



Isar

Indian Society for  
Assisted Reproduction

T H E N E W S L E T T E R

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## The Visionary & The Founder

ISAR'S Origins



## North-East State Chapter Contribution

# OBESITY & INFERTILITY



disruption or receptor mutation. According to a study published in Nature Genetics in 2000, 22 different Single Nucleotide Polymorphisms (SNP) near to MC<sub>4</sub>-R (Melanocortin 4 Receptor) gene were studied and scientists had identified an SNP named rs12970134 which was mostly associated with waist circumference because it caused permanent hunger in these people that led them to eat voraciously. This SNP was found to be highly prevalent in the group of 200 Indians in the study.

### TYPES OF OBESITY

Obesity can be Central or Peripheral based on the fat distribution. In central obesity, fat gets accumulated in the abdomen and is more prone for morbidity, whereas in peripheral obesity, fat around the thighs and buttocks has a protective effect. Various studies suggest that aging, physical inactivity, sex hormones and excess intake of carbohydrates are determinants of visceral fat accumulation around abdominal organs.

### EFFECT OF OBESITY ON FERTILITY

In females, obesity has been closely associated with Metabolic Syndrome, Insulin Resistance and Poly Cystic Ovarian Syndrome (PCOS) owing to neuroendocrine disturbances. Obesity causes increased peripheral aromatization of androgen to estrogen, while insulin resistance and hyperinsulinemia lead to hyperandrogenemia. This impairs the gonadotropin secretion. Also, it decreases other factors like Insulin-like Growth Factor Binding Proteins (IGFBP), Sex Hormone Binding Globulin (SHBG) and Growth Hormone (GH) but increases Leptin levels. Although less well documented, obesity in males impairs sperm concentration, motility, morphology and DNA fragmentation by disrupting the Hypothalamo-Pituitary-Gonadal axis through Testosterone and Oestrogen, and probably a reduced Sertoli cell function. Insulin resistance, hyperinsulinemia and hyperglycemia have shown to have a suppressive effect on sperm quantity and quality. Elevated temperatures within the scrotum, due to varicocele, using laptop on the lap, immersion in a sauna bath, etc. have deleterious effects like reduced sperm motility, increased oxidative stress and DNA fragmentation.

### INTRODUCTION

“Obesity does not run in family; it happens because nobody runs in the family!!”

Obesity has emerged as a growing public health concern over the past four decades, owing to the lifestyle changes in the population, intake of energy dense food and lack of proper health care system. WHO defines Obesity and Overweight as abnormal or excessive fat accumulation that presents a risk to health. Modern studies have proven that obesity is not merely a result of laziness and lack of willpower but it is a multifactorial health problem. On one hand, it causes an increase in the risks of hypertension, diabetes mellitus, coronary artery disease and malignancies like breast, endometrial and colon cancers, while on the other hand, it significantly disrupts the reproductive performance in both male and female.

### EPIDEMIOLOGY

About 13% of the world's population (11% of men and 15% of women) were obese in 2016. As per a study by ICMR INDIAB in 2015, India has a prevalence of obesity ranging from 11.8% to 31.3%.

### OBESITY IN THE INDIAN SUBCONTINENT

Asian population, particularly Indians, have a greater amount visceral adipose tissue compared to Europeans and African population. Also they have a genetic tendency towards central obesity. Leptin, also known as the “Ob Gene”, is a hormone located on chromosome 7 that balances food intake and energy expenditure. In experimental mice models, leptin has been found to cause obesity either due to signal



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### EFFECT OF OBESITY ON ASSISTED REPRODUCTIVE TREATMENT OUTCOME

Obese women respond poorly to ovulation induction, require higher doses of gonadotropins, longer duration for follicular development and yield less oocytes. It also leads to lower embryo quality, reduced pregnancy and live-birth rates and higher rates of miscarriages. Obesity, per se, may cause technical difficulties like ultrasound visualisation of the ovaries and oocyte retrieval. Whereas few studies suggest a poor endometrial receptivity in obese women, other studies blame the quality and yield of oocytes for higher rates of cycle cancellation. Raised BMI in men is associated with lower fertilization rates, poor quality embryos and reduced clinical pregnancy rates in IVF/ICSI cycles.

### HOW TO MEASURE OBESITY?

The various ways to measure obesity include – field methods like Body Mass Index (BMI), Waist circumference, Waist-to-hip ratio, Skin Fold Thickness, Bioelectrical Impedance, and more sophisticated methods like Dual Energy X-ray absorptiometry, Underwater weighing (densitometry), Air Displacement Plethysmography, Dilution method (Hydrometry), Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI).

Body Mass Index (BMI), previously termed as the Quetelet Index is calculated by dividing a person's weight (in kilograms) by the square of the height (in metres).

**Table 1 :- WHO classification of BMI.**

BMI (kg/m <sup>2</sup> )	CLASSIFICATION
< 18.5	Underweight
18.5-24.9	Normal weight
25-29.9	Overweight
≥ 30	Obesity

These values were also adopted by the National Heart, Lung and Blood Institute (NHLBI), NIH, North American Association for the Study of Obesity and published in their practical guide in the year 2000. In a consensus meeting in New Delhi in November 2008, as well as in Asia-Pacific Recommendations on "How to define Obesity?" in 2008, the cut-off for BMI for Asian population was set at a lower limit to include more number of people in the high risk group.

**Table 2 :- Asia-Pacific Classification of BMI.**

Limitations of BMI include failure to distinguish between body fat and lean body mass and it does not predict body fat in the elderly as it is in younger and

BMI (kg/m <sup>2</sup> )	CLASSIFICATION
< 18.5	Underweight
18.5-22.9	Normal weight
23-24.9	Overweight
≥ 25	Obesity

middle aged people. On the other hand, CT scan and MRI are considered to be the most accurate as they allow for measurement of fat of specific body compartments. However, disadvantages are high expense and limited mobility of the instruments and contraindication of CT Scan in pregnancy.

### WHY AND HOW TO TACKLE OBESITY?

Weight loss of 5-10% significantly improves endocrine parameters and hence, improves the reproductive outcome[10]. Various options to tackle the problem include lifestyle intervention (Diet, Exercise, Behaviour therapy), Pharmacotherapy and Surgery.

#### I. Lifestyle Intervention

##### a) Diet

The Obesity Guidelines recommends an energy deficit of 500-750 kcal/d that leads to an average weight loss of 0.5-0.75 kg/week[11]. Daily energy requirement can be calculated by the Harris-Benedict equation, the WHO equation[13] or the American Gastroenterological Association Dietary Guidelines.

**Table 3 :- The four types of dietary regimens are as follows-**

Diet	Daily Calorie Composition	Mean weight loss	Advantages	Disadvantages
Low Calorie	800-1500 kcal 55-60% carbohydrate <30% fat	~10% in 3-12 months.	Reduction in Blood Glucose, Serum lipids and Blood Pressure.	Difficult compliance in the long run.
Low Fat	1000-1500 kcal 20-25% fat	~5% in 2-12 months.	Reduction in Blood Glucose, Blood Lipids and Blood Pressure.	Less Palatable. Increases triglycerides.
Low and very low Carbohydrate	1000-1500 kcal 60-150g (low carbohydrate)	~5% in 2-12 months.	Faster initial weight loss than low fat diets. Reduces Blood Glucose, Blood	Ketosis when carbohydrate intake <50g/day.

### b) Physical Activity and Exercise

The American College of Sports Medicine (2009) recommended that exercise of moderate intensity for 150-250 min per week helps to prevent obesity. For maintenance of weight after a significant reduction, at least 200-300 min per week moderate intensity aerobic exercise is required. Exercise increases satiating efficiency of a fixed meal and thereby reduces the food intake.

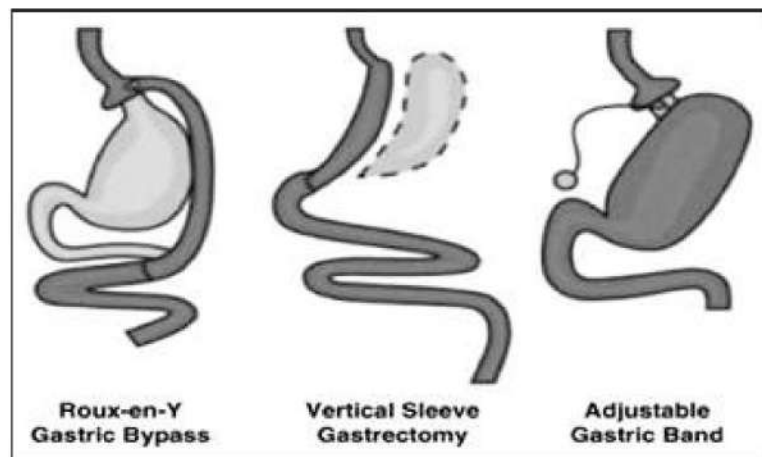
### c) Behaviour Therapy

It involves strategies to modify the eating habits and physical activity like weekly goal setting, problem solving, cognitive restructuring and coping with dietary lapses.

II. Pharmacotherapy-Pharmacotherapy has been recommended for patients who cannot achieve adequate weight reduction with only lifestyle modification. It helps the patients to adhere to dietary recommendations by increasing satiety or by reducing hunger. It also counteracts the hormonal alterations caused by weight loss and calorie restriction. Various drugs that may be used include – Orlistat, Cetilistat, Sibutramine, Lorcaserin, Phentermine/Topiramate, Naltrexone/Bupropion, Liraglutide. In a consensus meeting of ESHRE/ASRM in 2007, Orlistat and Sibutramine have shown a weight-loss independent effect on androgens and insulin resistance. Orlistat is a gastrointestinal lipase inhibitor that causes 2.9-3.4% weight loss of the initial body weight. However it has side effects like steatorrhea, flatulence, fecal incontinence and increased defecation. Although FDA approved, it was banned in 2010 due to reports of hypertension and heart problems. Cetilistat is a new drug that works in similar fashion like Orlistat. Sibutramine is an appetite suppressant that was banned due to its association with vascular accidents.

III. Bariatric Surgery-According to United States National Institute of Health (NIH) 2013 guidelines, bariatric surgery is recommended for patients with BMI  $\geq 40$  kg/m<sup>2</sup> without comorbidities or  $\geq 35$  kg/m<sup>2</sup> with comorbidities who fail to respond to non surgical methods. A recent Asian Concensus Meeting on Metabolic Syndrome recommended that surgery can be considered for Asian adults with BMI  $\geq 30$  kg/m<sup>2</sup> with central obesity and atleast two features of metabolic syndrome. Surgery can be reversible restrictive or irreversible malabsorptive. The most commonly used procedures include Roux-en-Y gastric bypass, Gastric banding and sleeve gastrectomy and less frequent procedure like biliopancreatic diversion. Roux-en-Y gastric bypass is the gold standard, it produces a median weight loss of 31.5% of initial weight at 3 years.

**Figure 1:** Types of commonly performed Bariatric Surgeries



### FERTILITY AND PREGNANCY AFTER BARIATRIC SURGERY

Various studies have shown improvements in sex hormone profile, improvement in luteal function and a shortening of follicular phase length that led to regular menses after bariatric surgery. The improvement in fertility is irrespective of the type of bariatric surgery performed but is related to the amount of weight lost and the pre-conceptional BMI achieved. As per guidelines, all women of reproductive age undergoing bariatric surgery should be advised contraception and pre-conceptional counseling alongwith life-long nutrient supplementation. As per the American College of Obstetrics and Gynaecology (ACOG) and the European Association for the Study of Obesity, the first post-surgical year is a catabolic time frame, when pregnancy may compromise fetal nutritional supply. Hence, post-operatively, contraception for 1 to 1.5 years is needed alongwith ultrasound monitoring for fetal growth.

### CONCLUSION

The detrimental effects of obesity on different systems are being studied extensively. Irrespective of the gender, obesity compromises the reproductive performance in natural as well as assisted conception. The main pathology behind obesity, i.e. visceral fat, is best assessed by imaging. Treatment strategy involves lifestyle modification, pharmacotherapy and surgery. After bariatric surgery, adequate contraception and pre-conceptional counselling is sine-qua-non. Newer obstetric challenges may pave the path to specific recommendations pertaining to reproductive health management after bariatric surgery.