

## Pharmacoepidemiological Profile Of Diagnosed Cases Of Infertility (A Cross Sectional Observational Study)

Dr. Darshan J. Dave

Associate Professor, Pharmacology, GMERS Medical College, Gandhinagar, Gujarat

**Abstract:** Background: The incidence of primary and secondary infertility is going to increase significantly. Amidst many causes, obesity is considered to be the most important cause. The aim of this work was to identify the epidemiological profile and prescribing pattern of drug therapy for women suffering from infertility. Methodology: Cross sectional observational study was conducted at multispeciality private hospital over a period of six months. Epidemiological details and drugs prescribed for infertility were recorded in a predesigned structured case record form. The age wise distribution and BMI wise distribution was prepared. Categorical data were expressed as number and percentage, and numerical data as mean and standard deviation. Results: There was nearly equal distribution of infertility in age group of 25-30 years (66,38.37%) and 30-35 years (62,36.05%) Majority of the females were in age group of 78 females (45.35%) were overweight and obese while rest were normal weight (73,42.44%) or underweight (21,12.21%). 116 (67.44%) were having primary infertility while 56 females (32.56%) were having secondary infertility. 41 females (53.80%) were having associated systemic illnesses. Clomiphene citrate, Metformin, Orlistat were prescribed in all the cases. Conclusion: Rate of infertility increases with age in both normal weight and obese females. No statistically significant differences between primary and secondary infertility in normal weight and obese persons were found. Associated systemic illnesses were higher in obese females, especially genital tuberculosis. Clomiphene citrate, Metformin and Orlistat are commonly prescribed agents for the management of infertility. Further research is required to clarify the role of Glucocorticoids and aspirin therapy as an aid to implantation. [Dave D Natl J Integr Res Med, 2019; 10(2):61-68]

**Key Words:** Obesity, Infertility, BMI, Clomiphene, Metformin

**Author for correspondence:** Dr. Darshan J. Dave, Associate Professor, Department of Pharmacology, GMERS Medical College, Gandhinagar, Gujarat E-mail: darshanjd79@yahoo.com M:8000380481

**Introduction:** Infertility is defined as a failure to become pregnant within one or more years of regular unprotected sexual intercourse. There are two type of infertility. Firstly, primary infertility means those patients who have never become pregnant. Secondly, secondary infertility designates previous pregnancy but failure to become pregnant consequently.<sup>1</sup> Some scientists represented subfertility as complete failure to conceive because of absence of sperm, premature menopause and complete tubal obstruction.<sup>2</sup>

The prevalence of infertility is projected between 12 to 14 % throughout the world.<sup>2</sup> According to WHO, primary and secondary infertility are 3% and 8% respectively in India.<sup>3</sup> The act of conceiving rely on the potential of fertility of both male and female. About 30-40% and 40-50% cases of infertility are directly related to male and female fertility potential respectively and both are accountable in about 10% cases of infertility.<sup>1</sup> Approximately 5% to 10% is unexplained or idiopathic infertility, when evident reason for infertility has not been detected by following all standard investigations. Ordinary reasons of male infertility are defective spermatogenesis, obstruction of the efferent duct system, failure to

put down high sperm in the vagina and mistakes in the seminal fluid. Causes for female infertility encompass tubal and peritoneal factors (25-35%), ovulatory factors (15-25%) and endometriosis (1-10%).<sup>1</sup>

The end result of many disorders like malformative, endocrine, autoimmune, infective, obesity and psychological can be the infertility. Currently, infertility is frequently treated with medications, it may act as cofactors by changing cellular and hormonal environment of body and trigger the development of ovarian, endometrial and breast cancers.<sup>4</sup> The fertility, menstrual function, metabolism, estrogen and androgen have been significantly affected by thyroid diseases (both hyperthyroidism and hypothyroidism).<sup>5</sup> Pelvic inflammatory disease (PID), sexually transmitted diseases (STD), and pelvic tuberculosis are associated with infertility. A women's ability to conceive has been significantly influenced by age. The numbers of women are increasing who have experience of age related infertility and pregnancy loss. Women older than 35 years should failed attempted to conceive as earlier if clinically indicated.<sup>6</sup> The incidence of existing psychiatric disorders (depression, obsessive compulsive symptoms,

anxiety, substance abuse and psychoticism) were drastically higher among infertile patients than among fertile patients.<sup>7</sup>

Globally, obesity (excess body weight) is the sixth vital causative risk factor for the development of overall burden of disease. The life expectancy by 7 years at the age of 40 years has been decreased by obesity.<sup>8</sup> Obesity is a serious, nutrition dependent pathology and having principally influence on the reproductive system, causes are unknown. It is characterized by the presence of an excess body fat, although it is frequently described on the basis of body mass index (BMI) or waist circumference. BMI is the weight in kilograms divided by square of the height in meters. Obesity is defined by a BMI greater than 29.9 kg/m<sup>2</sup>, while being over weight is defined by a BMI ranges from 25 kg/m<sup>2</sup> to 29.9 kg/m<sup>2</sup>.<sup>9</sup> Worldwide, the rate of obesity and mean BMI have been found normally higher in women as compared to men at all ages.<sup>8</sup>

Obesity can impairs the hypothalamic ovarian uterine axis at many level and alters The quality of oocytes and embryos have been altered by obesity because it can impairs the hypothalamic ovarian uterine axis at many level and increase the time for conception and decrease the pregnancy rates. So, the unique problems for women may develop including infertility, problem during pregnancy, hypertension, dyslipidaemia, insulin resistance, cardiovascular disease, type 2 diabetes mellitus, stroke, sleep apnea, gallbladder disease, infection, osteoarthritis, hyperuricemia, gout, cancer (post menopausal breast cancer, endometrial cancer, colon cancer, prostate cancer, uterus cancer etc.) reproductive hormonal irregularities, polycystic ovary syndromes, fetal defects from maternal obesity and mental health problems.<sup>9</sup><sup>10</sup>,<sup>11</sup> Obesity is connected with declined contraceptive effectiveness, irregular menstruation, early puberty, raised miscarriage rate, ovulatory disorders, and poorer assisted reproductive technology (ART) results. Many of these problems have been restructured by losing weight.<sup>12</sup>

Medical and surgical treatments (ART) are available for female infertility and given according to the requirement and the disorders identified.<sup>1</sup> Currant and future option for fertility preservation by using new techniques include preservation male fertility by sperm

cryopreservation, testicular sperm extraction, testicular tissue freezing and hormonal suppression and preservation of female fertility by embryo cryopreservation and cryopreservation of oocytes or ovarian tissue. Preservation research may enhance the quality of life of infertile patients.<sup>13</sup>

Base on the above information, obesity can be an independent risk factor for infertility. The aim of this work was to identify the epidemiological profile and prescribing pattern of drug therapy for women suffering from infertility by cross-sectional observational study.

**Materials and Methods:** A cross sectional observational study conducted at multispecialty private hospital, Ahmedabad. The study was conducted after getting approval of institutional ethics committee. Women diagnosed as having infertility were enrolled in the study based on the below mentioned inclusion and exclusion criteria (Table 1).

**Table 1: Inclusion and Exclusion Criteria**

Inclusion criteria	Exclusion criteria
Female patients having age between 20 to 40 years.	Severe male factor infertility
Male partner having normal semen analysis with a sperm concentration of >15 million total motile sperms, >1% normal forms by strict criteria, or >5 million total motile sperm on IUI prep.	Associated neoplasia
Patients with surgically corrected stages I and II endometriosis.	Gonadal dysgenesis or congenital abnormalities of the reproductive system.
Normal uterine cavity demonstrated by HSG, Sonohysterogram (SHG), or hysteroscopy; pathologies of uterine cavity amenable to operative hysteroscopy (cavity restored to normal and demonstrated by post operative study).	Couples using donor semen
The female patients undergo the infertility treatment because of tubal factors, hormonal factors, PCOD, endometriosis etc.	

Records of all the patients who follow the above mentioned inclusion and exclusion criteria were recorded from the hospital record data over a period of six months. Demographic details and all the details of treatment given were recorded in predesigned and validated case record form.

**Results:** The age wise distribution and BMI wise distribution was prepared. Categorical data were expressed as number and percentage, and numerical data as mean and standard deviation.

- Age wise analysis of infertile patients
- BMI wise analysis of infertile patients
- Provisional diagnosis
- Associated systemic illnesses
- Pharmacological agents prescribed

Distribution of patients according to primary and secondary infertility is mentioned in table 2.

**Table 2: Distribution of patients according to primary and secondary infertility**

BMI Ranges	Primary infertility	No. of patients having Secondary Infertility
Underweight	13 (61.9%)	08 (38.1%)
Normal weight	55 (75.34%)	18 (24.66%)

Over weight & Obese	48 (61.54%)	30 (38.46%)
Total	116 (67.44%)	56 (32.56%)

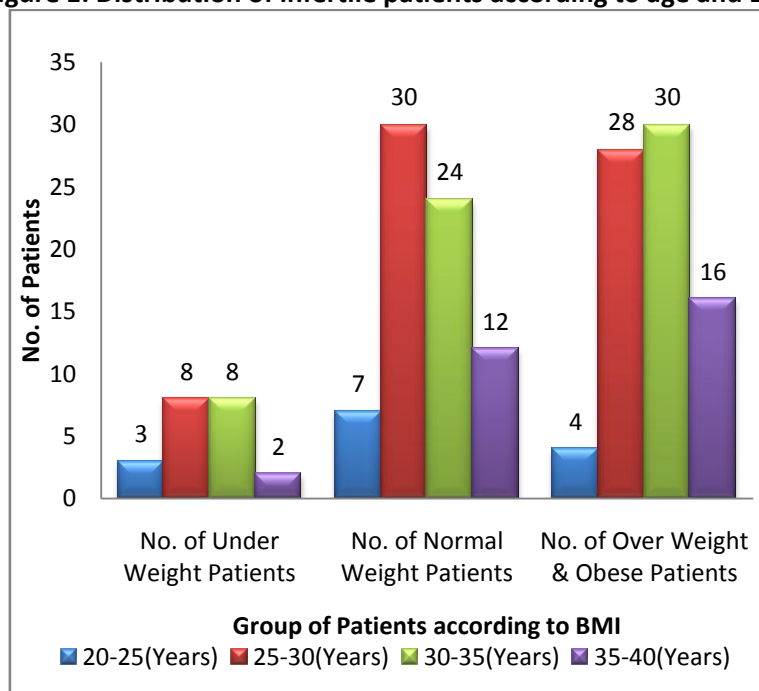
Use of Injectable Gonadotropins used for the Management of Infertility is shown in table 3.

**Table 3: Injectable Gonadotropins used for the Management of Infertility**

Different Gonadotropins	Name of Drugs
FSH and Recombinant FSH	Urofollitrophin alpha (Recombinant FSH), Lyoshere of Follitrophin Beta (Recombinant FSH), Menotrophin FSH, Urofollitrophin FSH.
GnRH agonist and antagonist	Luprorelin, Cetrorelix Acetate.
Human Chorionic Gonadotropins (Tropical Hormone)	Human Chorionic Gonadotropins, Highly Purified Human Chorionic Gonadotropins.

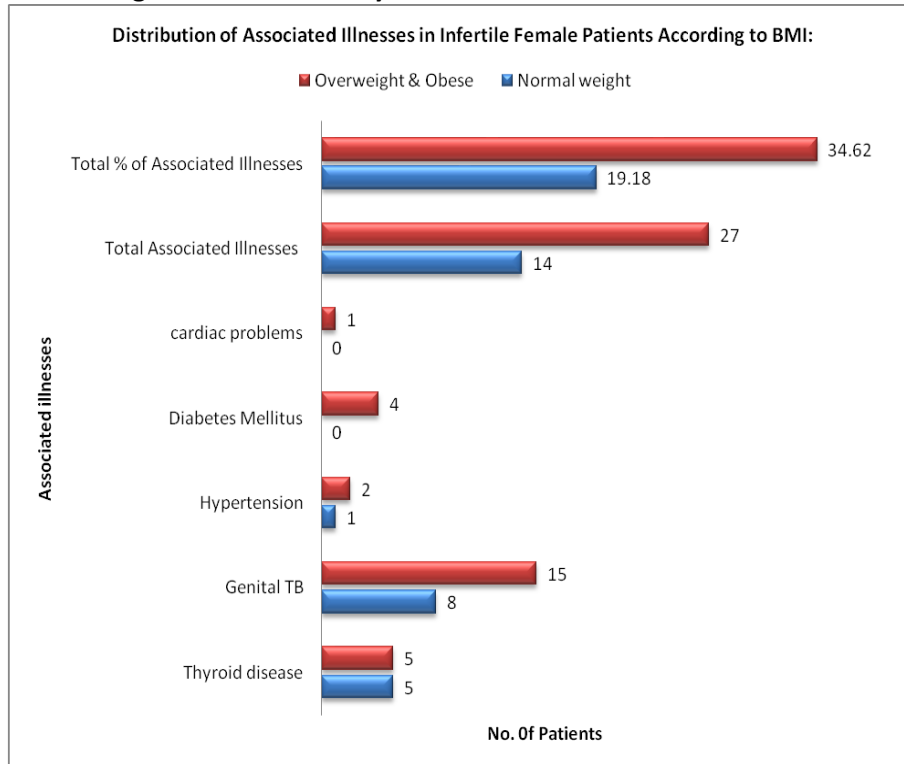
Distribution of patients according to age and BMI is mentioned in figure 1 Below

**Figure 1: Distribution of infertile patients according to age and BMI**



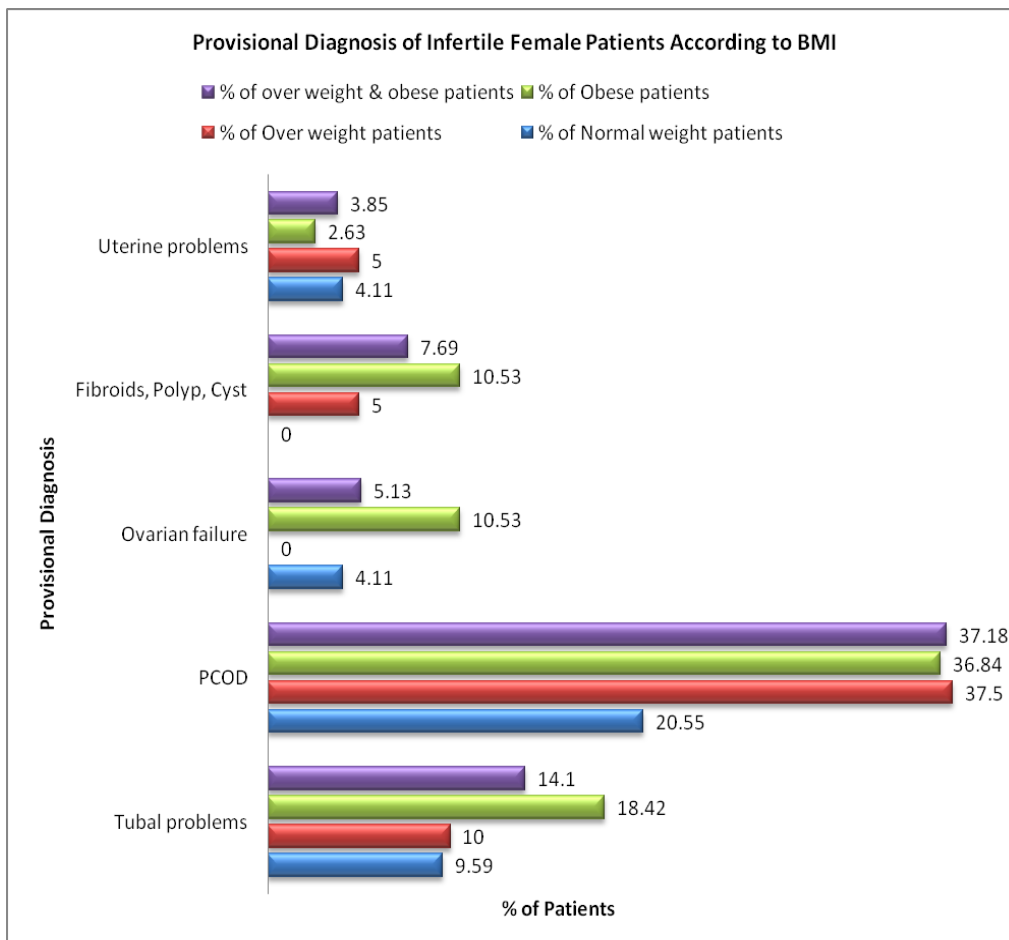
Comparison of associated systemic illnesses in normal, overweight and obese patients are shown in fig. 2.

**Figure 2: Associated systemic illnesses in infertile women**



Provisional diagnosis of infertility is shown in figure 3.

**Figure 3: Comparison of provisional diagnosis of infertility**



Injectable Gonadotropins were given I.M (intramuscular) / S.C (subcutaneous) as per the

requirement to infertile patients during ART. It was given in two fashions. Firstly, step up

regimen, the initial dose of FSH was 50 to 75 IU I.M or S.C. If no response was observed on USG, the dose is increased up to a maximum of 225 IU/day or more than that if required. Secondly, Step-down regimen, the starting dose of 150 IU/day of FSH was given. This dose was continued until a dominant follicle (greater than 10 mm) was seen on TVS (Trans-Vaginal Sonography). The dose is then decreased to 112.5 IU per day followed by a further decrease to 75 IU per day. The dose of FSH was increased, if the ovarian response was not observed after 3 to 5 days.

An ovulation inducer – clomiphene citrate (50 mg), an aromatase inhibitor – letrozole (2.5 mg), aspirin (75 mg), metformin (500 mg) and dexamethasone (0.5 mg) were prescribed to all patients. Anti Obese drug, ORLISTAT (120 mg) was prescribed only in overweight and obese infertile patients. Frequency and dose of the drugs were given higher in overweight & obese patients as compared to normal weight patients.

**Discussion:** Obesity (excess bodyweight) has serious impact on morbidity, mortality and reproductive system of female. Women are more susceptible to become overweight and obese than man.<sup>10</sup> The reproductive problems associated with obesity are increased because large number of women become obese. This is a challenge for doctors who are occupied in fertility care.<sup>14</sup>

The most important factors influencing fertility (reproductive system) in female is age because elder patients have poorer oocyte quality than younger patients (less than 30 years).<sup>14</sup> The decreased egg quality and increased FSH level has been associated with increased Age.<sup>6</sup>

In the present study, 172 infertile women, among them 128 (74.41 %) of infertile women are in between 25-35 years of age. It indicates that the majority of infertile women are in the highly effective reproductive period. Among them many women are obese; there is evidence that the fertility rate has been affected by obesity in women within the fertile age.<sup>15</sup>

The data suggest that the number of infertile women [46pts (58.97%) vs. 36 pts (49.32%)] having age greater than 30 years are more in the overweight & obese group than normal weight group and 92 (53.49%) women out of 172 women are between 30-40 years of age. It indicates that the reproductive system or fertility of female had

been significantly affected by increased Age. The risk of other disorders that may adversely affect fertility, such as fibroid, tubal disease, endometriosis and pelvic infection etc. has been increased with increased age.<sup>6</sup>

The female reproductive system has been influenced by the fat distribution and the severity of the obesity (excess body fat).<sup>16</sup> Infertility is more common in overweight and obese women because the hypothalamic ovarian – uterine axis has been disturbed by obesity at many level.<sup>9</sup> According to WHO, in the present study, 12.21% of women (under weight 21 pts) have BMI less than 18.5 kg/m<sup>2</sup>, 42.44% of women (Normal weight – 73 pts) have BMI 18.5 kg/m<sup>2</sup> to 24:9 kg/m<sup>2</sup>, and 45.35% women (over weight & obese 78 pts) have BMI greater than 24.9 kg/m<sup>2</sup>. Among 78 (45.35%) over weight & obese patients, 38 (48.72%) patients were obese (BMI greater than 29.9 kg/m<sup>2</sup>) and 40 (51.28%) were overweight (BMI between 24.9 kg/m<sup>2</sup> to 29.9 kg/m<sup>2</sup>).

The infertility rate was higher in obese women as compared to normal weight women (Infertility rates: obese 33.6% vs. normal weight 18.6%).<sup>16</sup> In the present study, the infertility rate was higher in overweight & obese patients than in normal weight patients (Infertility rate: Overweight & obese 45.35% vs. normal weight 42.44%). It means that significant no. of infertile patients having BMI more than normal. Hence there is a positive relationship between obesity and infertility. The probability of achieving pregnancy in women with higher body mass index (BMI) has been reduced because the reproductive cycle has been influenced by obesity.<sup>16</sup> Finally, it also alters the quality of oocytes and embryos because it may impair estrogen metabolism, sex hormone binding globulin (SHBG) concentration, hyperinsulinemia, and leptin levels.<sup>9</sup>

Obesity is increased the risk of other disorder such as fibroid, tubal disease, endometriosis pelvic infection etc.<sup>6,10</sup> Obesity probably accounts for 6% of primary infertility.<sup>11</sup> According to WHO, primary and secondary infertility are 3% and 8% respectively in India.<sup>3</sup> In the present study, among 172 infertile patients 116 (67.44%) were having primary infertility while 56 (32.56%) were having Secondary infertility. Secondary infertility was higher (38.46% vs. 24.66%) in overweight & obese patients as compared to normal weight patients. Normal weight patients were having greater primary infertility (75.34% vs. 61.54%) as

compared to overweight & obese patients. There is no statistical significance about primary and secondary fertility between normal and overweight & obese patients (P-value = 0.07).

In the present study, over all associated systemic illnesses were higher (34.62% vs. 19.18%) in overweight & obese patients as compared to normal weight patients. Genital tuberculosis, hypertension, diabetes mellitus and cardiac problems were higher 19.23% vs. 10.96%, 2.56% vs. 1.37%, 5.13% vs. 0% and 1.28% vs. 0% in overweight & obese patients as compared to normal weight patients respectively. There was no major significant difference of (Hypothyroidism) thyroid disease (6.41% vs. 6.85%) in overweight & obese compared with normal weight patients. It indicates that obesity is an independent risk factor for developing many medical problems including thyroid disease, genital tuberculosis, hypertension, diabetes mellitus and cardiac problems. Both hypothyroidism and hyperthyroidism have been found four to five times elevated in women as compared to men and alter estrogen and androgen metabolism, menstrual function and fertility. Severe hypothyroidism causes 50% to 70% of female infertility due to anovulation, menstrual irregularities, spontaneous first trimester abortions, still births and premature deliveries.<sup>5, 17</sup> Thyroid disorder is significantly increased in obese women as compared to normal women.<sup>2</sup> But in present study; there was no significant difference for thyroid disease in overweight & obese women as compared to normal weight women. To rule out the association between obesity, infertility and thyroid diseases are required further more studies.

Genital tuberculosis was higher (19.23% vs. 10.96%) in overweight & obese in the present as compared to normal weight patients in the present study. Pelvic tuberculosis in the female is confined principally to the reproductive tract, particularly the endometrium and fallopian tubes.<sup>15</sup> The development of diabetes, dyslipidaemia and the other metabolic syndromes, have been interacted with abdominal obesity, weight gain, endogenous inflammation and external sources of infection. In the present study, the overweight & obese patients were having higher hypertension and cardiac problem as compared to normal weight patients. Obesity increases the risk of developing hypertension,

insulin resistance, dyslipidaemia, type 2 diabetes mellitus, cardiovascular disease, sleep apnea, stroke, hyperuricemia, gallbladder disease, gout and osteoarthritis.<sup>11</sup> The risk of hypertension is five times higher in obese people as compared to normal weight people. 85% of hypertension arises in individual with BMI values above 25 kg/m<sup>2</sup>.<sup>8</sup> The risk of coronary heart diseases (cardiac problems) has been increased 3.6 times higher in the patients having BMI greater than 21 kg/m<sup>2</sup>.<sup>8</sup> In the present study, the diabetes mellitus was higher (5.13 % vs. 0%) in overweight & obese as compared to normal weight patients. Around 90% of individuals who develop type 2 diabetes have BMI higher than 23.0 kg/m<sup>2</sup> and the risk of diabetes being greatly increased by early weight gain.<sup>8</sup> Obesity is the causative risk for the development of gestational diabetes mellitus, with a risk of about 20%.<sup>17</sup> Gestational diabetes mellitus (GDM) during pregnancy has been connected with increased risk of type 2 diabetes, early obesity, metabolic disorders and poor pregnancy outcome.<sup>17</sup> Over all associated systemic illnesses are more in overweight & obese, among this particularly thyroid disease, genital tuberculosis and diabetes mellitus are more commonly associated which are known causative factors for infertility.

Excess body fat is strongly connected to disorders of the reproductive system. Obesity, central obesity and insulin resistance are the etiological factors for reproductive diseases. Insulin resistance and restoring ovulation and fertility have been achieved by short term weight loss. The menstrual regularity, ovulation, and infertility in women have been improved by moderate weight loss and diminution of abdominal fat. As such, weight loss is the preliminary treatment option for obese patients with infertility. In the present study, currently anti obesity drug, orlistat has been given to overweight and obese patients to reduce obesity and infertility of patients. The amount of patients with 5 % weight loss at 1 year have been achieved three to four times higher by the use of anti obesity drugs.<sup>16</sup>

Clomiphene is most effective in normogonadotropic anovulatory women as anti-estrogen for ovulation induction. It is act by blocking the negative feedback mechanism of estrogen in the hypothalamus and pituitary, and resulting in stimulation of follicle growth and follicular estradiol production.<sup>21</sup> Clomiphene-

resistant patients have been shown obesity, hyperandrogenemia and insulin resistance. If clomiphene was failed to achieve ovulations, medical or surgical treatment has been approached. In the present study, the dose of clomiphene was increased with increased BMI. Gonadotrophin injections are an effective alternative medical treatment for the induction of ovulation.<sup>16</sup> The obese women having poorer peak estradiol level and a drastically lower fertilization rate and needed drastically elongated stimulation with the help of more gonadotropin ampoules.

Insulin-sensitizers, metformin have been used to improve pregnancy outcomes in women with PCOS and to diminish hyperinsulinemia insulin resistance and hypofibrinolytic plasminogen activator inhibitor activity. Hence, folliculogenesis and oocyte quality has been improvement by metformin. Attention towards the prevention and treatment of ovarian hyper stimulation syndrome has been taken in patients undergo ovarian stimulation.<sup>16</sup> The doses of metformin are 500 mg three times daily and 850 mg twice daily.<sup>18</sup> The effect of metformin has been observed lower in overweight & obese patients as compared to normal weight patients.<sup>19</sup>

Aromatase inhibitor, Letrozole act by blocking the conversion of testosterone and androstenedione to estradiol and estrone, respectively. It increases the gonadotrophin secretion and stimulates the growth of ovarian follicles. Letrozole 2.5 mg daily dose is effective in the management of infertility.<sup>18</sup> In the present study, Letrozole 2.5 mg daily dose has been given to infertile patients.

Aspirin and Glucocorticoids have been given in infertile patients as adjuvant therapies. Glucocorticoids may reduce ovarian androgen levels, improve ovulatory function and reduce resistance to ovulation induction agents. Aspirin act as antithrombotic and vasodilator in low doses by inhibiting the synthesis of thromboxane A2 (promoter of platelet aggregation and a vasoconstrictor) more than that of prostacyclin (a vasodilator).<sup>18</sup>

**Conclusion:** To summaries and conclude, rate of infertility increases with age in both normal weight and obese females. No statistically significant differences between primary and secondary infertility in normal weight and obese persons were found. Associated systemic illnesses were higher in obese females, especially

genital tuberculosis. Clomiphene citrate, Metformin and Orlistat are commonly prescribed agents for the management of infertility. Further research is required to clarify the role of Glucocorticoids and aspirin therapy as an aid to implantation.

#### References:

1. Dutta D.C. Infertility. In: Konar H, editor. Textbook of Gynaecology. 4th ed. Kolkata: New Central Book Agency (P) Ltd; 2003. 212-41.
2. Poppe K, Velkeniers B. Female infertility and thyroid. Best practice & Research Clinical Endocrinology & Metabolism. 2004;18(2):153-65.
3. Widge A. Social cultural attitudes towards infertility and assisted reproduction in India. [apps.who.int/reproductive-health/infertility/11.pdf](https://apps.who.int/reproductive-health/infertility/11.pdf). Assessed on 19 June, 2018.
4. Cetin I, Cozzi V, Antonazzo P. Infertility as a Cancer Risk Factor – A Review. Placenta. 2008;29:S169-77.
5. Krassas GE. Thyroid disease and female reproduction. Fertility and Sterility. December 2000;74(6):1063-70.
6. The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and the Practice Committee of the American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. September 2008;90(3):486-87.
7. Sbaragli C, Morgante G, et al. Infertility and psychiatric morbidity. Fertility and Sterility. Vol. 90, No. 6, December 2008;90(6):2107-11.
8. Haslam DW, James WPT. Obesity. Lancet. 2005; 366:1197-209.
9. Robker RL. Evidence that obesity alters the quality of oocytes and embryos. Pathophysiology. 2008;15:115-21.
10. Haslam D. Gender – specific aspects of obesity. Jmbg. June 2005;2(2):179-85.
11. Khaodhlar L, McCowen KC, Blackburn GL. Obesity and Its Comorbid Conditions. Clinical CORNER STONE. Obesity. 2(3):17-31.
12. Lash MM, Armstrong A. Impact of obesity on women's health. Fertility and Sterility. May 2009;91(5):1712-16.
13. Lamar CA, DeCherncy AH. Fertility Preservation: state of the science and future research directions. Fertility and Sterility. Vol. 91, No. 2, February 2009;91(2):316-19.

14. Metwally M, Ledger LW. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta analysis of the evidence. *Fertility and Sterility*. Vol. 90, No. 3, September 2008.
15. Pasquali R. Obesity, fat distribution and infertility. *Maturitas*. 2006;54:363-71.
16. Parihar M. Obesity and infertility. Review in *Gynecological Practice*. 2003;3:120-26.
17. Yogev Y, Visser GHA. Obesity, gestational diabetes and pregnancy outcome. *Seminars in Fetal & Neonatal Medicine*. 2009;14:77-84.
18. Sterrenburg MD, Macklon NS. Drugs in reproductive medicine. *Obstetrics, Gynaecology and Reproductive Medicine*. In press 2009. doi.10, 1016/j.ogrm.2009.04.006.
19. Maciel GAR, Haidar MA, et al. Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. *Fertility and Sterility*. Vol. 81, No. 2, February 2004;81(2):355-60.

Conflict of interest: None
Funding: None
Cite this Article as: Dave D, PharmacoepidemiologicalProfile Of Diagnosed Cases Of Infertility, (A Cross Sectional Observational Study). <i>Natl J Integr Res Med</i> 2019; Vol.10(2): 61-68