is also seen that higher doses of fertility inducing treatment is needed in obese women compared to lean counterparts. It is also reported that there is increased occurrence of early miscarriages in obese women. This may be attributed to Polycystic ovarian disease or insulin resistance in some but not in all.

Weight gain in pregnant women especially when they are obese. This is important as these women fail to lose the weight gained during pregnancy. At present, permitted weight gain is 7 to 11.5 kg in overweight women (BMI 26-29) AND 6.8 for obese women (BMI > 29) (Institute of Medicine recommendation)

During pregnancy in obese person, there is increased incidence of Gestational Diabetes Mellitus. This is in parallel to the increased risk of type 2 diabetes with increasing BMI. Similarly, the risk of Pregnancy associated hypertension is increased. This is attributed to insulin resistance, dyslipidemia and low grade inflammatory state persisting in the obese pregnant patient. There is also higher incidence of preterm birth, post maturity, multifetal pregnancy, urinary infection and obstructive sleep apnea.

Problems during delivery

The duration of labor is increased in obese women. Myometrium from obese women removed during caesarian contracted less well than normal.³ Induction of labor is often needed with increased

rate of caesarian delivery and shoulder dystocia due to fetal macrosomia. Post partum hemorrhage and infection are more common in obese parturient. Duration of hospital stay is prolonged. Initiation of lactation, duration of lactation and quantity of milk are adversely influenced by obesity.

Post partum issues

Increased incidence of neural tube defect is noted in these subjects. Perinatal mortality is increased. Fetal macrosomia occur with higher frequency in the offspring of obese patient.

Cardiovascular risk in obese women

Available data does not suggest any increase in cardiovascular events in women with obesity compared to their male counterparts.

Management

Obesity is a lifestyle disease and major step in its management would be therapeutic lifestyle changes. The age at which obesity start has shifted to earlier years with affliction of children and adolescents.

Behavioral strategies

Behavior modification for obesity management goes back to 1967 with progressive increase in emphasis and length of aggressive technic over the years. 7 to 10% weight loss could be expected, most of this weight loss occur in first 6 months in motivated subjects. However, maintenance of lost weight is an important issue. Duration of behavior therapy training vary from 20 to 40 weeks. In this treatment strategy, it is presumed that obese individual has maladaptive diet and exercise habits and attempts are made to change these by behavioral inputs.

Behavior modification include the following elements:

Regular physical activity

At least 150 minutes per week – promote weight loss. This can be done as individual or as group with similar success.

Food discipline

Adhering to time, place and type of food is an important part of life style changes. Individual is encouraged to block signals which promote eating in different places, at all times and use of food materials which are energy dense (Fast food). Nutritional education and meal planning is a part of the training. Slowing the process of eating can reduce food intake and produce satiety. Realistic goals are set and achievement or failure are monitored regularly with regular reinforcement. Family (at home) and social support (in the work place) is an important element in these program.

Commercial and self help groups and internet based programs form an important tool in achieving weight loss.

Food content

Food content to promote weight loss has following properties:

1. Just enough calories to maintain basal requirement of energy. This can be achieved with 22 Kcal / Kg ideal body weight
2. Diet should contain balanced combination of energy yielding foods – carbohydrate (60%), fat and protein (20% each)
3. Fiber, vitamins and minerals in the same amount as nonobese.

Negative calorie input of 100 Kcal per day would promote one pound weight loss per month. Alcohol, sweet liquids and sweet are totally eliminated from diet aiming at weight reduction.

Drugs

Drugs approved currently for promoting weight loss include sibutramine (5 HT – Norepinephrine reuptake Inhibitor), orlistat (Pancreatic lipase inhibitor) and Rimonabant (cannabinoid receptor blocker). Metformin, in doses exceeding 1000 mg could also promote weight loss, if tolerated, even in nondiabetics as the drug does not produce hyperglycemia. Older drugs like amphetamine, fenfluramine, and dex fenfluramine are not used

because of addiction potential or potential toxic effects (Pulmonary hypertension). Similarly, thyroxine is not to be used as it promotes loss of lean body mass rather than excess fat.

Bariatric surgery

Among all modalities of treatment, surgery has unique place as it promotes weight loss and sustain it. However, there is an element of morbidity associated with surgery and irreversibility. Track record of bariatric surgery is extremely promising as many centers report 25% or more weight loss which is sustained over periods. In addition, effective surgery also reverses abnormal carbohydrate metabolism which is a strong association of obesity. At present, bariatric surgery is reserved for those with BMI above 40%. When there are compelling indications because of target organ damage like severe osteoarthritis, surgery can be done even when BMI is above 35%. Safety and technics of surgery is getting better.

Obesity in Polycystic Ovary Syndrome

Obesity is one of the constituent of polycystic ovary disease and an important issue to be addressed. Very often, the reason for presentation is for irregular periods, anovulation and infertility and features of hyperandrogenism like hirsutism, acne and male type of baldness. The disease is strongly associated with insulin resistance and hyperinsulinism. Acanthosis nigricans and warts noted in these subjects result from hyperinsulinism. Weight loss in these subjects would result in ovulatory cycles and pregnancy with disappearance of signs of hyperinsulinism like acanthosis nigricans.

Management of obesity in this disease does not differ from that of simple obesity even though they have other issues to be addressed like hyperandrogenism and anovulation. Therapeutic lifestyle changes are the first step. Drug therapy in polycystic ovary with obesity favor the use of metformin as baseline drug. Sibutramine and rimonabant are usually reserved as add on drugs.

When there is morbid obesity, drug therapy alone may not be sufficient and one has to consider bariatric surgery. The result of medical therapy is promising. More experience is to be gained before bariatric surgery can be considered as practice recommendation in polycystic ovaries considering the fact that these women may not have completed their family.

References

1. Krotkiewski, M, Bjorntorp, P, Sjostrom, L, Smith, U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest* 1983; 72:1150.
2. Larsson, B, Bengtsson, C, Bjorntorp, P, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women, Goteborg, Sweden. *Am J Epidemiol* 1992; 135:266
3. Smith DE, Lewis, CE, Caveny, JL, et al. Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. *JAMA* 1994; 271:1747.
4. Nuthalapaty, FS, Rouse, DJ, Owen, J. The association of maternal weight with cesarean risk, labor duration, and cervical dilation rate during labor induction. *Obstet Gynecol* 2004; 103:452.
5. Larsson, B, Bengtsson, C, Bjorntorp, P, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women, Goteborg, Sweden. *Am J Epidemiol* 1992; 135:266
6. Smith DE, Lewis, CE, Caveny, JL, et al. Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. *JAMA* 1994; 271:1747.
7. Krotkiewski, M, Bjorntorp, P, Sjostrom, L, Smith, U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. *J Clin Invest* 1983; 72:1150.
8. Larsson, B, Bengtsson, C, Bjorntorp, P, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women, Goteborg, Sweden. *Am J Epidemiol* 1992; 135:266
9. Smith DE, Lewis, CE, Caveny, JL, et al. Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. *JAMA* 1994; 271:1747.
10. Nuthalapaty, FS, Rouse, DJ, Owen, J. The association of maternal weight with cesarean risk, labor duration, and cervical dilation rate during labor induction. *Obstet Gynecol* 2004; 103:452.