پژوهشگاه رویان
معاونت آموزشی

گزارش صبحگاهی

ارتباط چاقی با ناباروی

دبیر علمی: دکتر فیروزه غفاری

سخنران: دکتر مژگان سلطانی

دبیر اجرائی: معصومه حاتمی

۱۵ اسفند ۱۴۰۲

پژوهشگاه رویان

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INTRODUCTION

- There has been a rising trend in obesity and overweight population in the past few years which has become an epidemic worldwide .
- In 2016, more than 1.9 billion adults aged 18 years and older were overweight.
- Women are affected most due to their small size and extra weight which is gained with each pregnancy.
- Obesity plays a significant role in reproductive disorders, particularly in women. It is associated with anovulation, menstrual disorders, infertility, difficulties in assisted reproduction, miscarriage, and adverse pregnancy outcomes

OBESITY AND IMPAIRED REPRODUCTIVE POTENTIAL

- A Dutch study prospectively evaluated the effect obesity has on fecundity and found that an increase in waist–hip ratio (WHR) by 0.1 unit led to a decrease in the probability of conception by 30% per cycle.
- Obese women suffer from menstrual cycle disturbances and anovulation more often than nonobese women.

OBESITY AND IMPAIRED REPRODUCTIVE POTENTIAL

- Negative effect of excess fat was reinforced by the fact that weight-loss programs led to the resumption of normal menstrual cyclicity , normal ovulation, and natural pregnanciesObese women are also found to have increased chances of miscarriages following natural conception, ovulation induction, and assisted conception

OBESITY AND IMPAIRED REPRODUCTIVE POTENTIAL

- A recent meta-analysis found an increased risk of miscarriage among women (BMI 30 kg/m2) undergoing assisted conception [in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI)].

- A further meta-analysis also found that patients with a BMI of 25 kg/m2 were found to have a significantly elevated odds of miscarriage regardless of the mode of conception.

FERTILITY RISKS IN OBESITY

- Higher rates of infertility
- Subfertility (increased time to pregnancy)
- Early pregnancy loss
- Fetal deaths, stillbirths, and neonatal deaths
- Congenital anomalies
- Pregnancy complication
- Greater risk of cesarean delivery and poor wound healing
- Increased difficulty and shorter duration of breastfeeding.

DIAGNOSIS AND CLASSIFICATION OF OBESITY

- As excess fat is the main variable that defines obesity, diagnosis of obesity requires measurement of body fat. There are several methods available to assess body fat.

  - *Body Mass Index :* BMI is useful but a crude indicator of obesity. It does not distinguish dangerous adiposity (such as waistline intra-abdominal fat) from potentially less harmful fat in other areas of the body or healthy ‘‘nonfat’’ body mass such as muscle.

  - *Distribution of Fat :* Fat deposition in abdominal or visceral region is important clinically as it plays the most significant role in the pathogenesis of metabolic syndrome.

TABLE 1: Comparison of body mass index (BMI) among European and Asian populations with respect to cardiovascular risk [World Health Organization (WHO), 2000].

Classification	*WHO BMI (kg/m²)*	*Asian BMI (kg/m²)*	*Cardiovascular risk*
Underweight	<18.5	<18.5	Low
Normal range	18.5–24.9	18.5–22.9	Average
Overweight	25–29.9	23–24.9	Increased
Obese I	30–34.9	25–29.9	Moderate
Obese II	35–39.9	= 30	Severe
Obese III	= 40		Very severe

DIAGNOSIS AND CLASSIFICATION OF OBESITY

- *Waist Circumference Measurement :* Waist circumference cutoff for increased risk of metabolic disease in Americans has been found to be ≥102 cm in men and ≥88 cm in women.
- *Waist–hip Ratio :* In Caucasians, a WHR >1 for men and WHR >0.85 for women are used as a measurement of visceral adiposity. However, waist circumference is preferred over WHR for measuring abdominal obesity

CONCEPT OF NORMAL-WEIGHT OBESITY

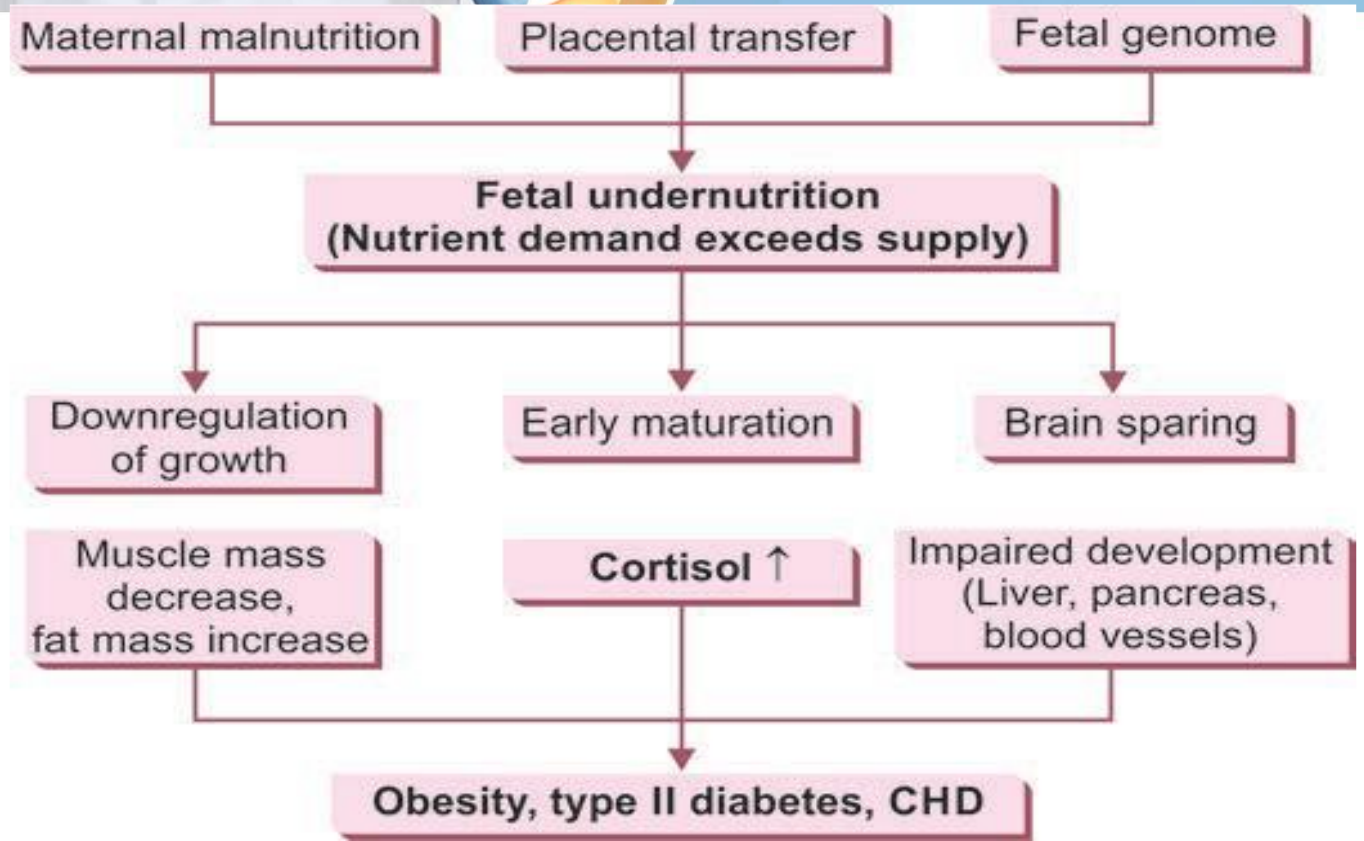
- normal-weight obesity (NWO) syndrome is a condition in which a person has an adequate BMI but an increased body fat percentage and a greater risk of developing noncommunicable chronic diseases. It is important to accurately diagnose individuals with excess body fat using more precise parameters other than BMI.

PATHOPHYSIOLOGY OF OBESITY
In Utero Programing

- Undernutrition and unfavorable intrauterine environment during early life can cause irreversible changes (in both structure and function) in developing systems of the fetus (i.e., programing).

- Research has found that children born small for gestation tend to develop adiposity an hyperinsulinemia . Precocious puberty (appearance of pubic hair before 8 years of age) has also been demonstrated as a part of this sequence, as well as anovulatory and hyperinsulinemia hyperandrogenism in late adolescence and adulthood.

Fetal origin of obesity.



ROLE OF GUT MICROBIOME IN ORIGIN OF OBESITY

- The gut microbiome is now recognized as a separate endocrine system and is involved in the body's homeostatic process.

- A diet loaded with excess fat increases gut permeability, resulting in increased levels of lipopolysaccharides in the body's systemic circulation. Lipopolysaccharides are endotoxins that are linked to inflammation-related processes such as obesity and insulin resistance.

ROLE OF GUT MICROBIOME IN ORIGIN OF OBESITY

- Altered gut microbiome influences gut epithelium and motility, leading to the extraction of more calories from food, increased calorie absorption, and fat storage.
- Gut microbiota also affects many other regulatory processes in the body, such as mitochondrial fatty acid oxidation, ketogenesis, glucose uptake/insulin sensitivity, insulin secretion, increased lipogenesis, and cholesterol and triglyceride synthesis.
- These processes all contribute to metabolic disease and obesity

Effects of a healthy gut microbiota

Healthy gut microbiota

- ↓ Gut permeability
- ↓ Endotoxemia
- ↓ Pro inflammatory cytokines
- ↑ Insulin sensitivity

Gut microbial ecology

Anti-inflammatory

Pathobionts- bacteroides, *clostridium difficile*

Symbionts- lactobacilli, bifidobacteria

Pro-inflammatory

Bacterial gene count

Dysbiotic gut microbiota

- ↑ Gut permeability
- ↑ Endotoxemia
- ↑ Proinflammatory cytokines
- ↓ Insulin sensitivity

High-fat sugar diet, stress, antibiotics

Environmental factors

Improved gut and metabolic health

Healthy diet lifestyle, prebiotics, probiotics, fecal transplantation

Metabolic diseases
Type II DM, CVD, IBD

ENDOCRINE FUNCTION OF ADIPOSE TISSUE—THE ROLE OF ADIPOKINES

- Adipose tissue is a highly developed, endocrine and paracrine organ, which produces a variety of adipokines such as leptin, adiponectin, resistin, visfatin, omentin …
- Adipokines function as signaling molecules (hormones), and any abnormality in adipokines can cause inflammation and abnormal cell signaling which in turn can negatively affect cell metabolism and function.

ADIPOKINES : *Leptin*

- Leptin is a peptide hormone with 167 amino acids and a molecular weight of 16 kDa and is synthesized from the “ob” gene in adipocytes. Its secretion is pulsatile, which increases with food intake and decreases during starvation. It thus reduces food intake and maintains energy homeostasis.

ADIPOKINES : *Leptin*

- It is a key signaling protein, relays the magnitude of the peripheral energy stores to the brain (hypothalamus), and also has metabolic and reproductive functions. Leptin has varied effects on reproduction and the target organs include hypothalamus, ovary, and endometrium.

- In the hypothalamic–pituitary axis, leptin has a stimulatory effect. It has been hypothesized that an elevated leptin level beyond a certain threshold is required for the activation of the hypothalamic–pituitary axis and the onset of puberty.

ADIPOKINES : *Leptin*

- The nutritional level of a person influences this central effect, with fasting causing a decrease in leptin levels resulting in the inactivation of gonadotropin-releasing hormone (GnRH) pulsatility.

On the contrary, in well-fed state or energy-positive state also, no effect on GnRH secretion is

seen due to the development of central leptin resistance leading to dysregulatory state in obesity.

ADIPOKINES : *Leptin*

- Leptin also influences steroidogenesis and folliculogenesis in ovarian cells. It modulates the stimulatory actions of gonadotropins and regulates perifollicular blood flow by promoting endothelial cell proliferation and angiogenesis.

- Leptin also regulates the levels of reproductive hormones such as progesterone during the menstrual cycle and estradiol and human chorionic gonadotropin (hCG) during pregnancy

ADIPOKINES : *Leptin*

- Studies have shown that leptin may also affect oocyte maturation and early embryo development. T
- he endometrium and developing placenta express both leptin and its receptor40 suggesting a possible role in the implantation of embryo and fetal growth.
- Leptin is produced in increased amounts with increasing adipose tissue.
- With high leptin levels as seen in obesity, a dysfunctional energetic state occurs suggesting a possible development of leptin resistance and altered leptin receptor sensitivity.

Effects of the adipokines on reproduction.

TABLE 2: Effects of the adipokines on reproduction.

Adipokines	*Serum levels in obesity*	*Effect in obesity*
Leptin[41]	Increase	• Dysregulation of GnRH secretion • Altered ovarian steroidogenesis • Dysregulation of folliculogenesis and perifollicular blood flow
Adiponectin[42]	Decrease	• Increased insulin resistance • Interference with folliculogenesis • Modulation of sex steroid secretion
IL-6[43]	Increase	• Increased insulin resistance • Impaired LH secretion • Impaired response to LH • Impaired estrogen secretion
PAI-1[44]	Increase	• Increased PAI-1 directly correlate with the development of metabolic syndrome • Increased miscarriage risk
TNF-α[45]	Increase	• Reduced insulin sensitivity • Inhibition of gonadotropin secretion • Impaired steroidogenesis • Induces corpus luteum regression • Impaired endometrial development

(GnRH: gonadotropin-releasing hormone; IL-6: interleukin 6;
LH: luteinizing hormone; PAI-1: plasminogen activator inhibitor 1; TNF: tumor necrosis factor)

Pathophysiology of obesity and female fertility

Pathophysiology of obesity and female fertility may be considered at the following levels:

- ✓Central effects on the hypothalamus and pituitary
- ✓Peripheral effects on the ovary and oocyte
- ✓Direct effects on the embryo
- ✓Effects on the endometrium
- ✓Effects on pregnancy.

Effect of Obesity on Hypothalamus and Pituitary

- Obese women have higher circulating levels of free fatty acids, which stimulate increased insulin release and also lead to insulin resistance which together combined lead to hyperinsulinemia
- The ovary is a target organ for insulin action via both insulin receptor and insulin-like growth factor 1 (IGF-1) receptor. Hyperinsulinemia, as seen in obesity, stimulates androgen

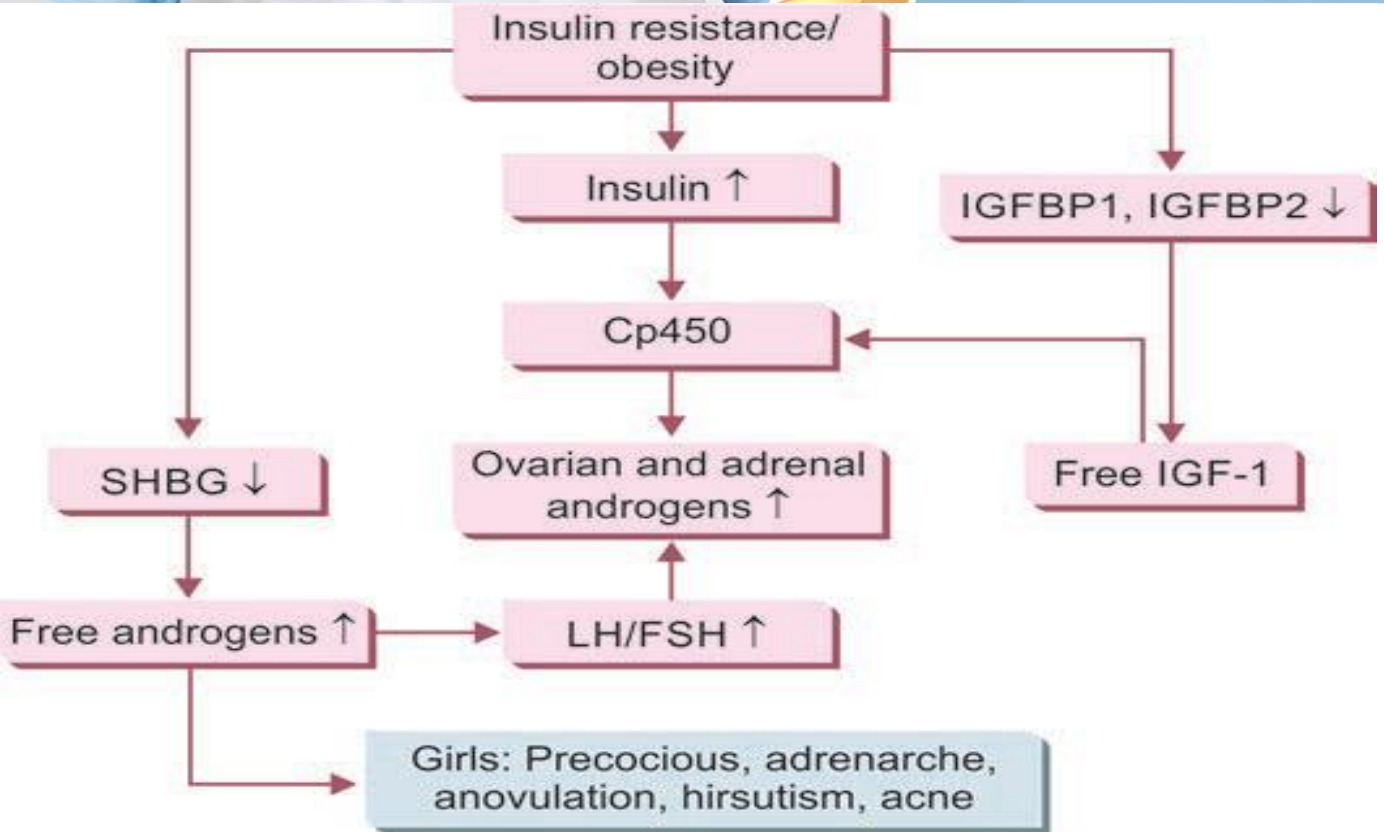
- production from the ovary directly by activating ovarian theca cells or indirectly by suppressing the synthesis of sex hormone-binding globulin (SHBG) from liver which in

- turn leads to increased free androgen levels. It also decreases the synthesis of IGF-binding proteins 1 and 2 in liver leading to high free IGF-1 levels which in turn stimulates androgen synthesis from adrenals and ovarian theca cells.

Effect of Obesity on Hypothalamus and Pituitary

- Raised androgen is aromatized to estrogen at increasing rates in the periphery owing to excess adipose tissue. This leads to negative feedback on the hypothalamic–pituitary–ovarian (HPO) axis and affects gonadotropin production .This manifests as *menstrual abnormalities* and *ovulatory dysfunction*.
- Furthermore, in obesity, there is altered hypothalamic leptin receptor expression. An increased neuropeptide-Y level is seen in the hypothalamus, leading to reduced central leptin sensitivity and decreased GnRH pulsatility.

Obesity leading to dysregulation of hypothalamic–pituitary –ovarian axis.



Effect of Obesity on Ovary and Oocyte Quality

Ovarian responsiveness to gonadotropins is impaired in obese women. Possible reasons suggested are as follows:

- Altered follicular environment with high levels of triglycerides, insulin, and inflammatory markers such as C-reactive protein (CRP)
- Elevated follicular leptin levels have an inhibitory effect on follicle-stimulating hormone (FSH).
- Insulin resistance has been associated with a relative gonadotropin resistance.
- Altered pharmacodynamics of gonadotropins though suggested has not been found to be responsible for increased dose requirement in obese women.

Effect of Obesity on Ovary and Oocyte Quality

- Relative hyperestrogenemia is found to be detrimental to endometrial receptivity.
- Elevated insulin levels have been associated with a reduced glycodelin and insulin-like growth factor binding protein 1 (IGFBP1).
- Elevated levels of acute-phase proteins and proinflammatory cytokines [including IL-6, plasminogen activator inhibitor 1 (PAI-1) and TNF-α]; these inflammatory markers are thought to exert a negative effect upon implantation and early embryonic development.
- Altered endometrial gene expression

Animal studies have shown:

- Poor endometrial decidualization in obese mice Decreased implantation sites
- Decreased response to hormonal stimulation in the endometrial stromal cells.
- Poor embryo-endometrial crosstalk, as embryo quality also suffers in obesity
- Dysregulation of leptin expression in endometrium

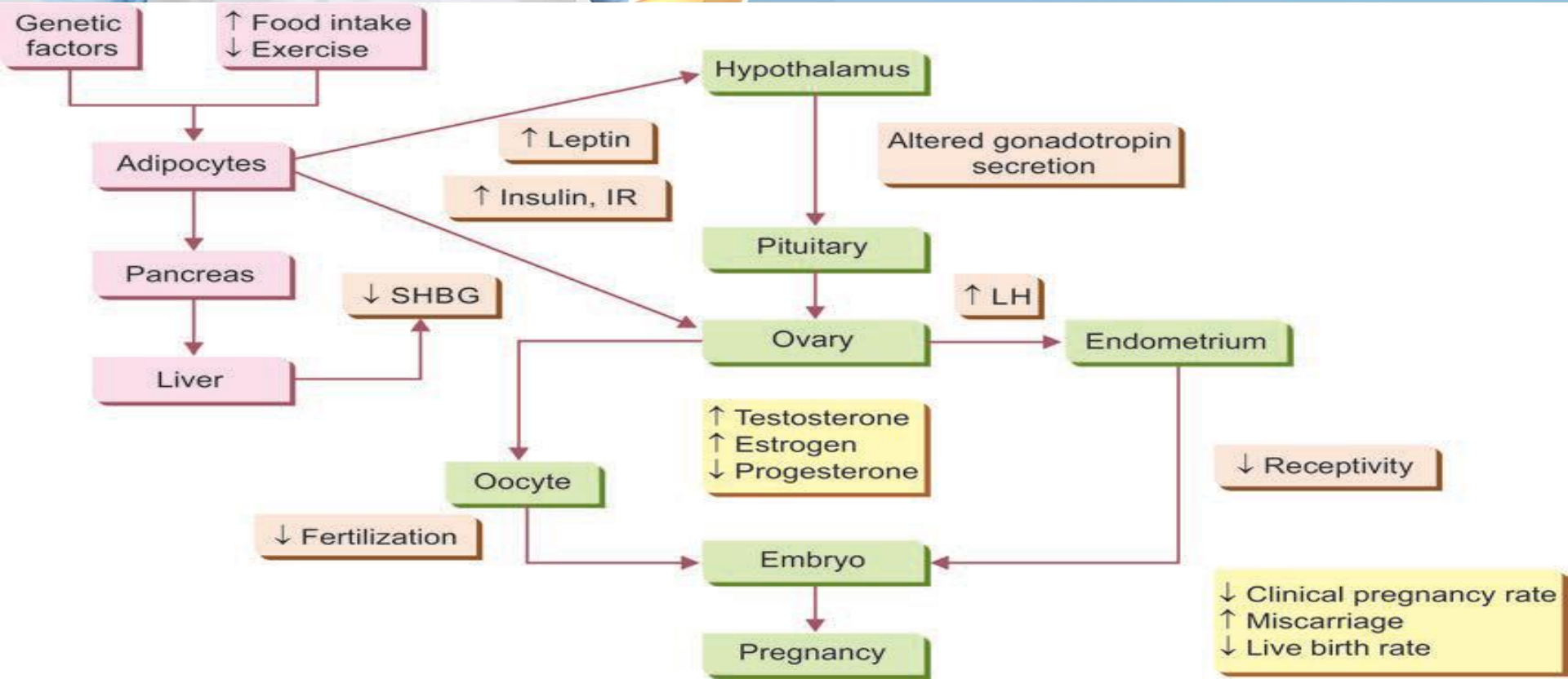
Effect on Pregnancy

- Decidualization and implantation defects may negatively affect the placentation process. Many of the pregnancy complications seen in obese women are linked to placental dysfunction, including stillbirth and pregnancy-induced hypertension.
- All the causes listed above may result in poor implantation, placentation, and adverse pregnancy outcomes.

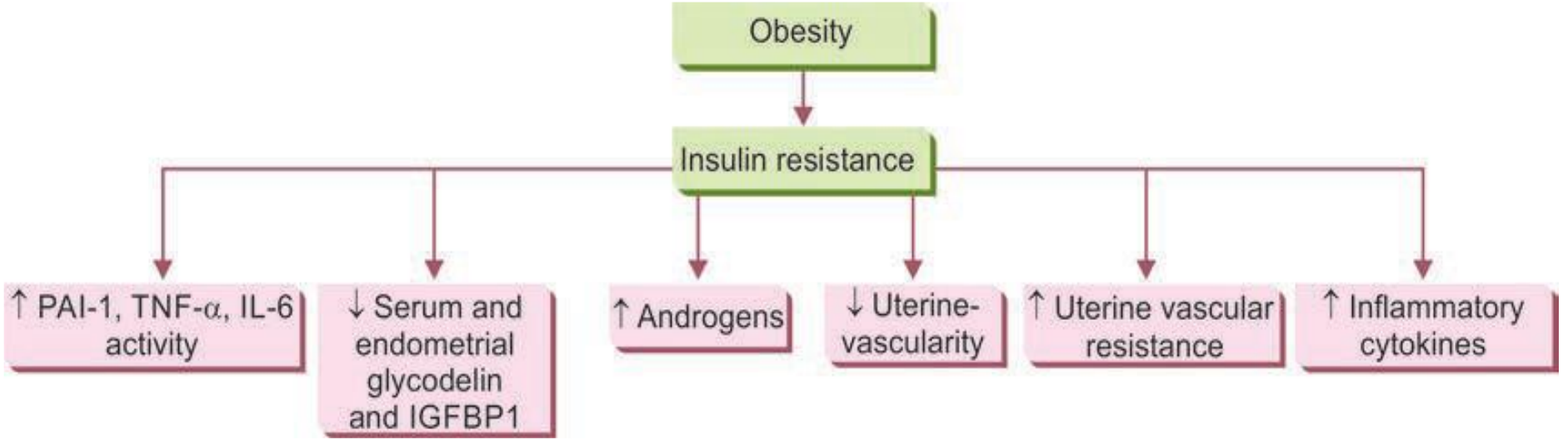
OBESITY AND POLYCYSTIC OVARY SYNDROME

- Obese women with polycystic ovary syndrome (PCOS) have a more severe phenotype and had a higher prevalence (78%) of:
  - Disturbed menstrual cyclicity
  - Increased insulin resistance
  - Impaired response to gonadotropin during superovulation
  - Increased chance of cycle cancellation
  - Reduced ovulation rates
  - Reduced chance of treatment success following assisted reproductive technology (ART)
  - Increased risk of miscarriage.

Pathophysiology of obesity and its effect on fertility



Possible causes of miscarriages in obese women.



RESPONSE TO GONADOTROPIN STIMULATION AND CYCLE CANCELLATION

- Obesity impairs ovarian responsiveness to gonadotropin stimulation, requiring higher dosages and longer stimulation, and fewer mature follicles are obtained. Several studies have documented a higher risk of cycle cancellation with increasing maternal BMI, with adjusted odds ratios (ORs) for women with BMI > 40 kg/m2 compared with normal-weight women ranging from 2.73 [95% confidence interval (CI) 1.49–5.00] to 3.46 (95% CI 1.85–6.49)

cohort study of women with PCOS

- In a cohort study of women with PCOS undergoing ovulation induction with either clomiphene or gonadotropins, it was observed that elevated BMI negatively affected ovulation rates. In this study,75 obese patients had significantly lower ovulation rates at 6 months of treatment: 79% in women with a BMI of 18–24 kg/m2 compared with 15.3% with a BMI of 30–34 kg/m2 and 12% if BMI is 35 kg/m2. Some authors, however, have been unable to demonstrate any difference in ovarian response to stimulation in obese women

Fertilization Rates

- Obesity alters oocyte morphology,78 reduces fertilization in some but not all studies, and impairs embryo quality in women less than 35 years of age.

Implantation and Pregnancy Rates (Embryo vs. Endometrium)

- A national study of ART in the United States reported reduced clinical pregnancy rates with increasing BMIs with the use of autologous but not donor oocytes and reduced live birth rates with increasing BMIs regardless of oocyte source and embryo status.
- Even studies limited to obese women using donor oocytes and eliminating the potential effect of older maternal age and lower quality of the embryos have reported significantly reduced implantation and pregnancy rates and higher abortion rates

- . This suggests that oocyte quality is a primary, but not the only factor impairing IVF outcomes in obese women using autologous oocytes.
- Obesity also appears to alter endometrial receptivity during IVF since third-party surrogate women with a BMI >35 kg/m2 have a lower live birth rate (25%) compared with those with a BMI <35 kg/m2.

Miscarriage Rate

- Obesity has been linked with increased pregnancy loss in many except few studies. A meta-analysis in 2008 of both spontaneous and assisted reproductive conception showed that women with a BMI >25 kg/m2 had a significantly higher risk of miscarriage at <20 weeks of gestation, with an OR of 1.67.
- A meta-analysis of 33 IVF studies including 47,967 cycles concluded that overweight or obese women have a higher rate of miscarriage compared with normal-weight women (BMI <25 kg/m2).

- In women with a history of recurrent pregnancy loss (RPL), obesity is a known risk factor for miscarriage in a subsequent pregnancy.
- A chromosomal analysis of 117 miscarriage specimens from patients with RPL demonstrated that obese women had a much higher rate of euploid miscarriage, again suggesting a potential independent effect of obesity on the endometrium.

Live Birth Rate

- Obese women undergoing IVF/ICSI have **lower live birth** rates. It is thought that this is the cumulative effect of lower implantation and pregnancy rates, higher miscarriage rates, and increased obstetric complications.

Technical Difficulties During In Vitro Fertilization

- Obese women are significantly more likely to encounter difficulty in observing the air bubble during ultrasound guided embryo transfer and are more likely to have blood on or in the catheter after embryo transfer.

BOX 1: Summary of effects of obesity on assisted reproductive technology.

Effect of obesity on ART

- Impaired USS image quality due to adipose tissue[77]
- Increased duration of stimulation
- Increased total gonadotropin dose required[70]
- Increased follicular asynchrony[70]
- Increased cycle cancellation[70]
- Poor response to superovulation[75]
- Reduced follicular hCG concentration on the day of ovum pickup[95]
- Relative reduction in the number of cumulus–oocyte complex recovered at ovum pickup[9]
- Relative reduction in metaphase II oocytes recovered at ovum pickup[9]
- Relative number of surplus good quality embryos available for cryopreservation[80]
- Reduced pregnancy rates[9]
- Increased miscarriage rates[90]

(ART: assisted reproductive technology; hCG: human chorionic gonadotropin; USS: ultrasound scan)

OBESITY AND MALE INFERTILITY

- Obesity has a negative effect on male fertility. In 2006, Sallmen et al. illustrated a dose–response relationship between BMI and male infertility, with worsening male fertility for every three-point increase in BMI >25 kg/m2, with an OR of 1.12. These results were later confirmed in several other studies.
- The mechanism suggested for the effect of obesity on male fertility includes thermal effects, hyperestrogenism, hypogonadotropic hypogonadism, diabetes mellitus, sexual dysfunction, and sperm epigenetic perturbations

Sperm Parameters

- The impact of obesity on sperm parameters is complex and likely multifactorial. Obese men are at a higher risk of:
- Oligozoospermia
- Decreased total progressive motility
- Raised deoxyribonucleic acid (DNA) fragmentation index

Sperm Parameters

The mechanisms suggested are as follows:

- Obesity is associated with the risk of diabetes and insulin resistance. Hyperinsulinemia leads to a reduction of sex hormone-binding globulin levels. This allows greater free testosterone levels, which aromatizes to estrogen in the
- periphery. This hyperestrogenemic state has a detrimental effect on the androgen axis affecting semen quality.
- Hyperestrogenemia downregulates the release of kisspeptin from kisspeptin neurons and decreases the activity of hypothalamic–pituitary–gonadal (HPG) axis by negative feedback and thus of FSH and luteinizing hormone (LH).103
- Leptin resistance seen in obese men with hyperleptinemia results in the failure of leptin to stimulate HPG axis. Sleep apnea is commonly found in obese men. Nocturnal sleep disturbances affect nocturnal LH pulsatility reducing testosterone levels. Intermittent hypoxia associated with sleep apnea can affect gene expression, sperm motility, and fertility.

Sperm Parameters

- Sleep apnea is commonly found in obese men. Nocturnal sleep disturbances affect nocturnal LH pulsatility reducing testosterone levels. Intermittent hypoxia associated with sleep apnea can affect gene expression, sperm motility, and fertility. Many environmental toxins are fat-soluble favoring adipose tissue for their accumulation making obese men susceptible to perturbation of the male endocrine axis and spermatogenesis.
- Increased lower abdominal and thigh fat leads to increased testicular temperature. This negatively impacts both testosterone synthesis and spermatogenesis.
- Obese men often suffer from sexual dysfunction resulting from decreased testosterone levels and vascular endothelial dysfunction secondary to inflammation.
- Obesity alters fertility by affecting the epigenetic patterns of sperm, that is, sperm micro-RNA content and DNA methylation variations. These important markers in sperm, when altered, are thought to be implicated in abnormal phenotypes in the offspring and perturbations In embryogenesis

Male Obesity and Advanced Reproductive Technology Outcome

- The impact of male obesity on ART outcome is conflicting. Some studies suggest that obese men undergoing ART have a statistically significant decrease in live birth rate compared with normal-weight men. Another study has reported a lower pregnancy rate in males undergoing IVF, but no significant difference if ICSI was used for ART therapy. In contrast, Thomsen et al. have reported no decrease in semen quality or IVF outcome in obese men undergoing ART. Further research is required to assess the exact impact of male obesity on ART outcome.

Male Obesity and Advanced Reproductive Technology Outcome

- Despite the associations between obesity and semen parameters, it is clear that men with high levels of body fat are, in general, still capable of siring offspring, which may be accounted by the fact that in some cases lower maternal age results in improved oocyte quality, which may independently improve outcomes but may also provide an improved opportunity for correction of some defects, such as sperm epigenetic abnormalities, after fertilization.

Management

Lifestyle Modification

- Weight management can be achieved through a lifestyle modification program that combines dietary modification, physical activity, and behavioral interventions, including psychological, behavioral, and stress management strategies. Current recommendations for lifestyle modification for obesity include a weight loss of 7% of body weight and increased physical activity to at least 150 minutes weekly of moderate activity such as walking.

Management

Diet and Weight Loss

- Calorie restriction is the mainstay of successful weight loss. Calorie restriction of up to 500–1,000 kcal/day from daily dietary intake leads to a weight loss of 0.5–1 kg weight loss per week. Dietary composition plays a less important role in weight loss. Though few authors have published about "fertility diets," characterized by low content of trans fats and animal protein and more of low-glycemic carbohydrates, high-fat dairy, and multivitamins. Similarly few observational studies have suggested the potential benefits of the Mediterranean diet, and found a lower risk of infertility and increased chances of pregnancy on adhering to the diet.

Exercise and Weight Loss

- Physical activity alone is less effective in producing weight loss. The addition of physical activity on top of a diet modification enhances weight loss.
- Studies examining the effect of physical activity on obese infertile population independent of weight loss have shown improved fertility. A recent study reported more than threefold higher pregnancy and live birth rates in obese women who exercised regularly compared with obese women who were not physically active. Because exercise reduces the oxidative stress characteristic of overweight and obesity, it may represent the best therapy currently available.

Exercise and Weight Loss

Exercise Programs

- At present, there are no evidence-based guidelines on exercise training programs to improve fertility. The following is the recommended framework for prescribing aerobic exercises to people who are overweight and obese.
- Patients starting a program of moderate exercise (e.g.,walking) do not require prescreening, whereas those starting vigorous-intensity programs should be screened for cardiovascular and respiratory adequacy.

Sperm Parameters

TABLE 3: Recommended exercise program for weight loss in obese.

	Recommendations
Frequency	≥5 days per week
Intensity	• Moderate to vigorous intensity • If body mass index (BMI) >35 kg/m^2, vigorous intensity is not appropriate • Gradual shift to vigorous intensity after an initial 4–12-week period of moderate-intensity activity
Time	The ultimate minimum goal should be to achieve 30–60 minutes of continuous aerobic exercise 5–7 times per week
Type	• *Aerobic isotonic exercise* is of the greatest value for persons who are obese • *Brisk walking*: Ideal for obese, sedentary individuals constitute moderate-intensity physical activity • *Cycling, swimming, water aerobics*: Ideal for BMI >35 kg/m^2 and joint problems constitute moderate-intensity physical activity • *Anaerobic isotonic exercises*, e.g., weight lifting and resistance training can be cautiously added as an adjunct after the aerobic goal described above is achieved • Not indicated for patients with hypertension and heart diseases

Drugs for Weight Loss

- Few medicines are available for the treatment of obesity.
- Examples of the (FDA)-approved drugs that may be considered for the long-term treatment of obesity include orlistat, lorcaserin, the combinations of phentermine and extended-release topiramate, and the fixed-dose combination of bupropion and naltrexone.
- According to Endocrine Society Guidelines, pharmacotherapy for weight loss is indicated in patients with a BMI ≥30 kg/m2 or ≥ 27 kg/m2 along with associated comorbidities (e.g., diabetes, hypertension).
- If a patient fails to lose at least 5% of baseline body weight, drugs should be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Drugs for Weight Loss

Weight-loss medications target important neurotransmitters involved in feeding behavior. Neurotransmitters govern the body's response to starvation and dietary intake.

- *Norepinephrine and dopamine:* Released by sympathetic nervous system in response to food intake. Fasting and starvation lead to decreased levels of these neurotransmitters.
- *Serotonin:* Low serotonin levels and high neuropeptide Y levels are associated with a craving for carbohydrate food.
- *Proopiomelanocortin* (POMC): Integrates multiple energy signals. Increased firing leads to the release of norepinephrine and dopamine and weight loss.

Drugs for Weight Loss

- β-*Endorphins:* Endogenous opioid peptide inhibits POMC firing, thus increasing appetite and cravings. Cravings for fatty and sugary foods among obese and bulimic patients involve the endorphin system.
- *Glucagon-like peptide 1* (GLP-1): It is a gut peptide. It amplifies glucose-dependent insulin release, inhibits glucagon release, suppresses appetite, and slows gastric emptying.

- Metformin has been proposed as a weight-loss medication. It is a biguanide that inhibits hepatic glucose production and increases peripheral tissue sensitivity to insulin, resulting in reduced circulating insulin and androgen levels accompanied by decreased body weight and visceral fat.

Drugs for Weight Loss

- Metformin alone is not associated with weight loss; however, when metformin is combined with a low-calorie diet, weight loss has been demonstrated.
- Drugs such as fenfluramine, dexfenfluramine, sibutramine, and rimonabant are no longer used due to adverse effects associated with them.

Mechanism of action drugs for weight loss.

TABLE 4: Mechanism of action of Food and Drug Administration (FDA)-approved drugs for weight loss.[126]

Drug	*Mechanism of action*	*Dosage*	*Side effects*	*Comments*
Orlistat	Pancreatic lipase inhibitor	120 mg b.d.	Flatulence, fecal urgency, fecal incontinence, steatorrhea	• Reduce absorption of fat-soluble vitamins • Recommended for patients with cardiovascular disease
Bupropion–naltrexone	Dopamine-NE reuptake inhibitor/ opioid receptor antagonist	360 mg/32 mg	Constipation, headache, nausea, insomnia, tremors	Weight loss: 1-year: 5%
Lorcaserin	Selective serotonin 2c receptor agonist	10 mg b.d.	Dry mouth, constipation, headache, dizziness, nausea, fatigue	Weight loss: 1-year: 5–6%
Phentermine–topiramate	Norepinephrine-releasing/Na^+ GABA modulating agent	18.5–37.5 mg/96–192 mg	• Hypertension, palpitations, tachyarrhythmia • Insomnia, dry mouth, constipation, depression, anxiety	• CI: Hypertension, glaucoma • Hyperthyroid • Weight loss: 1-year: 5–11%
Liraglutide	GLP-1 receptor agonist	3 mg s.c. daily	Nausea, vomiting, risk of pancreatitis	Recommended for patients with cardiovascular disease

(CI: contraindicated; GABA: γ-aminobutyric acid; GLP-1: glucagon-like peptide 1; NE: norepinephrine)

ROLE OF PRE- AND PROBIOTICS

- promising new treatment/preventive intervention for obesity has been proposed based on the principle of modulation of the intestinal microbial community in the form of probiotics and prebiotics in order to reduce the susceptibility to obesity.
- Probiotics are defined as "live microorganisms, which exert health benefits to host by supplying a healthier and more diverse population of microorganisms."
- Animal studies on probiotic-fed animals have shown less weight gain, fat accumulation, and white adipose tissue compared to placebo-treated animals. Specific strains belonging to *Lactobacillus* (*L. casei*, *L. gasseri*, *L. rhamnosus*, and *L. plantarum*) and *Bifidobacterium* species have been widely used as probiotic treatment.

ROLE OF PRE- AND PROBIOTICS

- Prebiotics are “nondigestible food ingredients and supplements that enhance the effect of probiotics by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon, e.g., galacto-oligosaccharides (GOSs), fructooligosaccharides (FOSs), soybean oligosaccharides, inulin, gluco-oligosaccharides, xylo-oligosaccharides, lactulose, and lactosucrose.”
- Pre- and probiotics exert their beneficial effect by changes in gut microbiota, correction of intestinal pH, lower inflammation, lower insulin resistance, and greater satiety.

MATCHING WEIGHT-LOSS MEDICATION TO A PATIENT'S PROFILE124

- Non sympathomimetic agents such as lorcaserin or orlistat should be considered for patients with a history of cardiovascular disease (CVD) or uncontrolled hypertension.
- GLP-1 agonist liraglutide should be considered as the first line in patients with diabetes; patients with both diabetes and CVD might also do well.
- For individuals with obesity and depression who are taking a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI), lorcaserin is not recommended due to the potential for serotonin syndrome. Phentermine/topiramate or phentermine alone should be considered
- Orlistat is safe for all individuals.

BARIATRIC SURGERY

- Bariatric surgery is generally considered for patients with BMI >40 kg/m2 or patients with BMI >35 kg/m2 and associated comorbidities or failure of other treatments for weight control. It is associated with significant and rapid weight loss. But, it is an expensive procedure.

BARIATRIC SURGERY

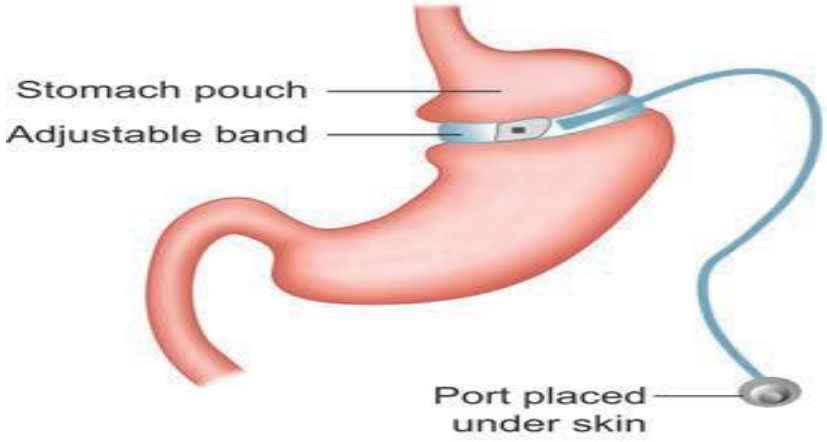
Salient features of bariatric surgery:

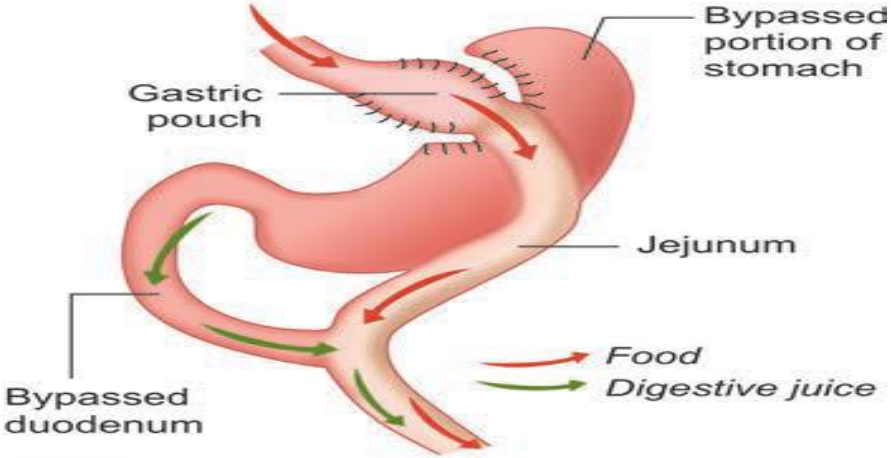
- Weight loss at 12 months, with gastric bypass averages close to 40% of the initial body weight
- Complete resolution or improvement of hyperlipidemia, hypertension, type II diabetes mellitus, and obstructive sleep apnea in >60% of patients
- Restores menstrual regularity, more ovulations owing to shorter follicular phase, reduces serum testosterone
- Improves sexual function in both males and females and increased chances of pregnancy
- Benefits maintained up to 10 years after surgery.

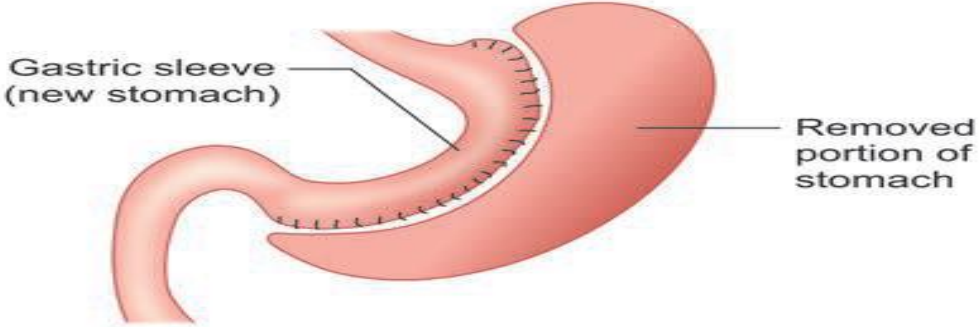
BARIATRIC SURGERY

- Bariatric surgery may not be so beneficial for male fertility. There are some case reports of worsening of semen parameters following bariatric surgery, perhaps from postoperative nutritional deficiencies, causing secondary infertility from spermatogenic arrest and impaired IVF pregnancy outcome.
- In another case series, however, semen parameters of three obese men remained stable up to 1 year following bariatric surgery. Without larger studies to confirm the impact of bariatric surgery on sperm quality, individualized management with cryopreservation of semen samples should be considered in selected circumstances.

Types of bariatric procedures.







In Vitro Fertilization and Pregnancy after Bariatric Surgery

- There are limited studies on the effect of bariatric surgery on reproductive outcome. Available evidence suggests that IVF after bariatric surgery is safe. Surgically induced weight loss reduces pregnancy complications associated with obesity such as gestational diabetes, preeclampsia, hypertensive disorders, and macrosomia.
- Surgical complications such as bowel obstructions, internal hernia, gastric ulcer, band events, and staple-line stricture can occur in pregnancy, but are rare.
- Some reports also suggest increased chances of preterm births and small-for-gestation age births in women undergoing bariatric surgery.

In Vitro Fertilization and Pregnancy after Bariatric Surgery

- Postsurgical nutritional deficiencies owing to rapid weight loss have been suggested as the possible cause and are most commonly seen in malabsorptive rather than restrictive procedures.
- Therefore, it is recommended that pregnancy should be delayed for a period of 1–2 years after the surgery and patient with supplemented with essential micronutrients. Sexually active women should be prescribed nonoral hormonal contraceptives as oral contraceptives may exhibit decreased efficacy due to malabsorption.

Preconceptional Weight Loss: Is it Worth the Wait?

- The benefits of postponing pregnancy in women to achieve preconceptional weight loss must be balanced against the risk of declining fertility with advancing age, although optimizing weight gain during pregnancy can lower the incidence of gestational diabetes.

Benefits are as follows:

- Spontaneous ovulation. Improved chance of unassisted conception
- Improved sperm count and morphology and increased testosterone levels
- Higher percentage and number of metaphase II oocytes in IVF.
- Decreased anesthesia-related morbidity associated with oocyte retrieval.
- Decreased pregnancy complications related to obesity.

Weight Loss and In Vitro Fertilization Outcome

- The research on weight loss and IVF outcomes has shown mixed results. There is insufficient evidence to suggest that preconception weight loss improves clinical pregnancy rates and live birth rates in IVF.
- In fact, the use of very low-calorie diets has been shown to have a negative effect on IVF outcomes. There are some studies that have shown improved conception rates and improved live birth rates following weight loss.
- Though outcomes after weight loss have been conflicting, we should keep in mind the possible benefits of decreased pregnancy risks and complications associated with obesity.

OBESITY AND ETHICAL DILEMMAS

- Many International Programs and National Health System recommend a BMI threshold for access to IVF to women with obesity above which fertility treatment is denied until the patient loses weight. Assuming weight loss as an achievable goal, increased anesthetic, surgical, and obstetric risks with obesity and fertility treatment are the most common cited reasons.
- There are several oppositions to this thought as denying a patient solely on the basis of arbitrary BMI cutoff violates the ethical principles of patient autonomy, beneficence/nonmaleficence, and justice. Regarding safety concerns, a recent evidence suggests that retrievals can be performed safely in women with class 3 and above obesity managed in the appropriate clinical setting.
- Individualized approach based on BMI should be practiced, patients with comorbidities should be evaluated before the day of surgery, and the anesthesia team should be consulted.

TRANSGENERATIONAL EFFECTS

- Evidence suggests that maternal obesity may confer a risk of metabolic dysfunction through multiple generations. Children born to obese mothers are more likely to develop obesity, type II diabetes, and cardiovascular disease as adults. This may be due to epigenetic modifications in utero. Some studies have suggested that metabolic syndrome may be passed down generations through aberrant oocytes with defective mitochondria.

NUTRIGENOMICS

- Nutrigenomics is a newer field of genomic science . It is the study of the effects of nutrients on the gene expression.
- Nutrigenomics aims to study the influence of one's genetic constitution on nutrient's metabolism with respect to its absorption, elimination, or biological effects using the technology of microarray and single nucleotide polymorphism (SNP).
- Due to genetic variability, every individual responds differently to a certain diet. Nutrigenomics aims to devise the means to optimize or personalize nutrition according to the patient's genotype and thus prevent obesity.
- Still in the research process, nutrigenomics will revolutionize the treatment of obesity and other nutrition-based diseases by identifying the ideal diet or nutrition based on one's genetic composition which will prevent lifestyle diseases and ensure proper function of all pathways involved in the maintenance of genome

CONCLUSION

- At the same time, pregnancy should not be delayed for weight loss due to declining ovarian reserve with increasing age. Obese women undergoing IVF should be carefully evaluated with a multidisciplinary team to determine the safety of oocyte retrieval under anesthesia.
- There is no available evidence to deny women IVF treatment based solely on BMI threshold. The obesity-associated reproductive morbidity is directly proportional to the duration of obesity.
- This makes obese children and young population, especially vulnerable in terms of their future reproductive potential. This population of obese adolescents should be the target of primary prevention such as lifestyle modification.

KEY POINTS

- Obesity is associated with decreased fertility and poor pregnancy outcomes.
- MRI is the most accurate and precise method for assessment of body fat.
- In utero programming and Gut microbiome may play an important role in onset of obesity.
- Preconception counseling and lifestyle modification are most important to improve the outcome in such patients.
- Pre-Pro Biotics and GLP-1 agonists are the promising new treatment in management of obesity.

THANK YOU FOR YOUR ATTENTION