



# Female infertility: dietary effects, effect of stress, chemical or toxicant, environment, stds, sexual violence.

Shubham Shubham<sup>1</sup>, Mayank Kumar<sup>2</sup>, KanwalPreet Singh<sup>3</sup>.

Department of Human Genetics, Guru Nanak Dev University, Amritsar<sup>1,2</sup>,

Department of Molecular Biology and Biochemistry, Guru Nanak Dev University Amritsar<sup>3</sup>.

## Abstract

There are so many factors including genetically as well as environmental which plays a crucial role in maintaining our overall health. Nature and nurture, both affect our health. Moreover, lifestyle factors, we will interact with our environment which affects our physiology. There are several factors which influence the female infertility that is lifestyle related factors, societal and professional pressure, age of child bearing in females have gradually moves to 30s. This delayed child bearing age with modern lifestyle provides the several lifestyle and genetic disturbances which affect the infertility. On the other hand, recent studies reveals that the correlation between lifestyle, environment as well as female reproductive health, where as the experimental studies also demonstrated the mechanism of action on animal models. In this paper we reveal interconnection of lifestyle and environmental factors with certain endocrine pathways and also demonstrate how this will affects the physiology of female's body in long term, causing infertility

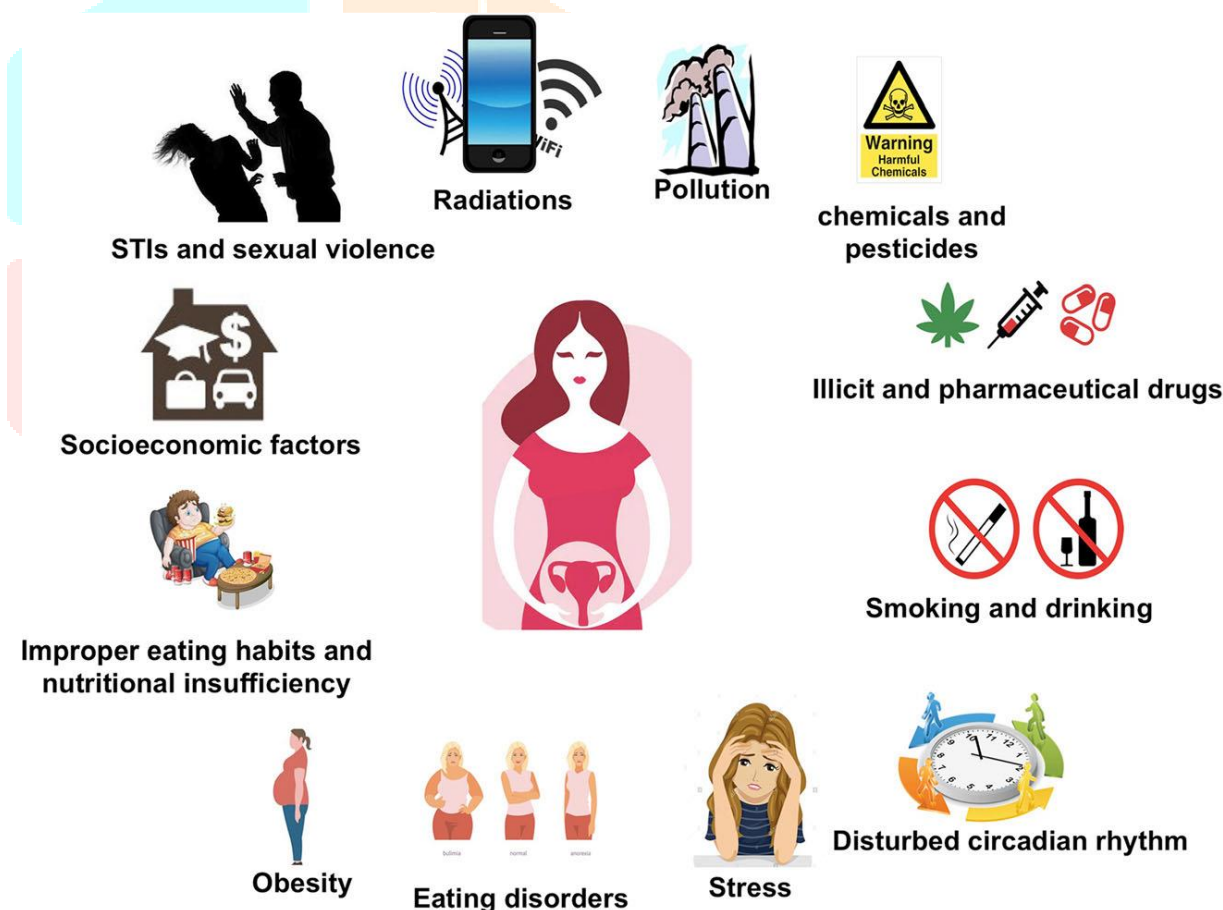
## Keywords

Lifestyle factors, endocrine factors, environmental factors, circadian clock, STDs and so on.

## Introduction

Fertility is defined as the ability to reproduce itself, whereas the female's fecundity is defined as the biological potential to reproduce based on the monthly possibility of conception(1). Infertility refers to as the inability of an individual to regulate the pregnancy after 12 months of unprotected sexual intercourse. About 15% of the population is affected by infertility(2). The incidence of infertility is gradually increases, pleasurable the attention to environmental factors but genetic causes is not well known yet. Etiology of female infertility is different and consisting many factors like genetic mutation, abnormality in chromosomal structure, lifestyle factors, ovulatory diseases, tubal factors endometriosis and so on. In the recent studies, lifestyle factors like eating habits, stress, drinking, smoking and obesity which affects the female physiology in long term. These have been reported widely decline the chances of conception in females(3-7).

The body of human unite with nutritional, hormonal and environmental factors which are responsible for maintaining homeostasis. Generally, lifestyle risk factors is the obesity, hyper-chloric diet affects the energy state that affects the metabolic phenomenon of the body. In addition to obesity, certain factors like nutritional insufficiency due to inappropriate food habits excessive difficult excercises, low peripheral body weight etc. plays the negative role in women's fecundity. It results in low energy state in the body of an individual and point the hypothalamic pituitary gonad axes at the level of CNS affecting GnRH pulse(8,9). This conditions change the hormonal profile and may disturb the down stream signalling like pathways of insulin and lipid, which plays the crucial role in reproductive health(10,11). Moreover, natural circadian rhythm as well as sleep wake cycle are maintained by melatonin levels in the anterior hypothalamus(12) and also affects the HPG axis(13). Disturbances in the timing of sleep in females with premenstrual dysphoria, menopause transition and some other pregnancy problems(14). Several pharmaceuticals drugs for satisfaction and hallucinogenic compounds in drugs can indirectly affects the neuronal system which have potential to decrease the level of GnRH(15,16). Several researchers demonstrate that prolonged exposure of several chemicals like EDCS in the form of pesticides, fertilizers, industrial products and so on, able to reproduce the fertility via changing the hormonal profiles or pathways(17). Prolonged exposure of environmental factors like air pollution, noise pollution, heavy metals, radiation exposure and occupational exposure may result the infertility. Such toxic chemicals may have long term developmental consequences on a child due to affect of neuroendocrine axis during development of fetus in the uterus of mother(18-22). Another factors like poverty, STDs, sexual violence are common cause for the infertility in females (Fig 1)(23).



### Effect of dietary factors, nutritional deficiency and results of reproduction.

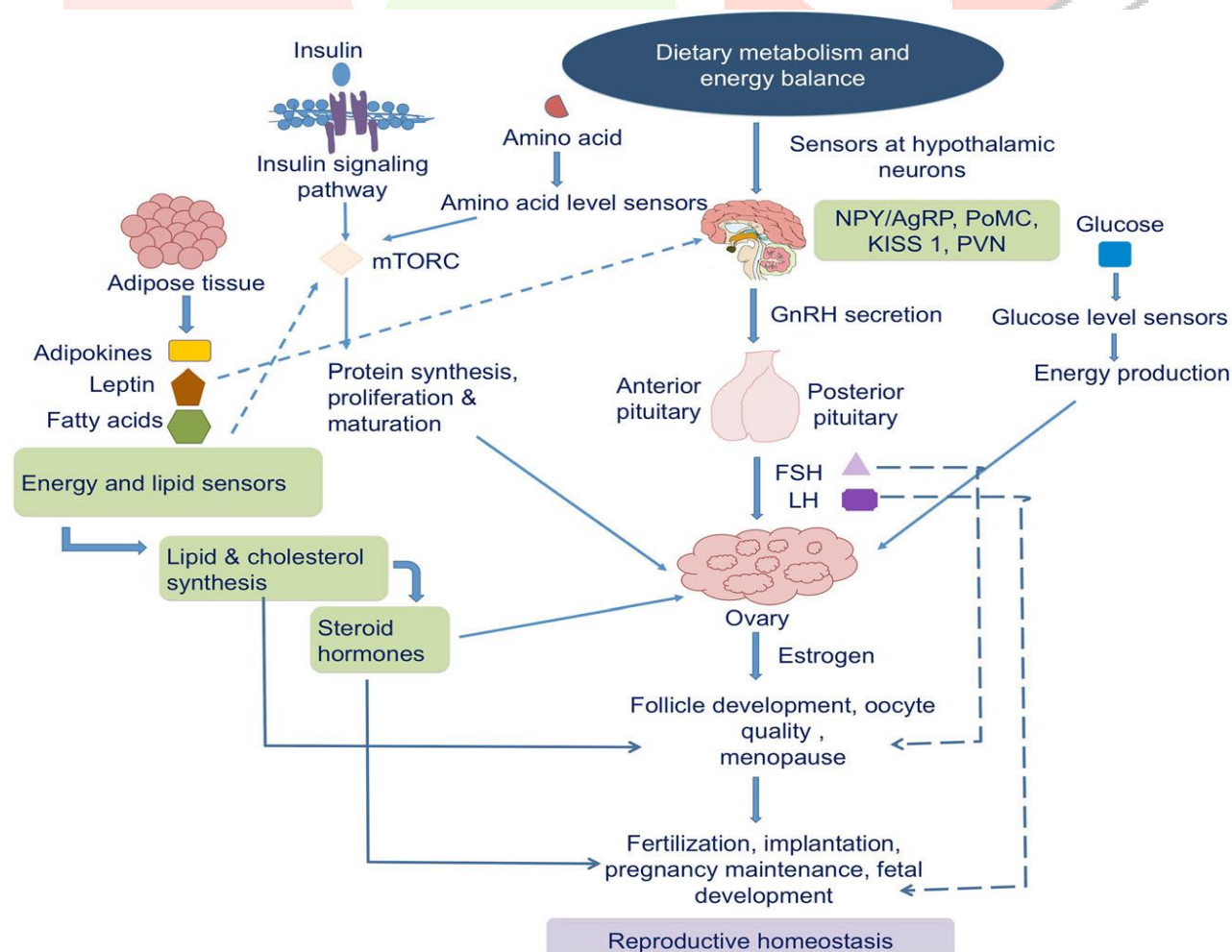
Metabolism of energy associated with human reproduction. Maintenance of nutrition plays a very very important role at the time of pregnancy, but also at the time of adolescent age as well as preconception period(9,24). Insufficient dietary habits are generally linked with either poor or excess intake of calories, accompanying insufficient intake of essential nutrients(25). In backward areas or in middle class families, undernutrition or malnutrition in women is common because of limited resources and lack of awareness about food habits. On the other hand, in developed areas, therefore, insufficient food habits, lifestyle respectively are responsible for the cause of undernutrition in women, as a result of which dysfunction of

reproductive organs occurs(26,27). Several studies reveal that decreased intake of food(28), prolonged malnutrition and negative energy balance maybe responsible for delaying in the timing of puberty(29,30), increased in the ovulation disorders(31) and also reduced fertility in females. Abnormal nutritional status and low energy state are usually seen in females and also suffered with polycystic ovarian disorders, hypothalamic ammenorhea and dysfunction of luteal phase(32). About 4-9% of normal reproductive age group females pron from huge risk of dysfunction of luteal phase, which is able to endometrium less receptive for the process of implantation, as a result loss of early pregnancy and eventually causing infertility(33).

Importance of good, healthy and poor food plays a crucial role in females of child bearing age, who want baby and for pregnant , lactating mothers at the time of perinatal, neonatal period and also at the time of first year of life of infant(34). Maternal nutritional status refers to as her capacity to conceive, attain healthy pregnancy, development of fetus, breast milk production(35). It is very interesting to know that the diet of mother and father at the time of preconception, is able to produce the healthy gametes and development of healthy fetus is not well understood. Recent research reveals that the consumption of essential nutrients, proteins, essential fatty acids, bioactive compounds are responsible for declining the risk of pregnancy related problems(36). Deficiency of Fe is mostly found in pregnant females and reproductive age group females(37) and this will increase the incidence of postpartum haemorrhage(38). Insignificant dietary habits and maternal undernutrition or malnutrition at the time of pregnancy, causing pregnancy problems like early miscarriage, gestational diabetes, PTB, LBW, IUGR, birth defects and so on(39,40).

### Nutritional effect at gene level and on neuroendocrine function

Deficiency of food leads to inhibit the hypothalamic pituitary gland axes at CNS level that affect GnRH pulse generator. When GnRH production is decline, it causes inhibitory effect on cascade pathway, it decrease the secretion of gonadotropin, reduced development of follicles, decrease synthesis of gonadal steroids. HPG axes may affect the nutrient status which affects fertility by different phenomenon (Fig 2).



Deprivation of glucose may affect the hypothalamic neurons. In gonads, the sufficient level of glucose is crucial for the process of oogenesis and also development of embryo(8). The signalling pathway of insulin controls the development of follicles and ovulation by insulin/ IGF receptor, AKT, PTEN, PI3K, IRS, Rheb and mTORC mediators(11). Increased or decreased levels of insulin may lead to incomplete maturation of follicles and cause anovulation, formation of ovarian cyst etc(41). Such signalling pathways often adjusted by adipokine hormones which is secreted by adipose tissue which plays the crucial role in preventing from various disease like obesity, cardiovascular diseases and various metabolic syndromes(42). Adipokine like adiponectin, resistin, apelin, chimerin and so on, that are responsible for associating HPG axes, formation of steroids, ovulation, implantation of embryo and also on pregnancy(43). Adiponectin in follicular fluid, oocyte, theca cells, corpus luteum, uterus, granulosa cells(25) indicates the significance in development of follicles, receptivity of uterus at the time preimplantation period(44).

PUFA is responsible for providing structure and also maintain oocyte's cell membrane. Beta oxidation of fatty acids is important for the maturation of the oocytes. Fatty acids are responsible for the prostaglandinogenesis and steroidogenesis that controls many reproductive functions. Inactivation of metabolism, genes, for lipids like LXR, PPAR, FXR etc, which is capable for sub fertility or we can say that sterility suggesting the function of fatty acids in male and female reproduction. mTORC complex acts on an amino acid sensor and is mainly dedicated to leaking as well as glutamic acid presence. Activity of mTORC is rapidly reduced or decline in the depletion of amino acid and as a result of which it reduces the reproductive ability(45).

### **Obesity and infertility**

In females, obesity is associated with various factors like PCOS, infertility, insulin resistance and irregular menses. The consequences of obesity in females include various metabolic, reproductive and psychological problems. These effects are related to alarms in neuroendocrine systems. Infertility risk is three times more in obese women than non-obese women. Researchers have found a decreased fertility rate with corresponding increase in BMI in obese women. Women with a BMI greater than 30 kg/m<sup>2</sup> are at a high risk to neural tube defects, spina bifida, orofacial defects during pregnancy. Obese women have a predisposition to maternal death, miscarriages, UTI infections, anencephaly, gestational diabetes, intrauterine death, post- pregnancy complications, postpartum hemorrhage, hypertension and miscarriages. The visceral adiposity is increased that increases the time of conception. The spike in miscarriage in women is a result of PCOS. These patients have an increased body fat ratio as compared to healthy women. The reproductive age is shorter in obese women because menopause is earlier in these women. Apart from body fat ratio, body fat distribution also affects fertility. The insulin resistance in obesity with PCOS women can lead to increased

androgen production resulting in premature follicular atresia and hyperandrogenism. The insulin sensitivity and ovulation can be regained in overweight women by weight loss.

The assisted reproductive technologies are also affected by obesity. IVF pregnancy chances are decreased by 0.84 with a mere increase of one unit in BMI. The metabolic fluctuations in obese women can cause complications in implantation and oocyte quality. The development of embryo is also affected. A slight resistance to exogenous gonadotropins and reduced fertility is seen in obese women undergoing IVF due to higher gonadotropin levels. PCOS and obesity are interrelated. Not all PCOS women are obese but most PCOS women have infertility problems. Some drugs and lifestyle mediations can manage PCOS. These women have high leptin concentrations than expected with their BMI. The pathophysiology of obesity and its metabolic and hormonal consequences are affected by several factors like leptin, insulin growth factor, insulin, estrogens, and some cytokines.



Obesity influences neuroendocrine system:

Adipose tissue turns as an endocrine organ and secretes bioactive adipokines that regulates the immune system, glucose and lipid metabolism pathways. Excess weight gain influences the hypothalamic-pituitary gland and consequently the luteinizing hormone. High LH concentration decreases the chances of conception. Hyperandrogenemia is caused by insulin fluctuations due to obesity which leads to the decrease in sex hormone binding globulin concentration. Estrogen levels are increased in obese women because obese women have more adipose tissue and aromatase in adipose tissue converts peripheral androgens into estrogens and these estrogen levels interfere with follicular development which inhibits FSH secretion and causes ovulation. Leptin is one of the factor that affects hormonal consequences of obesity. Leptin regulates the HPG axis and acts as an indicator of body fat ratio. The leptin stimulation can increase the basal metabolic rate and decrease appetite. In an experimental study on rodents, mutations in leptin and leptin receptor gene can cause obesity and infertility. The variations in neuroendocrine system can cause disturbed neuro-regulation of the hypothalamic-pituitary-ovarian axis in obese women that affects fertility, conception and post pregnancy consequences. Eating disorders and infertility

The abnormal eating patterns for weight regulation and diet consciousness about one's body shape and fit leads to some psychological medical conditions called eating disorders. Extreme controls of weight can lead to conditions like anorexia nervosa, bulimia nervosa and binge-eating disorder coexisting with other symptoms like depression, stress and anxiety disorders. Reproductive system is highly sensitive to any kind of stress whether psychological or physiological that can cause conditions like amenorrhea or irregular menstruation cycles. If eating disorder is undetected in conceiving women, it can cause several birth defects and is equally harmful to mother. Mothers with eating disorder have two times higher chances to have low birth weight babies as compared to non-eating disorder women. A recovery from ED and gaining normal weight still predisposes a women to 5-44% risk of amenorrhea because of prolonged history of under nutrition. Women with eating disorder have an increased risk of IVF failure than normal weight women. The abnormal eating habits of ED patients are often underestimated by them as their routine behavior but it can leave a long term damage. It has an impact on fertility that is associated with factors like physiological stress, lower BMI and under nutrition.

### **Physiological, psychological stress and reproductive function:**

Maintaining homeostasis is a very challenging task for human body. One of the major factors disturbing this homeostasis is stress and maintaining homeostasis in these stressful conditions demand additional efforts. Stress stimuli are triggered in these conditions that stimulate nervous, endocrine, and immune system and affects not only physically and psychologically but also physiologically. The effects of stress are adverse in females especially working women due to their constant juggle between professional and personal life in addition to societal pressures. Symptoms like mood swings and inappropriate dietary patterns eventually leading to malnutrition and obesity are caused due to stress induced hormonal changes which further leads to reduced fertility. Long lasting or chronic stress can root for rise in the levels of corticotrophin-releasing hormone (CRH) that promotes uterine myometrium contractions by cytokine induced labor pain. Along with this, it also causes anovulation, functional hypothalamic amenorrhea (FHA), irregular menstrual cycles, disruption, and reduction in hormones like Gonadotropin releasing hormone (GnRH), Follicular stimulating hormone (FSH) and Luteinizing hormone (LH) and result in disturbed neuro- endocrine function and subfertility.

**Effect of stress on neuroendocrine function:**

The HPG (hypothalamus, pituitary, and gonads) axis gets disturbed thereby altering the reproductive functions due to stressful conditions. The stress related hormones thus secreted show severity based on the magnitude and duration of the stress stimulus.

Adrenal gland plays a critical role in stressful conditions as it secretes stress hormones triggering various physiological responses in these conditions. The hypothalamus secretes corticotropin-releasing hormone (CRH) induced by stress stimulus which further releases adrenocorticotropin hormone (ACTH) from the pituitary. This signals adrenal gland to secrete corticosteroids, mainly cortisol. [52] The secretion of ACTH is administered by adrenal glucocorticoids by feedback mechanism. [52] A study showed that adrenalectomy interrupts the negative feedback mechanism and increases the release of CRH and ACTH along with vasopressin (VP) from the parvocellular neurons. An increase in the levels of cortisol in circulation triggers release of GnRH induced LH release which results in LH induced ovulation having critical dysregulation of the HPO axis and causing complication in follicle maturation, ovulation, and pregnancy. CRF acts as a mediator and a neurotransmitter in the CNS managing stress responses. The importance of CRF in stress- induced inhibition of reproductive functions is evident from close anatomical similarities between the CRF and GnRH releasing neurons along with the presence of CRH in the circulation during stressful conditions.

A study was performed on rats in which the rats were injected with CRF antagonists in their brain ventricles. This showed an inversion in the inhibitory effect on LH secretion. The CRF immunoreactive cells were seen not only in the parvocellular neurons of paraventricular nucleus (PVN) but also diencephalic, telencephalic, brainstem and paraventricular nuclei of preoptic area. Rats were monitored during estrous cycle, to check the activity of CRF neurons in the ventromedial parvocellular neurons of PVN. It proposed a latent role of CRH in regulating LH levels during non-stressful situations and hypothesized a possibility of direct interaction of CRF and  $\beta$ -endorphin neurons with GnRH neurons of Medial preoptic area (MPOA) decreasing its activity. [51]

Physical stress caused during inflammation produce cytokines that can activate the hypothalamus to release CRH and POMC (pro-opiomelanocortin) derived peptides that causes rise in the levels of glucocorticoids and obstruct steroid synthesis in the ovaries thereby causing reproductive dysfunction. [53] Chronic stress, if continued for a longer period do not control the pituitary signals and responses to GnRH due to desensitization after a certain point. High activity of Serotonin had been observed in the raphe nucleus during stress which suggested its involvement in the decreased GnRH activity. There is a correlation between stress and cortisol levels in regulation of many important endocrine functions. Estrogen and cortisol or glucocorticoids possess similar binding sites within the promoter region of similar target genes and due to overlapping signaling pathways they regulate the transcriptional activity of many genes antagonistically. An increase in the cortisol levels leads to a reduction in T3, T4 and TSH and regulate the effect of thyrotropin releasing hormone on TSH. Chronic stress also interrupts with the energy balance and change the homeostasis of the body from reproductive function to a survival viewpoint and suppressing the HPT (hypothalamic-pituitary-thyroidal) axis causing shift in anabolic to catabolic state. [53]

Every individual experience small amount of stress in day-to-day life but this stress when prolonged causes other physiological and psychological difficulties such as anxiety. Women have a profound effect of stress on their reproductive cycle. Whereas infertility in women leads to other cascade of stressful events due to reasons like failures in ART procedure, societal humiliation related to infertility and no conception after IVF, often aggravates stress. A psychological support and intense care by family members and proper therapeutic counselling can help in coping these situations.

### **Disturbed Circadian Clock and Reproductive Function:**

Circadian clock is a repeated sleep wake cycle that oscillates on a 24-hr rhythm observed in living beings. It is controlled by suprachiasmatic nucleus (SCN) located in the anterior hypothalamus region and regulated by melatonin which is responsible for pubertal development by regulating HPG axis. [54] It is known to suppress ovulation in humans by interfering with LH secretions. Evidence such as presence of melatonin in follicular fluid and presence of melatonin receptors on granulosa cells reveal the importance of melatonin in oocyte development. [54]

### **Alcohol consumption, smoking and caffeine**

Today generation belonging more to modernity has started using alcohol, smoking, caffeine and other substance as their lifestyle. Sometimes peer pressure and some other times personal choice in spite of being educated of their harmful effects, are consumed in full form. To escape from regular psychological stress and everyday tensions, they don't realize when their body get dependent on these. Major target of these are women pregnant women and women of reproductive age exposure to teratogenic and other severe components poses a direct link to pre-pregnancy and hence increase in infertility. [55]

### **Alcohol**

Being unaware of pregnancy till first trimester as most of the times when its unplanned, women unknowingly put their fetus at the risk of developing neuronal diseases, as major of these are those development takes place in the first month of gestation. Researches from so long has been till now, not succeed, in establishing direct link between alcohol and infertility [56-58]. However, a few studies have declared the effect of high doses that is more than 3 drinks in one occasion can direct link to menstrual irregularities, natural unwanted abortion, decrease birth weight, fetal hypoxia, fetal alcohol syndrome (FAS), IUGR, post natal stunted growth [59], birth defects, neural tube defects (NTDs) and developmental disabilities. [60]

One more study concluded that the reason for spontaneous abortion decreased conception rate by 50% and decrease implantation rate as consumption of alcohol ranging from one drink/week to 5 units/day. Regular increase in the congenital heart defects, esophageal atresia and matured depression is credited to preconception alcohol [56, 60, 61]. And risk of preterm delivery is all attribute to consumption of more than 7 drinks a week during pregnancy.

### **Effect of Alcohol on Neuroendocrine Function**

An increase in the plasma ACTH and glucocorticoids via the enhanced release of CRH from the Hypothalamus, and increase in the level of estrogens [62] and decrease in the hypothalamic secretion of GnRH & GRH have found to be directly associated with consumption of alcohol.

Increased estrogen level, decreases the FSH levels and effect follicular development and ovulation process. But research is still continued in exploring the exact mechanism. Hyperprolactinemia in females, which can interfere ovulatory function and thus cause galactorrhea (excessive milk secretion) [126], is

associated directly with intake of about 75-247 ml of alcohol. Evicardian Systems, which is necessary for controlling endocrine axis functions also suffers a lot due to chronic alcohol intakes. And this in turn "cause Dysregulation of clock genes period (Per 1, Per 2 Per 3) clock, small and Cryptochrom (Cryl 1, cryl 2). Oscilary characteristics of hormones secretion [63].

## **Smoking**

Increased cases of ovulatory disorders and after effects as early pregnancy loss, preterm delivery, low birth weights are all associated with excessive smoking (both direct & indirect) in young females[64]. Nicotine, the root cause of tobacco being severe to human body, can readily gain access to breast milk and fetal compartments, thus attacking neuro development of fetus [65]. Decrease in the rate of ovarian reserve, fertilization and pregnancy are easily detected in women who smoke [66]. Psychological stress is supposed to be the major reason for its intake, and thus this sensitize the child for developing depression in after stages of life, mostly in those who are light / heavy weight at birth [67, 68].

### **Effect of smoking on neuroendocrine system**

HPA axis hormones such as ACTH and cortisol are found to have been affected heavily by smoking [69]. Increase in FSH, so low estrogen level [70] and these altered levels of FSH and progesterone hormone in woman, with habit of smoking 10-20 cigarettes per day [71]. Alterations in endocrine hormone, with compromised uterine environment probably, are real reasons of menstrual irregularities, ovulatory disorders and lower pregnancy rates.

## **Caffeine**

Coffee, tea, cocoa, soft drinks and medications possess caffeine in them and excessive intake of this increase the risk of general toxicity, cardiovascular diseases, bone dysfunction, cancer, infertility and even can cross placental affecting fetal growth directly [72], also increase in risk of spontaneous abortion and LBW [73], and delayed conception [74]. Fetal loss at doses > 300mg/day, >400mg/day, and > 900mg/day compared with < 150mg/day has been noticed [75]. Even in animal models, caffeine direct effect on CNS such as neural tube closure has been reported [76].

### **Effect of caffeine on neuroendocrine function**

Few studies in one side reflected the increase level of SHBG, while others have shown decrease in E2 levels by caffeine intake [77]. In vivo analysis of caffeine's dose in female rats gave result as directly affecting vaginal opening, estrus cycle and ovarian weight [78]. Further study in animal models, proved inhibition of oocyte maturation and increased steroid synthesis via phosphodiesterase inhibition [79,80]. Interference in estrogen metabolism via inhibition of aromatase (key enzyme required for converting androgens in to estrogens) [81]. Increased risk of benign breast cancer has also been reported through some studies [82].



Majority studies came out with results which are associated effects, and only a few succeed to show the exact mechanism, showing clearly the pathways affected by consumption of smoke, alcohol & caffeine. The major effect of all these three is risk of infertility but again can be considered as an independent risk factor for their associated conditions.

### **Effects of Elicit and Pharmaceutical Drug intake**

Non- medical use of recreational drugs (Cannabis, cocaine etc) are associated on a social, behavioral, physical problems and their effect depends on duration of exposure, dose physical & menstrual status of individual, the route of administration [83]. Females, addicted to these during preconception period or pregnancy, result in pregnancy complications such as LBW, preterm delivery, IUGR, placental abruption, high risk of infant mortality, neonatal abstinence syndrome, higher chance of HIV transmission [84,85].

Marijuana and Cannabinoids disturbs[86] the processes leading to spontaneous abortions, infertility by have direct impact on implantation failure and embryo development [87]. Not much has been found on effects on cocaine on female. But a few studies do found a link between ovarian dysfunction, placental abruption and caffeine [88,89].

Psychoactive compound in marijuana and cannabinoid derivative is tetrahydrocannabinol (THC), cannabinoid receptor, found in neurological tissues, testis, vas deference, urinary bladder, ovary, uterine endometrium and the receptor CB2 is found in immune cells [90]. Endogenous cannabinoids and 2-arachidanoylglycerol also bind to some receptors as THC [91]. Although THC and other cannabinoids don't show direct estrogenic activity, they can interact with estrogen receptors [92]. Marijuana consumption can decrease plasma LH level was seen in follicular phase or post menopausal women [93]. Cannabis administration in rats resulted in decreased prolactin release [86]. In-vitro studies elucidated THC interferes with trophoblast proliferation [94] and turnover [95], during the entry stages of pregnancy, affecting placentation.

### **Chemicals & Toxicants Affecting Reproductive function Pesticides and Endocrine Disruptors.**

Breathing problems, headaches, neurological, skin problems, immune System dysfunctions, cancer and reproductive defects are found in humans when exposed to pesticide. Effects are directly related to the time for which they are exposed. In females, effect is seen on their fertility, premature child birth, spontaneous abortion, development aberrations, multiple ovarian disorders [96]. High level exposure is seen to alter time-to-pregnancy in female [97]. Women more exposed to pesticides are found to miss periods more often [98]. Pesticides are known to interfere with hormone, post receptor activation, hormone receptor recognition and binding, hormone synthesis, storage and release and so ovarian cycle dysfunction [99]. Pesticides can mimic endocrine hormones and bind the receptors [100]. These are direct effect on endocrine System a various environmental system and various environmental chemicals act as Endocrine disrupting chemical.

Data concerning effect of EDCs on fertility are limited, but wide studies have recalled their effects on reproductive systems of both sexes. And in females, are seen to effect intrauterine health and thus development of fetus as can easily transfer through placenta and present in breast milk [101]. DDT and methoxychloro possess estrogenic properties [99], and so they binding to estrogen receptor, cause decrease production of GnRH by hypothalamus via negative feedback system, resulting in decreased LH and FSH secretion and this in turn result in reduced levels of estradiol and a disrupted to hormonal cycle. Pesticides such as Prochloraz and fenarimol inhibit estrogen biosynthesis through the inhibitions of CYP19 aromatase activity in vitro, so preventing conversion of androgens into estrogens [102]. Dithiocarbonates such as sodium N- Methylthiocarbonate (SMD) and others have been found to hinder dopamine-beta-hydroxylase activity resulting in decreased conversion of dopamine to nor epinephrine [99]. So causing altered hypothalamic catecholamine activity responsible for generating proestrus surge in LH, which is stimulating ovulation in rats [99]. Ketoconazole possess the potential to inhibit CYP450 - dependent monooxygenases and progesterone synthesis [103]. These harmful chemicals have direct effect on endocrine system.

## **Exposure of Environment and Occupation**

### **Air Pollution**

Most common concern for human health is environmental pollution. Pollutants in the air generates free radicals or ROS such as NO<sub>2</sub>, O<sub>3</sub> and this produces stress that can effect production of ovary, follicles and various ovary functions (104). There is increase in chance of cell death, mutations and hypermethylation due to oxidative stress produced by ROS (17). It has been seen in various studies that pollutants has adverse effects on human health as in cases of LBW, preterm birth, fetal growth retardation. Various studies conclude that by 2050 premature mortality will be double due to air pollutants (105). Females who have exposure to benzene shows menstrual irregularities and those with exposure to automobile pollutants show decline in the level of estradiol in follicular and also in the luteal phase (106).

### **Noise Pollution**

Noise pollution can be the cause of agitation, depression, anxiety, sleep pattern disturbed, sexual impotence and instability of emotional state (107). High heart rate, increased level of blood lipids, hypertension, increase in epinephrine and the norepinephrine can be seen due to the daily exposure to noise that is in range of 65 and 85 dB (108). However there is no direct impact of noise pollutants on fertility so far.

### **Heavy Metals**

Reproductive problems can be caused by exposure of various heavy metals (lead, mercury, cadmium, etc.) as these metals accumulate in vital organs of the body. Exposure to heavy metals result in risk for spontaneous abortion, intrauterine fetal deaths and restriction in the fetal growth (20,109). In Chinese population based study it was found that there is an incline in risk of preterm birth when the mother is exposed to cadmium (110).

### **Occupational Exposure**

There are various health issues that results due to individual lifestyle choices and work space. Chemicals, solvents used in dry cleaning, paints, pharmaceuticals, farming, metal industry, mining, and other fields have impact on the reproductive health of individual (111). Females that work in homes are also at risk due to use of coal for cooking and heating that result in increasing the risk for neural tube defects in the infants (21).

## Radiation Exposure

Germ cells are affected due to radiation exposure which result in disrupted sex steroid formation. Various naturally occurring radiation or the radiation from medical sources or the radiation that are ionizing that include X-rays, gamma rays and radiation that are non ionizing that include ultrasound, electromagnetic rays they alter the tissue by changing the structure of DNA, proteins and producing free radicals can have long term effects(112). Ionizing radiation are more harmful as it changes structure of DNA, proteins and damaged the cells and the severity depends on the dose of radiation. Radiation dose of more than 0.1Gy (10rad) during the time of pregnancy increases the risk for the impanation failure, mental retardation and various NTDs(113). Cancer patients with exposure to gamma radiation shows premature ovarian follicles and depletion in ovarian follicles(114). Banking of embryos, oocyte cryopreservation as well ovarian tissue ,ovarian suppression and GnRH agonist therapy, ovarian transposition are some options that a female cancer patients can consider before radiation so that they can preserve their fertility (115).

## Socio-Economic and Demographic Factors

Infertility issues around the world is seen in 12% of couple a recent report shows. Causes of infertility are characterized to two categories primary and the secondary. Primary infertility is due to hormonal, genetic, congenital defect or reproductive system disorder. Secondary infertility is due to lifestyle or occupational disorders. Other factor include age, socio economic status and high parity (23). Awareness, education, better emploment rate, female literacy, family planning can reduce the chances of infertility (116). Age plays a key role as with advancing age (> 35 years) female fertility declines due to limited number of oocytes

Different socioeconomic populations show different trends in fertility, women in rural area have high fertility rate than the urban women. High socioeconomic status women tends to have better health due to frequent use of better medical facilities as compare to low status women. All these factors along with the genetic as well as environmental factors determine overall health of female and the progeny in whole a family(117).

## Infertility due to Sexually Transmitted infections and sexual violence.

Infections related to female reproductive tract can cause physical, psychological consequences, infections related with bacterial, candida, and trichomonas have no serious impact while chlamydia and gonorrhoea can result in infertility in females, STIs if not treated affect female reproductive system and cause inflammation of pelvic region, and increase risk of fallopian tube infertility, ectopic pregnancy and chances of contracting and transmitting HIV (23,120,121). It is seen that HIV positive women have lower fertility than HIV negative whether we use ART or not (122).

Physical and psychological trauma due to sexual violence affects the female reproductive system causes fallopian tube infertility that too is undetected (123). Studies shows women experiencing sexual and parental substance abuse in childhood experienced fertility problems with amenorrhea that lasts for long (124). Cases with IPV against women shows chances of unintended pregnancy, antepartum haemorrhage with preterm birth, and risk of miscarriage (125,126,127). Abusers controlling behaviour in case of abusive relations thus affect the reproductive health (126). Studies in coming years are intended to find mechanism behind associations of physical and psychological violence and the affect on female infertility.

## Conclusion

In this review infertility in women is associated with various lifestyle and environmental factors and some other factors that include stress, air pollution, obesity, noise pollution, alcohol consumption, smoking habit, socio economic factors. These factors result is malnutrition or obesity depend in which direction the imbalance curve goes it affects the HPG axis and GnRH secretion.

Insufficient nutrition and lifestyle behaviours that lead to obesity disrupts the insulin-signalling pathway which maintain the ovary formation thus result in ovarian dysfunction and other ovulatory disorders.

PCOS is among the major causes of the infertility when associated with stress and obesity. Cortisol level in women is 19% more than in men (118), and periodic secretion of cortisol is different at all the stages of the menstrual cycle. Exposure to stress due to various physical or sexual abuse or other factors for long time can indulge individual to depression, anxiety and other behavioral disorders and thus alter the basal level and increases ACTH levels. It is seen that women with stressed condition have low level of plasma estrogen and high androgen levels.

LH/FSH secretion affects ovulatory functions and it is seen is affected by high level of cortisol that affects secretion of CRF in the brain. Interaction between  $\beta$ -endorphin, CRF, and GnRH neurons is seen. Obesity in early childhood and depression in reproductive years results in higher levels of estrogen and increased glucocorticoids level that affects HPA and HPG axes. All these stressed conditions can be controlled by positive family interventions, psychological support and counselling.

The exact mechanism on reproductive function of melatonin is not yet known but alteration in its level result in menstrual irregularities and dysmenorrhea in females. In night shift workers there is difference in lipid and glucose metabolism which occur as result from risk of obesity, sleep deprivation and dietary patterns. Various studies shows that alcohol, caffeine, and smoking alter the level of estrogen E2, FSH, ACTH and HPA and HPG axes. THC in marijuana and other derivative of cannabinoid interacts with the estrogen receptor and reduced the LH level. Recreational drugs disrupts menstrual cycle, ovary formation, placentation as shown by in vivo and in vitro studies.

Environmental pollutants impact on human health is seen and its affect on reproductive health is proven in various animal models. Many toxicants and pollutants as they increase oxidative stress it affect ovulation, follicle formation and stages of menstrual cycle and can cause infertility.

Socioeconomic status affect the emotional health of female, while fertility rate is higher in rural areas than urban inspite difference in socioeconomic state but they are at the high risk for complication during the pregnancy due to lack of awareness and poor health status. Female health can be improved with family support, awareness, counselling, psychological support, awareness and improving the social stigma of anxiety, depression, drug abuse restrict the people from considering the professional help.

Considering negative affect of environmental, lifestyle factors on the reproductive health should be considered by the policy makers so as to provide low status people with better medical help so as to prevent the reproductive disorders and complications in infants due to exposure to chemicals during pregnancy.

## Diagnosis

1. For diagnosing the uterus and fallopian tube various screening method can be used that is ultrasound, hysterosalpinography, hysteroscopy, fertiliscopy and laparoscopy. Pap smear test for determining the sign of infection in pelvic regions. Adenomas that are small as 3-5mm can be detected by Magnetic Resonance Imaging (MRI) by combining these imaging methods we can confirm the diagnosis.
2. Chronic renal failure can be detected by measuring blood urea nitrogen and creatinine as it can be one of the cause.
3. If patient is postmenopausal or had a hysterectomy done pregnancy testing is not required while in all cases it is required for the diagnosis.
4. In cases of acromegaly IGF-1 is measured.
5. Plasma level of hormones is measured like luteinizing hormone (LH) for ovulation, discovering pituitary gland disorder, FSH for ovarian reserve and thyroid stimulating hormone (TSH) for thyroid gland disorder (128).
6. For detecting antisperm antibodies which can be present in the blood and vaginal fluids immunological test are done. Detection of various antibodies that destroy the spermatozoa is done by conducting antibody infertility blood test.



7. Soon after the intercourse postcoital test can be done for checking survival of sperm in the cervical mucous.

### **Infertility preventions:**

- Carrying out a healthy lifestyle -Smoking and alcohol should be avoided, regular exercises, maintaining balanced diet, taking vital nutrients and maintaining normal body weight.
- Detecting and treating pre-existing disease – Controlling the chronic disease such as diabetes, hyper and hypothyroidism help in improving fertility. Frequent screening and tests on regular basis for detecting early sign and symptoms of infections.
- STD's can be prevented by practicing safer sex or abstinence, usage of various contraceptive method such as male condoms and vaginal sheath.
- Not delaying parenthood – After 27 years of age fertility starts to decline and the rate of declining increasing after age 35(129). Females with mothers who have problems regarding pregnancy are at high risk of premature menopause this can be prevented by not delaying the age of fertility or parenthood.

### **Treatment:**

It includes-

- Weight declining tablets: In obese females who are anovulatory infertile females, a loss of 5-10% weight of the body often discovered to be sufficient to restore functioning of reproductive organs in 55-100% of females within six months (130).
- Baptism of releasing of ovum from Graffian follicle using gonadotropin, HMG respectively.
- Bromocriptine in the females who are suffered from hyperprolactinemia.
- Combination of Clomifene Citrate with HMG (131).
- Hormonal therapy like Pergonal.
- Surgical mediation.
- AI: It may be attained by Intracervical or Intrauterine Insemination.
- IVF: It often used to treat females with damaged fallopian tubes and Endometriosis or sometime in case of unsolved infertility. It requires the presence of a functioning fallopian tube and procedures like GIFT, ZIFT or ZIFT-ET, a combination of GIFT as well as IVF.
- ISCI: It is usually used when Male fertility is the major problem. It includes injected a single sperm cell into the egg which is obtained from IVF

**Abbreviations:**

LBW-low birth weight

PTB-Preterm birth

IUGR-Intra uterine growth retardation

PUFA-Poly unsaturated fatty acids

HPG axis-Hypothalamic pituitary gonads axis

SSBG-Sex hormone binding globulin

TGF-Transforming growth factor

MPOA-Medial preoptic area

ACTH- Adrinocorticotropin releasing hormone

HPA-Hypothalamic pituitary adrenal

HPT-Hypothalamic pituitary thyroidal

NTD-Neural tube defect

THC-Tetrahydrocannabinol

SMD-Sodium N-methyldithiocarbonate

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