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Assessment of infertility with related metabolic complications reported among the women of urban and Peri urban localities of Sindh, Pakistan

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ABSTRACT

The prevalence of infertility is increasing day by day in females all-round the globe. The major aim of this study was to analyze the prevalence of infertility and its related metabolic problems and risk factors among the urban areas of Sindh, Pakistan. The data was collected using a questionnaire which was analyzed precisely. The results of the analysis showed that out of 90 infertile females 43 (47%) were found positive, with affiliated metabolic disorders including, diabetes, polycystic ovarian syndrome (PCOS) & malnutrition. It was found that single infertile female displayed multiple metabolic disorders, thus results indicated that polycystic ovary syndrome (PCOS) was reported with highest prevalence 62%, followed by diabetes (48%), malnutrition (44%)& obesity (30%). The prevalence of metabolic disorders was highest at Hyderabad, followed by Tando Muhammad Khan, and lowest at Tando Allahyar. The exploration of major under lying causes, risks factors along with major metabolic disorders and syndromes associated with infertility in women causing infertility and the prevalence of infertility due to these issues can provide comprehensive data and assistance to counter and anticipate the treatment and management of different infertility issues related to metabolic disorders.

Keywords: Infertility, Metabolic complications, Women, Urban, Peri urban, Sindh, Pakistan**.**

INTRODUCTION

Globally the issue of infertility is critical for childbearing age women. Because of the changes in lifestyle and due to a range of environmental anxiety and stress, the infertility prevalence and incidence is increasing extensively and is observed to be the third most severe ailment, followed by cancer and the disease associated with cardiovascular system (Vander et al.,-Borght & Wyns, 2018). According to ESHRE (The European Society on Human Reproduction and Embryology) infertility is defined as the major handicap that prevents the people to achieve the major goal of life which is having the children. Treatments of infertility allow the infertile couples to articulate their sovereignty by realizing the choices of reproductive that leads to the increase in the feeling of well-being (Hudson et al., 2011). Infertility can be described as the defect related to the health of reproductive system which is considered different as compared to many other ailments and diseases. It is not considered and proved to be life threatening disorder, but the negative pressure of infertility to the effected patients, their families as well as the entire community cannot be underestimated regarding the effects of infertility(Macaluso et al., 2010; Trent, 2013).

According to the reports about the statistics of couples encountering infertility worldwide showed that 10% to 15% of the married couples account for infertility (Janisch & Schubert, 1991). In 2010 the systematic research analysis on the incidence of infertility in 190 countries of the world and regions round the globe revealed that, the women with the age between 20 years to 44 years suffered from primary infertility with the percentage of incidence to be 1.9%, and 10.5% incidence rate was observed in women suffering from secondary infertility (Mascarenhas et al., Flaxman,Boerma, Vanderpoel,

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& Stevens, 2012).

Pakistan is currently one of the most populous countries, with almost 2% growth rate of population. It has also high infertility rate with 21.9% (Khan et al.,2021). According to the survey reports on infertility prevalence in Pakistan, overall 5% cases of infertility represent the primary infertility while the secondary infertility accounts for 18.4% (Shaheen, Subhan, Sultan et al., 2010). One of the major and common causes is polycystic ovarian syndrome (PCO) (Ahmed et al., 2020). The prospective study conducted in Sindh including 1289 showed frequency of infertility in PCOs female to be 38.5%. The other factors causing infertility were pelvic inflammatory disease 44%, endometriosis 12.3%, hyperprolactenemia 2.9%, and hypothyroidism 1.35% (Arain et al., 2015).

Due to one of the major concerns regarding human reproductive health because of infertility and its impacts on the human risk factors of infertility and its related metabolic disorders have attracted major attention and concern in the health care system. Nevertheless, the comprehensive patho-physiological as well as the epidemiological research studies on the infertility risk factors is still not soundly acknowledged and documented in the literature (Meng et al., 2015). Typically, the parameters like age of the patient, obstetrical history, alcohol and smoking patterns, abnormal cycle of menstruation, Body mass index (BMI), environment related factors and the lifestyle of the patient are considered as the most important risk factors that results in the infertility (Sharma et al., 2013). Nevertheless, it is worth analyzing the major risk factors and affiliated disorders of infertility in certain countries.

Metabolic disorders can be defined as the abnormalities which are due to the malfunction of the process of metabolism in body. The major metabolic disorders that are affiliated with infertility are diabetes, obesity, and dyslipidemia that collectively results in them etabolic syndrome which is also known assyndrome X or insulin resistance syndrome that is the collection of different abnormalities in the metabolic system (Shalini et al., 2013). It is a syndrome which is characterized by intolerance of glucose, hypertension, dyslipidemia and central obesity (Hadaegh et al., 2013; Shahini et al., 2013). The prevalence and incidence of the major metabolic syndrome is increasing day by day worldwide (Shaliniet al., 2013).

(PCOS is also type of metabolic disorder which is most common in females (Khmil, Khmil, Marushchak, Halnykina, & Khmil, 2020). The major abnormalities which are interrelated to the metabolic syndrome that also results in the infertility includes dyslipidemia, blood pressure elevation, and increase in the level of plasma in blood (Amudha et al., Rani, Kannan, & Manavalan, 2013). There are observed to be the three major abnormalities which contribute directly towards the pro-inflammatory state as well as the state of pro-thrombic that results in the outcome which predisposes the person towards the progression of type 2 diabetes mellitus and cardiovascular system disorders majorly atherosclerosis (Roa et al.,, Aguilar, Dieguez, Pinilla, & Tena-Sempere, 2008). Hyper insulinemia and resistance of Insulin resistance are underlying and the primary abnormalities of the metabolic system observed in polycystic ovarian syndrome PCOS. Insulin resistance and the high insulin level in the circulating blood leads to the induction of adverse changes in the hormones secretion including the high production of androgen and metabolism of lipids by theca cells (Akter et al., 2013). The major risk factors of infertility usually includes; Hypertension, Polycystic Ovary Syndrome (PCOS), Blockage of fallopian tubes , Diabetes, Malnutrition, Smoking, Obesity etc. It is frequently related with abdominal adiposity, obesity, which also triggers insulin resistance, hyper insulinism (endogenous), and high lvels levels of adrenal and ovarian androgen (Benito et al., 2020). The higher production and release of hormones androgensin the body result in various issues of metabolism which also results in the distribution of dyslipidemia and fat centrally. In the women with obesity the high levels of circulating insulin and Dyslipidemia may also leads to the development of polycystic ovarian syndrome along with metabolic syndrome (Amudha et al., 2013).

There is not much research conducted in Sindh and also due to high prevalence of infertility it was necessary to conduct research regarding infertility and its related disorders especially in the urban and peri urban areas of Sindh. There was also observed the lack of information and awareness regarding the causes, risks factors of infertility and the scarcity of health seeking behavior in the couples encountering infertile in Pakistan. In this research study, we have analyzed and investigated the infertility prevalence and its associated metabolic disorders in urban areas of Sindh, Pakistan to develop awareness regarding infertility and provide assistance in the anticipation and management of infertility in women.

MATERIALS AND METHODS

Methodology

The study comprised of 90 infertile females to check prevalence of associated metabolic disorders those visited private and government hospitals of Hyderabad, Tando Muhammad Khan & Tando Allahyar during the period of 4 months, starting from August 2018 to December 2018. The hospitals included in the study were LUMHS Hyderabad, DHQ Tando Muhammad Khan and DHQ Tando Allahyar after seeking approval by the ethics committee of all three hospitals.

Data collection

The data for the study was collections by using specifically designed questionnaire, x-rays reports, ultrasound reports and other laboratory test reports in order to analyze the infertile females. Questionnaire was designed to collect the information like general demographic data of the participants which includes weight, age, height, address, occupation, education, number of children, pregnancies etc. Body mass index was calculated according to the criteria by (WHO, 2007) using the weight of females in kilograms divided by taking the height square in meters (kg/m). The BMI of less than 18kg/m is considered as underweight; 18.5–24.9 kg/m as moderate; 25.0–29.9 kg/m as overweight and greater than 30 kg/m falls in the category of obese (WHO, 2007)

The analysis of the collected data was done using the software SPSS version 20.0 for statistical analysis. The results of the data were tabulated using the mean and the standard deviation. The statistically significant value was considered as the value of $P < 0.05$. The major significance of the variables selected in this research study are that all the variables like age, height, Number of children and age at the time of marriage known as marriageable age, data regarding the number of abortions and pregnancies etc. given below in table I.

RESULTS AND DISCUSSION

General study parameters

Table I: Parametric data of respondents

Factors	Infertility	p-values
Total	90	
Age	35.50±5.18	0.049
Age at Marriage	23.35±5.35	0.0007
Marriage age limit	15.50±9.09	<0.0001
No. of Pregnancies	1.85±0.98	0.0066
No. of Abortions	0.39±0.54	0.0001
Weight	58.89±7.86	0.4371
Height	158.45±3.69	0.8287
BMI (Kg/m^2)	22.54±2.24	0.3978

Women infertility and Metabolic Disorder

Total 90 women were included in the study. Data obtained from the hospitals LUMHS Hyderabad, DHQ Tando Muhammad Khan and DHQ Tando Allahyar showed that out of the total sample population of 90 females included in the study for evaluation of the association of metabolic disorders affiliated with infertility revealed that out of the 90 females43 females that accounts for (47%) of the sample females were found to be positively associated with metabolic disorders as shown in fig1.

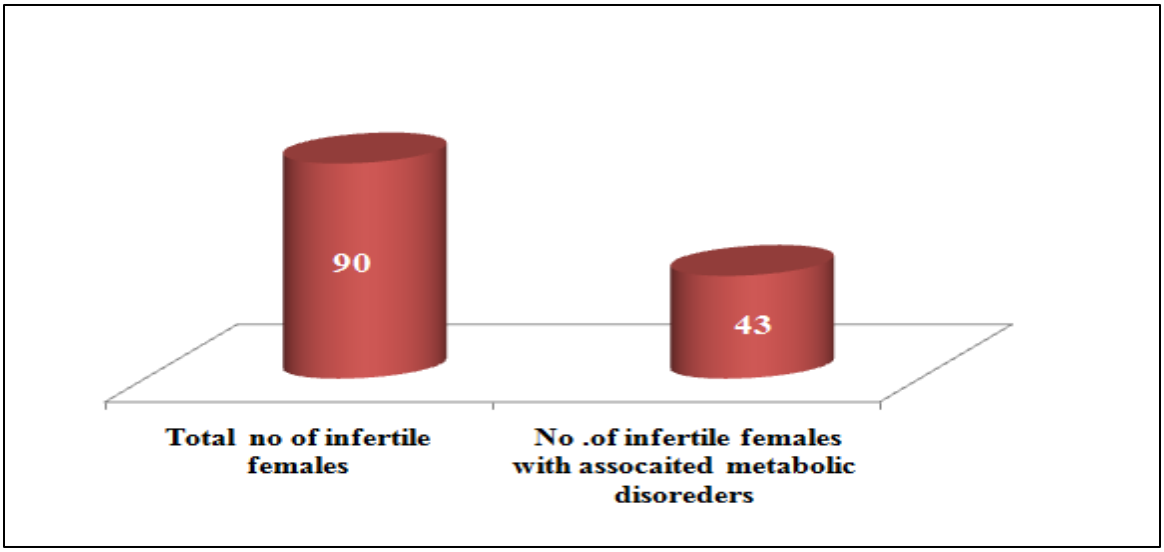

Fig1: Number of interfile females associated with metabolic disorders

Out of 90 infertile females 43 (47%) were found positive, with affiliated metabolic disorders including, diabetes, polycystic ovarian syndrome (PCOS) & malnutrition. It was found that single infertile female displayed multiple metabolic disorders, thus result indicated that polycystic ovary syndrome (PCOS) was reported with highest prevalence 62%, followed by diabetes 48%, malnutrition is 44% & obesity 30%. The prevalence of metabolic disorders was highest at Hyderabad, followed by Tando Muhammad Khan, and lowest at Tando Allahyar. Results also indicated that various associated disorders including polycystic ovary syndrome, diabetes, malnutrition & obesity were reported amongst the infertile females. Poly cystic ovary syndrome was abundant associated disorder reported in infertile females, whereas obesity was least abundant associated disorder reported infertile females. The research findings also indicated that obesity that is major metabolic syndrome's component, has momentous impact on fertility of female and showed high prevalence of obese females in population of infertile. Obese females have decreased level of insulin sensitivity, which leads to the high risk of adverse pregnancy outcomes (Scott, Harrison et al., 2017). Hyper triglyceridemia is also associated with cervical cancer affecting the fertility of women. High triglycerides level promotes the cancer cells proliferation and activity of anti-apoptosis by process of developing oxidative stress and reactive oxygen species production that leads to the induction of damage to DNA (Xie et al., 2020).

The onset of the puberty as well as fertility is determined by the storage of energy and its metabolism in the body. However the underlying mechanisms involved in the whole process is still not clear (Castellano et al., 2010; Hill et al., 2008). According to the reports of trials by researchers conducted on rodents and primates revealed that the metabolic stress conditions and negative balance of energy in the body like the condition of type 1 diabetes mellitus (Castellano et al., 2010; Kalamatianos et al., 2008) restriction in chronic diet taking behaviors and the condition of acute inflammation in mice and rats plays a very important role in effecting fertility (Tatone et al., 2010; Wahab et al., Ullah, Chan, Seminara, & Shahab, 2011).

All of the conditions lead to hypo-gonadism by the mechanism causing the suppression the of KiSS/ kisspeptin expression by hypothalamus. It in turns suppress the neurons of Kiss1 neurons expression which are very sensitive to the changes in the status of metabolism of the body (Ethel Codner et al., 2011). The use of kisspeptin-10 in the chronic treatment has shown to significantly revolutionize various short and long term deficits of reproduction in the patients of diabetes (J. Castellano et al., 2009). It is demonstrated that the defective tone of Kiss1 in the brain's hypothalamus considerably plays a vital role in hypogonadotropichypogonadism (García et.al., -Galiano, Pinilla, & Tena-Sempere, 2012).

It is frequently observed in the individual patients who are associated with poorly controlled type 1 diabetes mellitus (Abbade, Fernandes, Zantut-Wittmann, Parisi, & Pavin, 2020). Moreover, the women and females who are diabetic and obese have been associated with the higher complications risk related to pregnancy (Vahratian et al., 2009). Particularly, the control of glycemic

level of blood has also been related to the detrimental effects on the reproductive system of females suffering from all major types of diabetes mellitus respectively. Poorly or totally uncontrolled diabetes mellitus is also been observed to be linked with the females sexual dysfunction. It is also greatly associated with the elevated risk of mortality and morbidity of the newborns(Downs et al., 2010).

Women infertility and Polycystic Ovary Syndrome

The analysis of the data collected showed that out of the 43 infertile females which are positively associated with the metabolic disorder the 27 females out of 43 females that accounts for 63% of the sample size were suffering from infertility are also associated with the PCOS which is one of the leading foundation of infertility in females all over the world. The results are shown in fig 2.

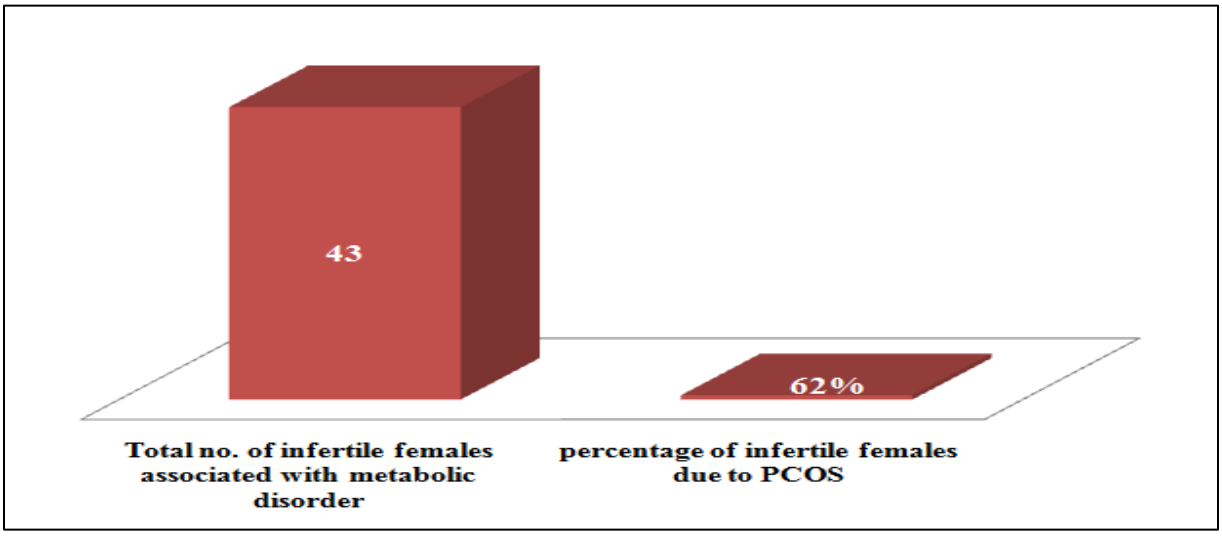

Fig 2: Percentage of infertile females due to PCOS

The prevalence of hypogonadism which is the main cause of PCOS is being reduced due to the development of novel and concentrated diabetes treatment which also resulted in the reduction of prevalence of amenorrhea (Whitworth et al., 2011). However, the rapid increase in abnormalities of reproductive system their incidence is also increased due to the use of excess insulin, predominantly in the condition of polycystic ovary syndrome by the patients, hyper androgenism and the excessive gain of weight has also been reported due to it (E Codner et al., Merino, & Tena-Sempere, 2012).

Polycystic ovary syndrome (PCOS) is the major disorder of hormones which is common in the females during the age of reproduction. Females suffering from with polycystic ovary syndrome have prolonged and infrequent menstrual cycle and/or have the higher levels of androgen which is a hormone secreted in males. The ovaries of the females also develop various tiny fluid collections known as follicles and also fail to release the eggs regularly. The ovaries of the polycystic ovary syndrome female may have distended follicles which are surrounding the eggs which results in the failure of ovaries to function normally and regularly (Elsheikh & Murphy, 2008).

Women infertility and Diabetes mellitus

Diabetes mellitus leads to additional problems that may affect fertility. The risk of infertility is therefore likely to be higher for couples in which one or more partner has diabetes. The data analysis showed that out of the 43 infertile females which are positively associated with the metabolic disorder the 21 females out of 43 females that accounts for 48% of the sample size were suffering from infertility are also associated with the diabetes as well shown in fig 3.

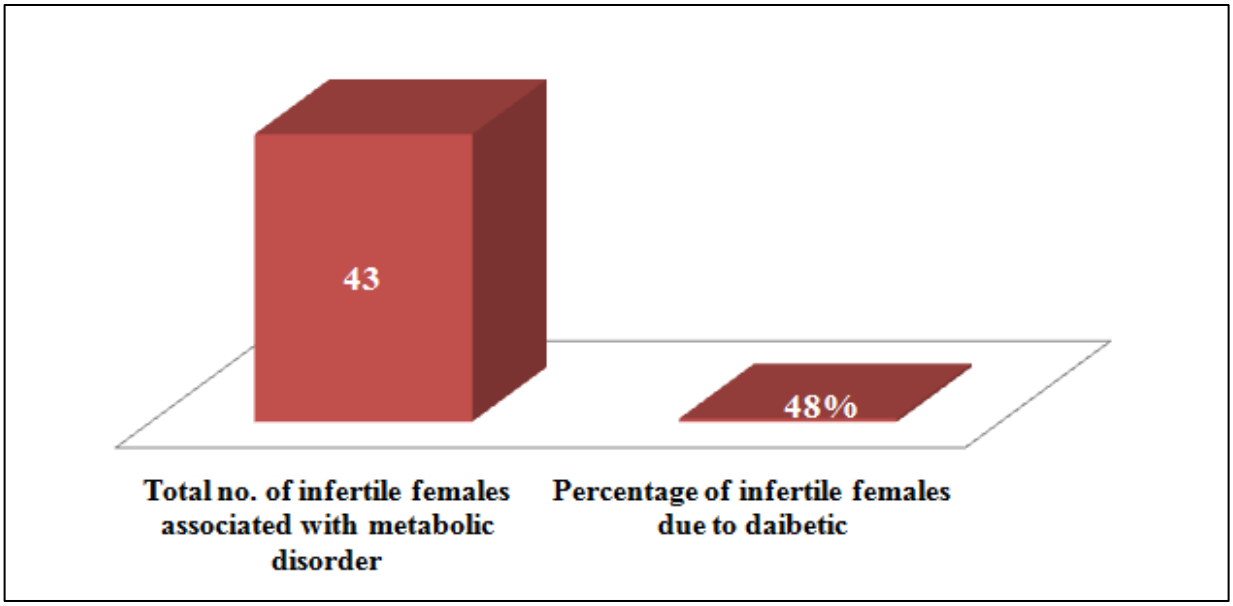

Figure 3: Percentage of infertile females due to diabetes

Hyperglycemia which is referred as diabetes and insulin resistance are involved in the induction of oxidative stress which results in the imbalance of the activity of free oxygen radical and the defense mechanism of antioxidant activity at cellular level in the body(Wender et al., 2011). The deterioration of the fetal development is also greatly associated with oxidative stress during the development of fetus (Samara-Boustani et al., 2012).

The research studies conducted on male and female animals also showed that the diabetes which is uncontrolled leads to profound state of hypogonadotropism, specified by the production and secretion of gonadotropins and sex steroids at low basal levels, the defective response of gonadotropin results in gonadectomy, and the lower level of LH pulsatility leads to the development of disturbed, negative and abnormal responses of feedback mechanism(Esposito et al., 2012).

In females the disruption of positive feedback mechanism is associated with the cause of delaying or diminishing of preovulatory LH anovulation and surges. According to some studies ovarian alterations in the females is also associated with diabetes which leads to major deficits of reproductive system (Cust et al., 2007; Harvey et al., 2011). Abnormalities regarding survival, growth of follicular, elevated granulosa and the apoptosis of follicles, and majorly the impaired communication of oocyte-granulosa, oocyte, abnormal maturation, and also the formation of ovarian follicles are being observed in many diabetic study animals (Cust et al., 2007).

Additionally, the deficiency of insulin deficiency is also associated with the ovulation defects that can be prevented and reversed by giving insulin in rodents with diabetes (Penaranda et al., 2013). These all study reports suggests the harmful and direct effects of low levels of insulin and hyperglycemia on the functions of ovarian in females which have the direct impact on the fertility of women (Barone et al., 2008).

Women infertility and Malnutrition

The performance of the reproductive system is certainly prejudiced by the intake of type of foods and nutrition (Silva et al., 2019). The intake of the diet which has unbalanced calories and protein contents because of the poor consumption of food is responsible for the under-weight, over-weight, or severe obesity, which results in the alterations of function of ovary with consequent amplification of infertility (Gambineri et al., 2019).

The data analysis showed that out of the 43 infertile females which were positively associated with the metabolic disorder the 19 females out of 43 females that accounts for 44% of the sample size were suffering from infertility are also associated with malnutrition as well shown in fig 4. Malnutrition is also the cause of infertility as a consequence of hormone abnormalities such as Polycystic Ovarian Syndrome (PCOS).

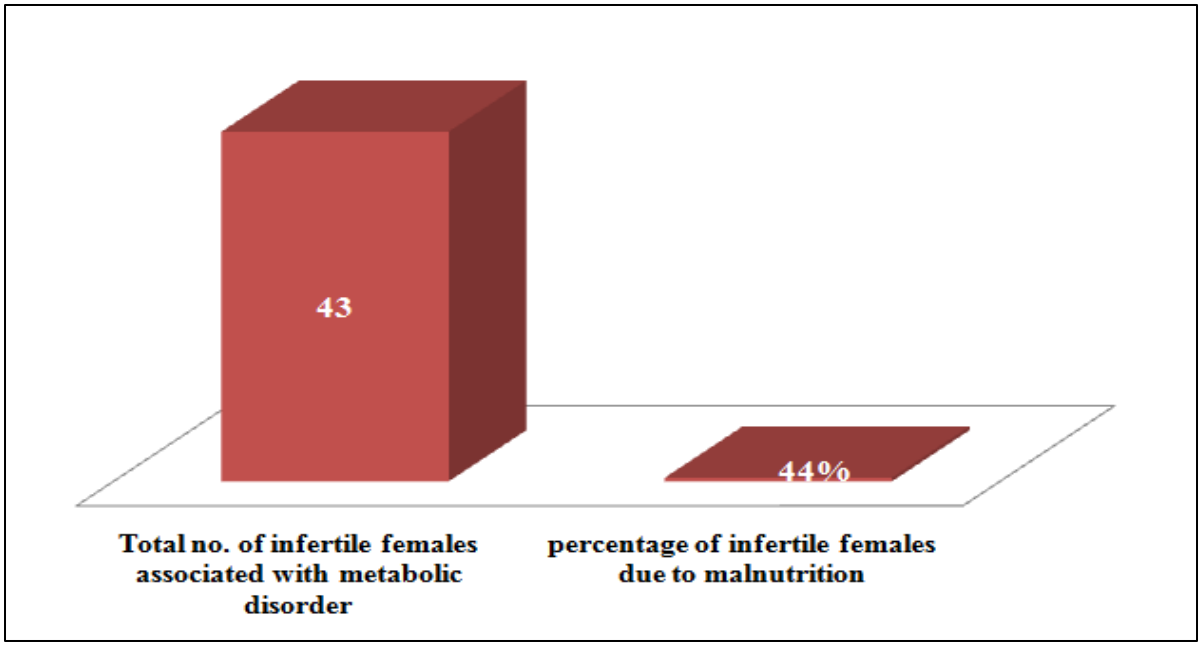

Fig 4: Percentage of infertile females due to malnutrition

Women infertility and Obesity

The incidence of infertile in the obese females is much higher, and there is found major and well known among infertility and obesity. The association among the functions of reproductive system and obesity is well explored. The females of overweight category have been associated with the high prevalence of an ovulation as well as menstrual dysfunction (Pettigrew & Hamilton-Fairley, 1997). The data analysis showed that out of the 43 infertile females which were positively associated with the metabolic disorder the 13 females out of 43 females that accounts for 30% of the sample size were suffering from infertility are also associated with obesity as well shown in fig 5.

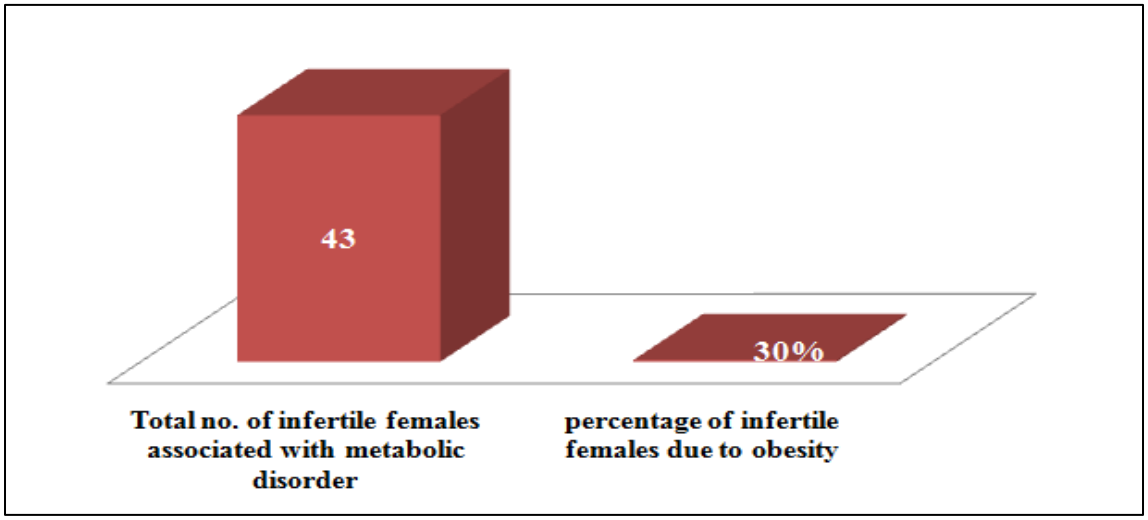

Fig 5: Percentage of infertile females due to obesity

Changes in lifestyle also have both positive and negative effects on the fertility of women. One of the major components of metabolic syndrome is Obesity, which is been highly and significantly associated with the cause infertility of females. In the infertile population there is found a high prevalence of obese females. Likewise, the obesity is also associated with infertility (Zain & Norman,

2008). The obese females have been observed to have the increased risks of 10% to 15% regarding the condition of preeclampsia, which is highly related to the hazardous outcome of abnormal pregnancy (Barton & Sibai, 2008). Obese females also have the lower concentrations of globulin which is sex hormone binding protein as compared to the lean females (Catalano, 2010). Additionally, the sub-fertility in obese female is partially attributed due to the lower or the absence of ovulation frequency (Barton & Sibai, 2008).

Moreover, the obesity can also hamper the precise ultra sonographic imaging of trans-abdomen during the transfer of embryo. The all the mechanism involved describes the low implantation and pregnancy rates in obese females who undergoes the assisted techniques during reproduction. Obesity that results in the overweight is also been observed to be associated with irregularities in menstrual cycle and low conception rate. Furthermore, obesity also increases miscarriage risks and contributes towards them aternal and perinatal complications (Elbers et al., 2011).

CONCLUSION

Reproduction plays a significant role in the lives of human beings. The metabolic disorders have the major adverse effects on the reproduction of women by affecting the fertility. Metabolic disorders which include diabetes, hyper lipidemia and obesity can affect the fertility of females directly and/or indirectly due to the interference with the function of ovarian and pituitary-hypothalamus. In conclusion, the study results suggest that infertility rate is high which is highly associated with Polycystic Ovary Syndrome (PCOS), Diabetes, Malnutrition, Obesity etc. having had a negative impact on fecundity which highly affects women by putting severe pressure on females in our society.

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