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INTRODUCTION

During the last fifty years the world has made tremendous progress in several fields such as modernization, industrialization, urbanization, science & technology. Newer and newer technology, diagnosis and treatments are being developed for a large number of diseases like, Cancer, HIV, genetic disorders, including Hypothyroidism & infertility.

Although incidences of infertility is continuously increasing in the world, Because of the increasing in the population, however the rate of infertility have remained relatively stable in last two decade (WHO, 2013). This is due to more awareness of ART (assisted reproductive technology).

The life of a woman is not completed, unless she bears a child and enjoys the happiness of motherhood. But still there are women who remain away from this happiness of motherhood. There are several factors which are responsible for infertility in the female, one of the most important factor is the life style of the female which included modernization, drinking, smoking, stress, hurry, worry all these factors ultimately induced depression, hypothyroidism etc. which are responsible for infertility in women.

In a woman’s life most important moment comes when she bears and delivers a child. Therefore, Motherhood is the highest, holiest and happiest gift from God, this gift is equally important for a husband, in-laws and other family members and for a society. But unfortunately all the women are not fortunate enough in this regard, and therefore, do not conceive and bear a child.

Infertility has often stronger negative outcomes in developing nations compared with those in Western nation. In India where, usually, having kids is compulsory in conditions of family cheerfulness and numerous people still think about infertility as a "woman’s problem". This problem develops crucial social existence (Jumayev, Harun, 2012)
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Childlessness may not be a threat to physical wellness but acquires with it enormously undesirable social and psychological significances. As a outcome of their infertile category, they undergo physical and mental cruelty, neglect, abandonment, economic scarcity and social isolation as well as exclusion from certain public activities and traditional ceremonies. Instead of that infertility is a major cause of family disruption, second marriage, divorce, physical and mental harassment of female. (Rajan, 2012)

Reproduction is one of the most significant biological function for everyone life. Age is a factor which can affect the fertility of a man and women. Because of pursuit of educational activity and other factors, many couples prefer to delay childbearing. In men and women along with the age (time) fertility reaches its peak and then started to decrease. Therefore Age and reproductive timeline should be a one aspect to consider when deciding the ideal time to begin a family. (Stewart, Kim, 2011). Below the age of 30, a woman’s chances of conceiving may be as high as 71%; whenever over age of 36, it may only be 41% (Mutsaerts, Groen, 2012).

For a sizeable minority the hope for children is so powerful but it is not easy to be fulfilled. Hereditary abnormalities, environmental factors, and certain infectious disease are factors which can affect fertility. To maintain fertility understanding of the potential risks and corrective actions are essential. (Peterson, 2005, UNFPA.url.india.unfpa.org/drive/fertility.pdf)

The journey for people who are facing infertility may also suffers unrecognized health problems; and having difficulties in obtaining services that usually are not included by health insurance policy. Success with physical requirements and high cost of medical facilities may results in unexpected adverse outcome on the quality and health of person and their children (Martin, 2007).

Each moment of life having infertility is affected by the interacting physical, social environment, biological background and individuals’ behavior. On the huge scale, these social and physical interactions cause disease, deployment of services, and outcomes of this is an issue for public debate. The queries aroused as a result of debate includes identify and manage risk factors for infertility. Other issues raised are addressing racial and economic disparities, ethical and financial implications and

Many conditions like genetic abnormalities, infectious or environmental factors, and certain behaviors are the challenges to reproduction. Natural aging is one of the limiting factors for reproduction. Causes of infertility in females include disturbances in hormonal or endocrine level (menstrual irregularity), tubal factors (occlusions, pelvic adhesions and other tubal abnormalities), acquired non-tubal factors (cervical or uterine disturbances), sexual dysfunction and congenital abnormalities (Jejeebhoy, 1998).

Fertility window varies from female to female and it closes earlier for some than expected. Recent approaches toward the natural limits of reproduction have highlighted postponing age at first pregnancy and accelerated the progress and utilization of medical technology to get over such limits. Since 1975 to 2006 the proportion of first birth increases from five percent to twenty percent in women aged 30 years and older. During this period the number of these births increases from 69,000 to approximately 405,000 (Ventura, 1989, Hamilton, Martin, 2007).

Prevalence

Among 200 million people worldwide and about 20 million Americans suffering from thyroid disease. Greater than 12% Americans suffers thyroid complications at some stage in their entire life. Possibly the most arresting datum is that up to sixty percent of thyroid patients are unaware of their condition. Probability of thyroid complications is 5 to 8 folds more in women than men (Kumar, 2015; Anderson, 2011).

Indian thyroid society statistics shows that near about 4.2 million people suffered from thyroid complications in India, while 60% of them are females. Owing to busy life schedule of women, there were no proper time for rest and poor nutritional habits especially in rural areas of India. Therefore decreased the activity of thyroid gland (sluggish activity) in women, that’s why they are more prone to thyroid disorder. (www.patrika.com/health, 16 may 2015, Times of India, 2015).
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The prevalence of hypothyroidism was found 3.9% in India (Menon and Sundaram, 2009). In reproductive age women, prevalence of SCH is about 0.5-5 percent (Krassas GE, 2010). Incidence of hypothyroidism is still high in pregnant women in comparison to non-pregnant women (Khanal M, 2009).

Prevalence in Rajasthan was 11.4% in women as compared to man having hypothyroidism prevalence of 6.2%. (Menon and Sundaram, 2009) Incidences of thyroid problem in Udaipur are 9.09%. It means that one person in eleven person is affected by thyroid problem (Dhalal, 2015). In our institute (Geetanjali medical college and hospital) prevalence of hypothyroidism is 9.30% reported by data obtained from attending outdoor patients department during period from 2013-2017.

Infertility prevalence

Globally, it is figured out that 60-80 million couples suffers from impaired fertility every year. Sharath and Najafi, 2013; Chander and Indira, 2000, World Health Organization, 2016). It is estimated that 7.3 million American females with aged group between 15-44 had impaired fecundity (i.e., impaired fertility) (Chandra, Martinez, 2005). Decreased level of hormone FSH and LH its lead to in proper ovulation causes infertility in hypothyroid women.

In the United States nearly 2 million couples were infertile (Chandra, Martinez, 2005) WHO issued that at the end of the year 2012, one in every four couples in developing countries had been found to be suffered from impaired fertility. (Mascarenhas, Flaxman, Boerma, 2012).

The absolute number of couples affected by infertility in developing countries increased from 42.0 million (39.6 million, 44.8 million) in 1990 to 48.5 million (45.0 million, 52.6 million) in 2010. Data shows increasing trends of infertility in developing countries. (NFHS, 2001)

In India, on an average, infertility varies from 1 per cent to 12 per cent across country. The incidence of primary infertility generally varies from 1 to 8 per cent and secondary Infertility is as high as 35 per cent [National family Health survey (NFHS), 2011].
Data obtained from NHFS, 2011 shows 4.9% prevalence of infertility in Rajasthan. According to National family Health survey (NFHS, 2011) in Udaipur district prevalence of infertility is 8.0%, while its nearby district Dungarpur and Rajsamand have higher infertility prevalence 9.2% and 9.0% respectively. In Rajasthan, lowest infertility prevalence 1.7% is reported in Jaisalmer district. Considering the increasing trends of infertility and its association with geographic, environmental and life style related factors.

In present institute (GMCII, UDAIPUR) data obtained during 2013-2017 from outdoor of gynecology and infertility shows 13.95-23.25% higher prevalence of infertility. Difference between prevalence of data in our institute because it’s run an infertility clinic, where patients come from all over Rajasthan and Madhyapradesh not only from Udaipur. Above 8.0% prevalence is only for those who are residing in Udaipur according to survey of ministry of health and family welfare, 2011.

Statistics of infertility treatment

- 6% women become pregnant after ovulation treatment.
- 3% after IVF and ART.
- 4% by intrauterine insemination alone (IUI).
- 17% by IUI and use of fertility drugs.

Iodine (atomic number, 53; standard atomic mass, 126.9) is a rate-limiting element for the synthesis of thyroid hormones. Currently, the functional role of iodine is to synthesize thyroid hormone in human body. In the twentieth century the kinship between deficiency of iodine and thyroid complications was unknown (Escobar, 2007; WHO, 2005; Zimmermann, 2009)

Dietary iodine uptake is mandatory for the synthesis of thyroid hormone. (Pearce, 2013) Developed and developing nation across the world facing the iodine deficiency as significant health problem. Availability of iodine in diet determines the prevalence and manifestation of thyroid disorder. (Mark and Vanderpump, 2015)
The regions of the world where diet is iodine deficient, the thyroid gland can become significantly enlarged, specify as endemic goiter. Pregnant women on a iodine deficient diet can deliver infants having deficiency of thyroid hormone which is called as congenital hypothyroidism. The manifestation of the deficiency includes retardation in development of physical growth and brain (termed as endemic cretinism). (Venturi, Sebastiano, 2011, Chernobyl, 2010, Patrick L 2008)

The iodine content of staple food depends on soil iodine on which the crops are grown. (Murray, 2008). On the basis of goiter prevalence, the Udaipur district has been identified as one of the endemic area having the deficiency of iodine in the soil (Pradhan 2003). Deficiency of iodine is an crucial health problem across the world. Mostly, on earth iodine exists in the form of iodide ion (I⁻), is found in oceans, and the level of iodine in the soil differ from region to region. The level of iodine in the soil is depleted by accelerated deforestation and soil erosion. The most severely iodine-deficient areas in the world include mountainous regions, such as the Himalayas, Atlas, Andes, and Alps; flooded river valleys, such as the Ganges River plain in India; and many inland regions, such as central Asia and Africa, central and eastern Europe, and the Midwestern region of North America are among. (Zimmermann, 2012). World highest (>10-12%) infertility rate is reported from south and central Africa. (Syamala, 2012)

Some substances that inhibit the functioning of thyroid called goitrogens are found in some vegetables and crops, e.g., millet, sweet potatoes, beans, and cruciferous vegetables (e.g., cabbage, broccoli, cauliflower, and Brussels sprouts) (Fekete, Lechan et al., 2014) Some chemical goitrogens like flavones, genistein and daidzein interfere with the functioning of thyroid (Hendler et al, 2008). Iodine deficiency manifestation includes goiter, intellectual impairments, retarded growth, neonatal hypothyroidism, and increased complications in pregnancy and infant mortality. (Pearce et al., 2013)

**History of Thyroid Research**

In 1600 BC found the first reference to thyroid gland when in the treatment of goiter Chinese applied burnt sponge and seaweed. Tumour of the neck (bronchoceole) was first discovered in 150 AD, by Celsus. Galen recommended the use of ashes of
Poriferans for the treatment of goiter, in 150 AD and he also affirms (incorrectly) that the function of thyroid gland was lubrication of larynx.

Sun Ssu-Mo was the first to use mixture of dried powdered molluse shells, seaweed and crushed thyroid gland for goiter treatment in 650 AD. Anatomical description of thyroid was given by Wang Hei in 1475 and prescribed the treatment for goiters and it should be dried thyroid. After 50 years later, Paracelsus identified goiter as a mineral impurities in the water. At last in 1656, Thomas Wharton called it as thyroid gland, due to its shape and resemblance with a shield in ancient Greece.

In 1811 A scientists, Paris, found iodine in the ashes of seaweed and gave the idea that iodine was the main component prescribed for the treatment of goiters. After 10 years Prout was the beginner to use iodine for the prevention of goiters. In the meantime, many investigators worked on goiter and suggested various treatments. In 1880, a German physician, Ludwig Rehn, accomplished the first amputation of the thyroid (thyroidectomy) for exophthalmic goitre in.

Theodor Kocher, a scientist in 1800s, did nearly 2000 thyroidectomies, and concluded that thyroidectomy is one of the main reasons for hypothyroidism. He, consider thyroidectomy as a cause for Grave’s disease, having a 13% mortality rate. His prescribed treatment for thyroidectomy was “half a sheep’s thyroid lightly fried and taken with currant jelly once a week”. In 1909, Kocher gave the advanced treatment for hypothyroidism and for this he was awarded the Nobel Prize for Medicine. in the end of the century it was found that thyroid makes an iodine containing material In fact, thyroxin was at first isolated by Edward Calvin Kendall in 1914, which found in form of an active hormone of thyroid gland. Entertainingly, Kendall specified the wrong structure to L- thyroxin but his crystalline extract was the right structure and biological active. Kendall erroneously thought that the compound contained an indole nucleus. Nobel Prize was awarded to Kendall for adrenal gland hormones in 1950 in field of medicine.

In 1920s, thyroxin became available to clinicians but it was costly. 33 grams of thyroxin was synthesized from three tons of animal thyroid. In 1952, Rivers et al discovered and synthesised tri-iodothyronine showing it was biologically more active than the thyroxin.


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For the normal functioning of ovaries and maturation of eggs, there is correlation between reproductive hormones (estrogens and progesterone) and thyroid hormones in females (Boivin, Bunting, 2007). The balancing of thyroid hormone is thus essential for normal fertility in women. The functions of reproductive hormones can be altered by hypersecretion or hyposecretion of thyroid hormones (Bercovici, 2000) and results in thyroid related infertility includes ovulating disorders, irregular menses, and problem in conceiving a baby (Bercovici, 2000).

While few recognize infertility as an excellence of-life issue, the American Society for Reproductive Medicine (ASRM) consider infertility the same as a disease (ASRM, 2006). According to Americans Disabilities Act by U.S. Supreme Court that any condition which interfere in reproduction should be considered as disabilities because, fertility is an important life function (Bragdon, 1998).

A number of the states in India, many of them as large as the crowded areas in the world, in exacting the states namely Andhra, Himachal, Delhi, Tamil, and Maharashtra have been undergoing a dramatic and exceptional fertility diminution, reaching under replacement range of total fertility rate (TFR) of 2.1 in the current earlier period (Maternal & Child Mortality and Total Fertility Rates, 2011). A Delhi IVF Fertility Research Centre reported that the severity of the difficulty can be estimated by the fact that approximately one in six couples in the metros have problem conceiving on their individual and require treatment (Dutta, Guha, 2007).

Unusual body weight can be responsible for infertility in some ways. It has been shown that sometimes obese women are having complexity becoming pregnant. Menstrual cycle disturbances are commonly linked with Obesity. Thirty percent to forty percent of overweight and obese adult female have irregular menses according to data found in previous studies. Because of Irregular menstrual cycle increases the complexity in ovulation. An additional significant reality is, —The impact of obesity on reproduction can be accredited mainly to endocrine mechanisms (ASRM, 2013).

Male and female both can feel symptoms of hormonal imbalance, but female absolutely appear to get the bigger contribute in the pie when it comes to hormonally driven indications. Hormones are responsible for asserting so many functions like frame of mind, fertility, sleep, sexual characteristics, and capacity to handle anxiety.
Therefore it stands to reason that when hormones are imbalance. The variety of symptoms is broad and unpredictable depending on the individual and what life is distributing at that moment. (Health & Wellness Institute, 2015)

During the reproductive years, Females are frequently diagnosed and treated with major depressive disorder (MDD). Women who have complained of depression usually come across themselves evaluating treatment selections in anticipation of a pregnancy or quickly after becoming pregnant. Especially women who were not able to conceiving represent this type of complications. The persistent stress of infertility treatments and the indefinite time course and consequences for a possible fertility may create challenges in the continuous treatment of MDD. (Boivin and Bunting, Collins, 2007)

Depression and anxiety may negatively affect overall health, nourishment, appetite. Involvement in health care services, tobacco and ethanol use, or other substances, ambivalence about or decreased stimulus for pursuing infertility treatments in the appearance of failed attempts to conceiving, increased person pain, and distress in personal relationships. All of these factors in turn may harm fertility. women who smoke, chew tobacco or consume alcohol has 1.16% higher risk of infertility. In accumulation to these possible effects of depression and nervousness in fertility (Pariante, Lightman, 2008).

The markers for anxiety response contain cortisol and HPA axis dysregulation, and inflammation, with possible markers together with CRP and IL-6 (Young, Korszun, 2002). Interleukin-6 is a protein which is encoded by IL-6 gene; interleukin-6 acts as both pro-inflammatory cytokine and anti-inflammatory cytokine.

IL-6 is released by T cells and macrophages to provoke immune response like during illness and after trauma, particularly burns or in tissue injure leading to inflammation. Expression of both fibrinogen and CRP are induces by IL-6 which is an pro inflammatory cytokines. (Landmark, Diderholm, 2001) last studies were showed the special effects of psychological influences over reproduction have importantly deal with the negative effects of psychological “stress”, that is commonly assumed to have a central influence in infertility (Wischmann 2003).
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Elevated IL-6 is usually marked in the altered cytokine profiles feature of unexplained infertility, frequent spontaneous abortion, preeclampsia and preterm delivery. Especially, there is compelling data representing changed systemic Interleukin -6 trans-signaling in female prone to repeated miscarriage, with extreme Interleukin-6 bioavailability potentially suppressing production of CD4+ T regulatory cells mandatory for pregnancy tolerance. Inadequate local Interleukin 6 may also lead to fetal loss, since IL-6 expression is decreased in the endometrium of female with frequent miscarriage. (Prins et al., 2012)

Stress is a category of pain that involves the body and mind. Stress has been the basis of much theoretical uncertainty and has been defined numerous ways. Any event because of that disturbance occurs in person’s normal state and response is known as stress. Pregnancy failure can be a distressing experience in the face of the gestational period of the fetus or baby. First trimester losses are linked with improved risk for the beginning of depression and stress up to a period of three years later (Blackmore et al., 2011). The loss of a late gestation baby, a stillborn, and neonatal death is generally deeply painful for the parents; these wounded are psychologically complex and can reason of severe stress reactions and long-lasting symptoms of sorrow. (Cacciato & Bushfield, 2007).

Two thirds of Americans were expected to look for help for depression and 50% were anxious about the intensity of stress in their day by day lives; reported by a survey of American Psychiatric Association (2004). According to this survey 44% of populations were between 18 and 29 year age, and 46% of people were 30 to 49 year age; 40% were females and 35% were male. (Bjorn and Oddens, 1998).

Cytokines act as modulators of the immune system, they take part in the regulation of the ovarian cycle through endorsing follicular growth and leading the infiltration and activation of leukocytes essential for ovulation and remodeling of tissue during rupture of follicle, luteinization as well as luteolysis. (Bücher et al., 1999; Revelli et al., 2009).

IL-6 may lead to maturation of oocyte, IVF pregnancy failure were associated with decreased levels of Interleukin -6 in the pre ovulatory follicular fluid (Kawasaki et al., 2003; Bedairwy et al., 2007). In contrast, higher levels of
Interleukin-6 have been observed in females with ovarian hyper stimulation disorder and endometriosis. (Rizk \textit{et al.}, 1997; Garrido \textit{et al.}, 2000)

In the same way, acute coronary events occur predominantly in the early follicular stage of women having regularly menstruating when estrogen present in minimum level (Mukamal, Muller, 2002; Hamelin, Me’hot, ., 2003). CRP is used as a marker of inflammation (Rifai and Ridker, 2001). In healthy females, high CRP is one of the most substantial predictors of cardiovascular illness and heart attack risk (Boekholdt, Hack, 2003; Pradhan, 2002; Ridker and Hennekens, 2003).

Cardiovascular disease is the most important cause of death in most developed nations for both male and female. (AHA, 2001; Mosca and Manson, , 1997). The main key factor for the increase of cardiovascular complain is dyslipidemia, which may be coupled with complain liked diabetes mellitus and obesity (Howard et al, 1987; Shen et al, 2007). Dyslipidemia generally involve high levels of triglycerides, total cholesterol (TC), LDL and a decreased level of HDL cholesterol in plasma. (Franz and Bantle, 2002).

AIP is a marker of plasma atherogenicity. It is calculated as log (TG / HDLc). (Dobieová and Frohlich, 2001). People who are at higher risk of CAD have increased AIP. (Tan and Johns, 2004). Esterification rate of apo-B lipoprotein is representing close to the AIP Value. AIP indicate the delicate metabolic interactions in the lipoprotein complex (Dobieová and Frohlich, 2001).

In women, the danger of a coronary incident develops significantly after menopause consequent to decreased levels of endogenous estrogens (Davison and Davis, 2003). Other new markers which may assist recognize persons at danger for cardiovascular disease comprise inflammatory markers such as CRP, IL-6, and fibrinogen. (Topol and McCarthy, 2001).

CRP may be vigorously linked with the atherosclerotic process. Endothelial dysfunction characteristically precedes development of atherosclerotic lesions. CRP collects in fatty streaks as well as fibrous plaques of the atherosclerotic vessel wall, suggestive of a local inflammatory event (Vlaicu, Rus, 1985; Reynolds, Vance, 1987). Two other inflammatory markers, interleukin-6 or myeloperoxidase, have been newly proposed as important intermediates of coronary artery disease.
Impaired fecundity from infertility higher then distinguish according to cited statistic. All fertility impairments are including in infertility. Miscarriage is a part of impaired fecundity, different from infertility (ASRM, data).

Societal and behavioral changes in the previous one-quarter of the 20th century may have exaggerated levels of infertility, while this is uncertain whether the incidence of fertility impairments has altered over time (Stephen EH, Chandra A. 2006). In part due to "baby boomers" (that is the generation born between years 1946 and 1964) have gradually delayed the age at which they decide to conceive their first kid, and in part because new applied science have made it feasible for a few couples to defeat infertility and have made information with spectacular effects that as high-number of multiple births (Schieve and Meikle, 2002). Americans are gradually more sensitive and anxious about infertility, communal and ethnic disparities in health condition and in the incidence of certain risk factors (overage, late marriage, hypothyroid, stress, environmental, life style) that may direct to infertility (Chandra, Martinez, 2005).

A recent report from the CARDIA shows that among non–surgically infertile females, African and American females had two time increase in probability of describing a record of infertility. (Wellons and Lewis, 2009). Economic problem limit access to diagnosis, estimation, as well as treatment and may direct to selectively underestimating the incidence of infertility in the similar population groups (Peterson, 2005).

Till date a very few studies have been done in the area of hypothyroidism in reproductive age group of women along with their physical, hormonal and mental status and risk of cardiac diseases in southern part of Rajasthan, which is endemic area for hypothyroidism. (Pradhan, 2003).

Especially in the Indian context data on levels, trends and consequences of infertility are very limited. In recent decades due to significant economical development resulted in changes in life style, environmental factors and economical development and biological aspects, which in turn have an impact on fertility outcomes. That’s why we have planned this study on hypothyroid reproductive age
women along with their BMI (physical status), biochemical parameters like FSH, LH, PRL, T3, T4, TSH (hormonal status), IL-6, AIP, Lipid profile, CRP.

The purpose of this research work was to outline the reasons why infertility is a public health concern in hypothyroid reproductive age group of women with stress and without stress and open a discussion about the role of AIP, CRP, IL-6, BMI, FSH, LH, PRL, T3, T4, TSH and Lipid profile in hypothyroid reproductive age of women. So that the public health community (like Asha’s, health welfare, teacher’s, surpanch, NGO’S) can play a role in addressing the problem and Propose specific solutions and awareness in urban and rural areas.