Outcomes of Fertility Inducing Drugs at Family Guidance Association of Ethiopia Obstetrics and Gynecology Special Clinic, Addis Ababa: A Retrospective Cross Sectional Study

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A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment of the Requirements for the Master of Pharmacy Degree in Pharmacy Practice

Addis Ababa University

Addis Ababa, Ethiopia

June, 2018

Addis Ababa University

School of Graduate Studies

This is to certify that the thesis prepared by Demilie Abate, entitled: Outcomes of Fertility Inducing Drugs at Ethiopian Family Guidance Association Obstetrics and Gynecology Special Clinic, Addis Ababa: A retrospective cross sectional study and submitted in partial fulfillment for the requirements of the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Outcomes of Fertility Inducing Drugs at Ethiopian Family Guidance Association Obstetrics and Gynecology Special Clinic, Addis Ababa: A Retrospective Cross Sectional Study

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Infertility refers to the inability of couples to conceive a clinical pregnancy after one year or more of trying to conceive. The cultural practices and attitudes of nations and nationalities in Ethiopia uphold reproduction as the most important function of families. Childlessness remains to be the most undesirable experience within marriage for most couples. Unfortunately, due to the long standing traditional outlooks of the vast majority of the society, women are expected to carry the burden of impaired fertility in a family. Like in many other populations, impaired fertility is an important health concern for Ethiopian women. There are many reasons why a couple may not be able to conceive, or may not be able to conceive without medical assistance. Currently the use of medical assistance to achieve fertility among couples who can't conceive regardless of their trial to get pregnant is on the increase. In Ethiopia, evidence showed that infertility treatment has been provided since the past two decades.

The aim of this study was to assess the outcomes of fertility inducing drugs at Ethiopian family guidance association obstetrics and gynecology special clinic.

The study was conducted at family guidance association of Ethiopia (FGAE) from April-June, 2016, employing a three year (July 1, 2012- June 30 2015) patient charts review supplemented by qualitative data from key informants. A structured check list was used to collect quantitative data, whereas qualitative data was collected using in-depth-interview guide.

Among the total of 422 patients, 82.5% were females and majority of the patients were on monotherapy (44.3%). Primolut N was the commonest monotherapy used (44.3%), while the combination of primolut N and clomiphene were 26.3%. on the other hand primolut N three times was used only 3.1% and clomiphene three times was 1.9%, and their combination was 3.6%.

Key words: infertility, fertility inducing drugs, outcomes

Acknowledgment

I would like to gratefully and sincerely thank my advisor Prof. Ephrem Engidawork for the continuous constructive advices and priceless comments. Besides my advisor, my special thanks goes to my wife Altayework Mekonnen without her support and encouragement I wouldn't have been here.

My thanks also goes to all of my friends for all their support and encouragement.

I would like to thank all the staffs of Ethiopian family guidance association obstetrics and gynecology special clinic for their persistent effort during the data collection. I would also like to thank Addis Ababa University for giving me this chance.

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Acronyms and Abbreviations

AoM: Age of Menarche

ART: Artificial Reproductive Technology

COR: Controlled Ovarian Hyperstimulation

CVD: Cardiovascular Disease

ESHRE: European Society of human Reproduction and Embryology

FGAE: Family Guidance Association of Ethiopia

FIDs: Fertility Inducing Drugs

GBD: Global Burden of Disease

GIFT: Gamete Intra-fallopian transfer

ICSI: Intra-Seminal Sperm Injection

IUI: Intrauterine Insemination

IVF: In-vivo Fertilization

MCH: Maternal ans Children Health

NCCWCH: national Collaborating Center for Women's and Children's Health

OHSS: Over hyperstimulation Syndrome

PCOS: Polycystic Ovarian Syndrome

PPRoM: preterm prelabor rupture of membranes

STD: Sexually Transmitted Disease

WHO: World Health Organization

ZIFT: Zygote Intrafallopian transfer

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1. INTRODUCTION

1.1 Background

Parenthood is undeniably one of the most universally desired goals in adulthood, and most people have life plans that include children. However, not all couples who desire a pregnancy will achieve one spontaneously and a proportion of couples will need medical help to resolve underlying fertility problems. Infertility has been recognized as a public health issue worldwide by the World Health Organization (WHO) (Vayena *et al*., 2001).

Infertility refers to the inability of couples to conceive a clinical pregnancy after one year or more of trying to conceive. However, definitions for infertility vary widely depending on the type of information available and the purpose for which the information is collected. For example, some clinical definitions of infertility include women aged 35 years or older after six months of trying to conceive. In contrast, demographic definitions of infertility often encompass the inability to have a live birth among sexually active (Gurunath et al., 2011; ASRM, 2013).

In many cultures, womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. Moreover, in the absence of social security systems, older people are economically completely dependent on their children. Childless women are frequently stigmatized, resulting in isolation, neglect, domestic violence and polygamy (Araoye, 2003; Gerrits, 1997; Hollos, 2003; Papreen et al., 2000; Richards, 2002; Sundby, 1997; van Balen and Gerrits, 2001; van Balen, 2002; Wiersema et al., 2006).

There are many reasons why a couple may not be able to conceive, or may not be able to conceive without medical assistance. Common believes are that it is easy to have a child and is often people are is surprised when the woman does not fall pregnant as soon as they start trying for a baby. The chance of getting pregnant in each menstrual cycle (each month) is very high. However, it may take a long time to conceive, even if everything looks normal, because some may just be a bit weak. Eight out of every ten women trying for a baby will fall pregnant within the first six months. Women who do become pregnant without any medical assistance generally do so within eight months of trying (SART, 1991). It is common for couples to seek help and advice if there is difficulty in conceiving. Overall, around 15% (one in six) of all couples will seek help. The point at which they may want to seek help will depend on various factors. For

example, if they are over 35 years of age or if they have any worrying symptoms, such as infrequent periods and so on, the couple should seek help after about six months of trying (Gaware *et al.*, 2009)

The global health community has had great success in improving maternal and child health in the past decade, partly through a focus on reproductive health. Currently the use of medical assistance to achieve fertility among couples who can't conceive regardless of their trial to get pregnant is on the increase (WHO, 1995; Cousens *et al*., 2011). In Ethiopia, evidence showed that infertility treatment has been provided since the past two decades (Deribe *et.al*, 2007*)*.

Therefore, this study is designed to identify effectiveness of fertility inducing drugs and their drawback in Addis Ababa, Ethiopia.

1.2 Statement of the Problem

Parenthood is undeniably one of the most universally desired goals in adulthood, and most people have life plans to have children. However, not all couples who desire a pregnancy will achieve one spontaneously and a proportion of couples will need medical help to resolve underlying fertility problems (WHO) (Vayena *et al*., 2001).

Infertility is a critical component of reproductive health. It has a profound effect on women and men worldwide. It has been recognized as a public health issue worldwide by WHO. The inability to have children affects men and women across the globe. According to the World Health Organization (WHO) Demographic and Health Survey (2004), one out of every four couples in developing countries are willing to parent and this has not changed significantly over the last decade. In populations<60 years old, infertility is ranked the fifth highest serious global disability. The extent of infertility varies considerably among countries (WHO, 1975; Vayena *et al*., 2001; Mascarenhas *et al.,* 2012).

Fertility and parenthood are highly valued in developing countries to the extent that procreation is usually considered the most important purpose of marriage (Okonofua *et al*., 1995; Hollos, 2003). Infertility management therefore takes on an added dimension which is beyond the physical and organic and which is firmly embedded in the social and cultural environment of that region. It is a devastating burden on the social, economic and personal wellbeing of those affected, a burden that is disproportionately borne by women. Psychological stress, economic hardship, stigma, isolation, mental and physical violence have all been described as consequences of infertility. Women not only suffer because they are mostly blamed for infertility, but they lose a very important chance to enhance their status. They are treated as outcast, after they die their bodies are buried on the outskirts of the town. Traditional customs such as having to wear a scarf until a woman has a child also contributes to more pressure on women who suffer from infertility (Tabong and Adongo, 2013). It is also associated with marital instability, both males and females are engaged in sex with multiple partner to prove their fertility. Consequently, infertile women commonly fear abandonment, divorce and polygamy. There are also psychosocial consequences because, couples themselves view infertility as a tragedy, which carries social, economic and physiological consequences like distress and

depression (Sundby, 1997; Leonard, 2002; Tangwa, 2002; Tabong and Adongo, 2013). Moreover, in the absence of social security systems, older people are economically completely dependent on their children and infertile couple fail to pursue this chance (van Balen and Gerrits, 2001).

The treatment of infertility can either be traditional or biomedical. Traditional infertility treatment are common in Africa, and is an important alternative source of understanding, coping and managing health problems including infertility. Medical therapy on the other hand is used to correct ovulation dysfunction. If there is no underlying problems of ovulation, the first line treatment is oral medication to induce regular menstrual cycles. For males, low sperm counts, deformed spermatozoa and inability to sustain an erection (impotence) are managed using drugs. The drugs include; the antiestrogen clomiphene citrate (CC), human menopausal gonadotrophin (hMG), which contains FSH and luteinizing hormone (LH), human chorionic gonadotrophin (hCG), and gonadotrophin-releasing hormone agonists (GnRH), ART, and metformin. They can be used alone or in combination depending on the cause of infertility and the protocol used.

Many anovulatory infertile women are resistant to antiestrogens and need gonadotropins, which can be combined with intra uterine insemination (IUI). IUI is a very effective treatment, but it requires an advanced infrastructure, monitoring of treatment and training of personnel. Therefore, it is expensive including the drug costs, the need for the laboratory facilities, the cost of ultrasound machine and trained staff.
ART can also be used for unexplained infertility, tubal damage, male factor infertility and premature ovarian failure. In most developing countries, however, ARTs are either unavailable or inaccessible.
Surgical techniques for tubal infertility have been tried and have success rates of around 50%, but depend on severity of the damage, associated abnormalities, technique of surgery (open versus microsurgery versus laparoscopic) and training of the surgeon.

While treatment options are available for management of infertility, infertile people may not attend or adhere to this services to the extent that treatment becomes effective. This might be due to lack of information , accessibility and affordability problems, privacy issues and loss of hope when the effect of treatment is not seen with in short period of time. Individuals/couples

who attend treatment passing all the obstacles also may suffer from side effects of the fertility inducing drugs (FIDs) such as multiple pregnancies, ovarian hyperstimulation syndrome (OHSS) leading to ovarian tumors, and ectopic pregnancies (Beerendonk *et al.,* 1998; Semba *et al.,* 2000; Mathur *et al.,* 2007).

Multiple pregnancies are the most important adverse outcome of ART. Women who conceive with clomiphene have approximately a 10% chance of having twins. Triplet and higher order pregnancies are rare (<1%) (ASRM, 2012). Perinatal and maternal mortality/morbidity rise dramatically compared with singleton pregnancies. Almost 50% of twin pregnancies are associated with preterm labor and/or preterm prelabor rupture of membranes (PPRoM) often leading to premature delivery (ESHRE, 2000). OHSS is another adverse effects. It is supraphysiologic complication of ovarian stimulation. The syndrome is almost exclusively associated with exogenous gonadotropin and is only rarely observed after CC treatment. With rare exceptions, it occurs only after a luteinizing hormone surge or exposure to hCG. After gonadotropin superovulation for in-vivo fertilization (IVF), the reported incidence of moderate OHSS is 3% to 6%, and for severe forms is 0.1% to 2%. The mild form occurs in about 20% to 33% of IVF cycles (Beerendonk *et al.,* 1998; Semba *et al.,* 2000; Mathur *et al.,* 2007). Risks of ovarian tumors is one of adverse effects of women using fertility drugs suggest that there are few if any long-term risks. However, some studies suggest that women taking fertility drugs for 12 or more months without a successful pregnancy may have an associated increased risk of borderline ovarian tumors later in life (Mayo Foundation for Medical Education and Research, 2016).

Despite this, there has been no political will to directly address the problems associated with infertility. The effect of infertility on an individual's quality of life is immense and disproportionately affects women and the poor. Infertility treatment should therefore not be given a lower priority than other medical conditions

This study is intended to answer research questions such as infertility treatment accessibility for those in need, if yes how effective is it and what side effects were experienced.

1.3 Literature Reviews

1.3.1 Epidemiology of infertility

Although all around the world, 8-12 percent of couples suffer from infertility, infertility rates vary dramatically between countries and regions (WHO, 1999*)*. According to WHO data, infertility becomes a public health problem when its frequency exceeds 15% (CDC, 2014).

Worldwide more than 70 million couples suffer from infertility, the majority being residents of developing countries. Negative consequences of childlessness are experienced to a greater degree in developing countries when compared with Western societies. One of the most important and underappreciated reproductive health problems in developing countries is the high rate of infertility and childlessness, despite of exact prevalence of infertility in developing countries is unknown due to a lack of registration and well-performed studies (Bergstrom, 1992; Chachamovich *et al*., 2010; Cue, 2010; Leke *et al*., 1993).

In the United States, the rate of infertility in married women age 15–44 is 6% based on the national survey of family growth, although prospective studies suggest that it may be as high as 12–15%.The infertility rate has remained relatively stable over the past 30 years in most countries. However, the proportion of couples without children has risen, reflecting both higher numbers of couples in child bearing years and a trend to delay child bearing(Avison and Furnham,2015).

This trend has important implications because of an age-related decrease in fecundability: the incidence of primary infertility increases from ~8% between the ages of 18 and 38 to 25% and 30% between the ages of 35 and 39 and 40 and44, respectively. It is estimated that 14% of couples in the United States have received medical assistance for infertility; of these, two-thirds received counseling, ~12% underwent infertility testing of the female and/or male partner, and 17% received drugs to induce ovulation (Harrison, 2015).

In Russia the birth rate over the period from 1987 to 1994 fell from 17.1 per 1000 to10.8 per 1000 and since 1992 the reduction in the population has clearly been discernible (Kulakov and Frolova, 1994).

Sparse data are available from Asia and Latin-America, but a report compiled by the WHO indicated that the prevalence of infertility in these regions fell within the globally expected range 8–12% of couples of reproductive age and was thus lower when compared with African countries (WHO, 1991).

Estimates suggest that in the developing world, the overall burden of infertility is over three times higher than developed countries.

In India, the burden of primary infertility among couples ranged between 4 to 17% (Unisa, 1999; Rutstein and Iqbal, 2004). As per the estimates from Indian census data 2001, 1991 and 1981, researchers showed that childlessness in India has risen up. In 1981, approximately 13% of ever-married women of reproductive age were childless, which increased to nearly 16% in 2001 (Ram, 2006). An Iranian study also showed more than 20% of Iranian couples experience infertility during their reproductive life (Vahidi *et al*., 2009; Akhondi, *et al*., 2012).

Fertility and parenthood are highly valued in Africa to the extent that procreation is usually considered the most important purpose of marriage (Okonofua *et al*., 1995; Hollos, 2003).

In sub-Saharan Africa, the prevalence differs widely from 9% in the Gambia (Sundby *et al*., 1998) and 11.8% in Ghana (Geelhoed *et al*., 2002) 10% in Togo and Ruwanda and 32 % in Nigeria (Larsen, 2000; Ombelet *et al.,* 2008) compared with 21.2% in northwestern Ethiopia Haile, 1990).

With the view of the importance attached to parenthood in societies, childless couples experience negative consequences in terms of their status, respect and authority. Regardless of the medical cause of infertility, couples experience a sense of failure, loss, and exclusion. They are treated as outcast and also they lack equal opportunities in family functions and religious events (Greil , 1997; Rutstein and Iqbal , 2004).

Infertility is often associated with marital instability and many other psychosocial consequences because, couples themselves view infertility as a tragedy, which carries social, economic and physiological consequences (Sundby, 1997; Leonard, 2002; Tangwa, 2002). Moreover, in the absence of social security systems, older people are economically completely dependent on their children and infertile couple fail to pursue this chance (van Balen and Gerrits, 2001). Infertility can also lead to distress and depression. The inability to procreate is frequently considered a personal tragedy and a curse for the couple, impacting on the entire family and even the local

community. Negative psychosocial consequences of childlessness are common and often severe (Daar and Merali, 2002; Dyer *et al*., 2002, 2004, 2005, 2007; Umezulike and Efetie, 2004).

It is also not surprising that childlessness affects women to a greater degree when compared with men (Phipps, 1993; Bharadwaj, 2002). In many cultures, womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. Childless women are frequently stigmatized, resulting in isolation, neglect, domestic violence and polygamy (Gerrits, 1997; Sundby, 1997; Papreen *et al*., 2000; Balen and Gerrits, 2001; Richards, 2002; Balen, 2002; Araoye, 2003; Hollos, 2003; Wiersema *et al*., 2006).

Women in China, India, and other countries in Asia typically have a low social status. One of their key roles is to produce healthy offspring, namely sons. Having sons increases a woman's social status. Women who do not have sons, or worse yet, do not have any children, have a lowered social status. Indeed, women suffering from infertility have diminished quality of life. They experience social ostracism ranging from lowered social status to divorce (Qui, 2001). Moreover, they typically experience psychological, emotional, and physical abuse not only from their husbands but also from their families and community at large. It is estimated that nearly 70% of infertile women are punished in a violent physical manner for their infertile condition because it is seen as a failure by spouses and family members. In addition to this abuse, infertile women "have nobody to talk to or share their pain with. The childless woman is considered inauspicious and feels unworthy and unwanted" (Widge, 2001).

In developing parts of the Middle East, women rely upon their procreative abilities to establish their social status. According to Serour(2001), "Prevention of infertility and its relief are of particular significance in the Middle East area because a woman's social status, her dignity and self-esteem are closely related to her procreation potential in the family and in society as a whole."

In Latin American women suffering from infertility rarely discuss their condition with others out of fear of their husbands' response due to the machismo culture. Indeed, women feel forced to hide their infertility so they do not bring shame upon their husbands and families. Carrying the burden of their infertility without any social support can be stressful and socially isolating. In addition to suffering in silence, Latin American women who are infertile have limited treatment due to the strong influence of Catholicism and Christian Evangelicalism on their countries' official policies regarding ART. For example, an amendment to Costa Rica's Constitution only

allows homologous insemination and bans all other forms of ART. In Mexico and Argentina, a woman may only receive ART if she is married or in a relationship (Luna, 2001).

In many African countries, the purpose of marriage is to produce children. Children are economically necessary to married couples because they carry a part of the workload and are responsible for taking care of their parents when they become elderly and unable to care for themselves. People without children have less help with work tasks, thereby causing women (and men) to take on more work themselves. Women are made especially vulnerable in old age if they are childless because they are sometimes seen as a disposable segment of the family and population. There are also religious reasons why children are so highly valued in many African cultures. For example, in certain cultures, children are thought to play an active role in their parents' transition to the afterlife. As Godfrey Tangwa(2001) explains, "on the approach of death, a childless person is particularly terrified because, while death is considered a transition into the realm of the ancestors, the living-dead, life, wellbeing, and prosperity in that real misbelieved to depend on the reciprocal interaction between the progeny and the ancestors, between the living kin and the living dead. In other words, women and men without children may be quite stressed and fearful at the end of life because they do not have children to assist them in a good after life.

1.3.2 Fertility Treatments and Related Problems

While treatment options are available for management of infertility, infertile people may not attend or adhere to this services to the extent that treatment becomes effective. This might be due to lack of information , accessibility and affordability problems, privacy issues and loss of hope when the effect of treatment is not seen with in short period of time. Individuals/couples who attend treatment passing all the obstacles also may suffer from side effects of the fertility inducing drugs(FIDs) such as multiple pregnancies (Elster, 2000; Cohen, 2003; Ombelet *et al*., 2005), Ovarian hyperstimulation syndrome (OHSS) leading to ovarian tumors (Beerendonk *et al.,*1998;Semba *et al.,*2000;Mathur *et al.,* 2007), and ectopic pregnancies

WHO has classified infertility as a disease affecting approximately 15% of reproductive-aged couples. It is a disease that is not characterized by mortality but rather by the morbidity it inflicts

on the individual and the couple. This morbidity includes social, economic, relationship and psychological aspects but is not confined to these. Women especially may be caught in a spiral of attempts to achieve their one social and evolutionary need namely to have a child. Infertility can be primary, in couples who have never conceived, or secondary, in couples who have previously conceived. A cause of infertility is not identified in 30% of couples. In a further 27% of couples the cause is attributed to female related factors such as ovulatory disorders; in 14% of couple's tubal damage. Isolated male factor infertility affects approximately 17% of couples seeking treatment However, the presence of disorders in both the man and the woman has been reported to occur in about 39% of cases (Menken *et al*., 2004).

A study done in Canada revealed that social trends have led to women delaying child-bearing into their 30s and, in some cases, their 40s. The average age of women giving birth has increased from 27 to 29.3 over the last 20 years. In 2006, the fertility rate for women aged 30 to 34 was the highest of any age group, surpassing that of the previous highest group, women aged 25 to 29. The percentage of first-time mothers who are > 30 years of age increased steadily from 11% in 1987 to 26% in 2005. During the same period, there was a significant rise in first-time mothers > 35 years of age, from 4% in 1987 to 11% in 2005, and a corresponding decrease in the group who are < 25 years. Similar trends have been seen in other parts of the world (Maher and Macfarlane, 2004; Statistics Canada, 2008).

Advanced age is also common demographic factor associated with female infertility/impaired fecundity. Ovarian function declines as women approach their later reproductive years until menopause, and increasing age is associated with lowered fecundity. Women experience a decline in natural fertility that begins in the mid-30s indicating that unexplained infertility is substantially higher in older women accounting for 27.5% (Gilbert *et al*., 1999; Leridon, 2004; Menken *et al*., 2004; Maheshwari, *et al*., 2008).

Bilateral tubal occlusion due to sexually transmitted diseases (STD) and pregnancy-related infections is also the most common cause of infertility in developing countries. In Africa, over 85% of women had an infertility diagnosis attributable to an infection compared with 33% of women worldwide. In another study from sub Saharan Africa, a history of STD was reported by 46% of participating men (Gerais and Rushwan, 1992). A study of 5800 couples in 33 WHO

centers in 25 countries showed that almost 50% of the African couples and 11–15% of other patients in other parts of the world had infectious tubal disease (Sciarra, 1994). Individual studies from Nigeria, South Africa and Egypt have reported a prevalence rates of tubal factor infertility ranging from 42 to 77% (Otolorin *et al.,* 1987; Okonofua *et al*., 1989; Otubu *et al*., 1990; Serour *et al.,* 1991; Chigumadzi *et al*., 1998; Ikechebelu *et al*., 2003). It has been estimated that 70% of pelvic infections are caused by STD while the other 30% are attributable to pregnancy-related sepsis (Ericksen and Brunette, 1996), post-partum pelvic infections and obstetric fistulas (Leke *et al*., 1993). Similarly, most cases of male factor infertility are caused by previous infections of the male genitourinary tract (Meheus *et al*., 1986; Kuku and Osegbe, 1989). Nigerian studies have shown a prevalence of male infertility in 26–43% of cases (Adeniji *et al*., 2003; Ikechebelu *et al*., 2003; Olantunji and Sule, 2003).

Another major cause of infertility is unsafe abortion. It was estimated that between 20 to 40% of reproductive tract infections following unsafe abortion would result in secondary infertility. The same assumptions as in global burden of disease (GBD) 1990 were used to estimate the proportion of unsafe abortion which will lead to infertility (Abouzahr and Ahman*,* 1998).

Female genital mutilation is also considered as one of the most important causes of infertility. It has been estimated that between 100 and 140 million girls and women have been subjected to some form of female genital mutilation in Africa and, to a lesser extent, in some countries in the Middle East (WHO, 2005). Limited knowledge about the principles of aseptic techniques and the underlying anatomy of the performers cause injury and infection that can result in infertility and other complications such as sepsis, haematocolpos, dysmenorrhoea, dyspareunia, obstructed labour, fistula formation and haemorrhage (Davis *et al*., 1999; Obermeyer, 2005).

Common causes of male infertility identified includes oligospermia and asthenozoospermia (Adetoro, 1999). A study in Nigeria showed that 53.2% of male infertility accounts to a problem of sperm motility of less than 50%. A low sperm count or quality is thought to contribute to infertility in 19% of couples (Loto, 2004).

Up to 30% of couples who are unable to conceive are determined to have unexplained infertility (Dodson *et al*., 1987). Traditionally, this diagnosis is made only after the basic infertility evaluation fails to reveal an obvious abnormality. It might arise from a defect in fecundity that cannot be detected by the routine infertility evaluation (Silverberg, 1996). In a review of studies of unexplained infertility, the average cycle fecundity in the untreated control groups was 1.8% in 11 nonrandomized studies and 3.8% in 6 randomized studies (Guzick *et al*., 1998). Challenges in seeking for and maintaining adherent to infertility include: absence of Information about infertility treatment, lack of access (ESHRE Task Force on Ethics and the Law, 2009, Nachtigall, 2006, Inhorn, 2009).

1.3.3 Management of Infertility

The use of Fertility drugs as treatment option began around 1955 with follicle stimulating hormone (FSH), followed by clomiphene citrate (CC) and human menopausal gonadotrophin (hMG) 10 years later (Lunenfeld and Insler, 1993;Wysowski, 1993). Before and during this period, treatment for infertility also included pituitary irradiation and administration of pregnantmare serum gonadotrophins, conjugated estrogen, oral contraceptives, and diethylstilbestrol (Lunenfeld and Insler, 1993, Shapiro,1995).

Currently, there are four major drugs being used for infertility treatment, all of which can induce ovulation: i) the antiestrogen CC; ii) hMG, which contains FSH and luteinizing ormone (LH); iii) human chorionic gonadotrophin (hCG), iv) gonadotrophin-releasinghormone agonists (GnRH). These hormones are used alone or in combination depending on the cause of infertility and the protocol used. In vitro fertilization programs and other assisted reproductive technologies include luteal phase support by exogenous administration of natural progesterone or synthetic gestagen preparations (Blacker, 1992; Derman, 1994). Ovulation induction regimens may be used to induce ovulation or superovulation. Super ovulation is defined as ovulation of greater than the normal number of ova, usually the result of menotropin or clomiphene therapy. Superovulation is used mainly for unexplained infertility or in association with in vitro fertilization, gamete intrafallopian tubal transfer, and intracytoplasmic sperm injection programs (Blacker, 1992).

The most common cause of infertility in women is anovulation. The first line oral treatment is

non-steroidal selective estrogen receptor modulators (SERM) (Broun *et al*., 2009). CC stimulates ovulation by causing the pituitary gland to release more FSH and LH, which stimulate the growth of an ovarian follicle containing an egg (Ecochard *et al.,* 2000; Reindollar *et al*., 2009; Goldman *et al*., 2014). Since 1962 it has been the drug of choice for oral ovulation induction over the last 50 years (Badaniwy *et al.,* 2006; Sipe *et al.,* 2006; Ganesh *et al.,* 2009). It can induce ovulation in 80% of anovulatory women but only 40% of women became pregnant (Richard *et al.,* 2005). Pregnancy rate per cycle can be 10-20% (Fisher et al., 2002) and as high as 60% after six cycles and 97% after 10 cycles (Messinis, 2002). Unfortunately, 20-25% of the women are resistant to CC and fail to ovulate (Quintero *et al*., 2007).

Tamoxifen is another anti-estrogen used for ovulation induction; there are no appreciable differences in ovulation or pregnancy rates after treatment with tamoxifen or clomiphene for isolated anovulatory infertility. Many unovulatory infertile women are resistance to antiestrogens and need another treatment. Alternative treatments are aromatase inhibitors. Aromatas is a cytochrome P-450 hemoprotein and catalyzes the rate-limiting step in the production of estrogens Letrozole belongs to a class of drugs known as aromatase inhibitors and works in a similar fashion to clomiphene. Letrozole may induce ovulation. However, the effect this medication has on early pregnancy isn't yet known, so it isn't used for ovulation induction as frequently as others(Richard *et al*., 2005; Bayar *et al*., 2006)

In a comparative study in Iran, where demographic characteristics particularly age and duration of infertility were similar in three groups taking tamoxifen, letrozole and clomiphene, a total of 567 cycles were studied in 150 patients. The cumulative pregnancy rate in three groups was 77 (51.3%) at 6 months. Compared with tamoxifen and letrozole pregnancy rate was higher with clomiphene. Although number of pregnancies were higher in the letrezole group than tamoxifen group, this difference was not significant. There were 17 (22%) pregnancies that ended in miscarriage and 83 (78%) of pregnant women successfully delivered. The clomiphene group have significantly higher miscarriage rate. One twin pregnancy was occurred with clomiphene and tamoxifen, but all pregnancies with letrozole was singletons. Number of higher order pregnancies (triplet or higher pregnancy) and no OHSS occurred with oral induction ovulation (Seyedoshohadaei *et al.,* 2012).

Metformin acts indirectly to induce ovulation by reducing the circulating concentration of insulin. It's onset of action is slower and gradual: up to 6 months of treatment with metformin may be needed to clinically improve ovulation. Given the differences in action and pharmacodynamics properties, clomiphene would be expected to be more effective than metformin in rapidly inducing an ovulation in a woman with polycystic ovarian syndrome (PCOS) as has been borne out in several studies (Essah *et al*., 2006; Palomba *et al*., 2007). As documented in a meta-analysis (Creanga *et al*., 2008) of 17 rigorously conducted studies performed between 1996 and 2007 that included 1,639 subjects, ovulation is improved in many women with PCOS when treated with metformin. A clinical experience from an academic center also suggested that menstrual cycle and ovulation improve in approximately 69% of women with PCOS treated with metformin, with 88% of responders achieving normal menstrual cycle (Essah *et al.,* 2006).

Gonadotropins are given as injected treatments and stimulate the ovary directly. Gonadotropin medications include hMG and FSH. All act to stimulate production of multiple eggs. Another gonadotropin, hCG, is used to mature the eggs and trigger their release at the time of ovulation. Metformin is used when insulin resistance is a known or suspected cause of infertility, usually in women with a diagnosis of PCOS. Metformin helps improve insulin resistance, which can make ovulation more likely to occur. It is effective as a treatment for anovulatory infertility amongst women with PCOS. A Cochrane review of seven RCTs involving 702 women found that the clinical pregnancy rate for metformin versus placebo was significantly increased [odds ratio (OR) 2.31, 95% confidence interval (CI), 1.52 to 3.51]. However only three RCTs involving 115 women examined the outcome live birth, therefore this analysis was consequently underpowered and did not find a significant benefit (OR 1.80, 95% CI, 0.52 to 6.16) (Tang *et al*.,2012).

2. OBJECTIVES

2.1 General objective

- Assessment of the outcomes of fertility inducing drugs at family guidance association of Ethiopian special clinic

2.2 Specific objectives

- To assess the available of fertility inducing drugs used in infertility management
- To assess the unwanted effects of fertility inducing drugs
- To identify factors associated with the outcomes of FIDs treatment

3. MATERIALS AND METHODS

3.1 Study Setting

Family guidance association of Ethiopian (FGAE) is located in Addis Ababa city administration-kirkos sub-city. It has obstetrics and gynecology special clinic at head office. The clinic has the following activities with 3 OPDs and 5 beds: provision of reproductive health information, family planning and contraception services, screening of HIV/AIDS, obstetrics and infertility treatment, legal abortion, antenatal, delivery and postnatal services, maternal and child health (MCH) services including immunization, diagnosis, treatment of sexually transmitted disease(STD), counseling and treatment of raped individuals. It has 13 health professionals and 4 administrative staffs.

3.2 Study Design and Study Period

This was a cross sectional study employed quantitative and qualitative data collection methods. A three year retrospective clients' chart, from Jan.1, 2013 to Dec. 31, 2015, were reviewed and supplemented by a qualitative data from interviews of selected key informants (physicians and Nurse) working there. The study was conducted from April-June, 2016.

3.3 Population

3.3.1 Source population

All clients who visited EFGA obstetrics and gynecology special clinic for reasons related with infertility

3.3.2 Study population

Clients who had been attending FGAE obstetrics and gynecology special clinic for fertility related cases and took fertility inducing drugs from 1 January 2013 to 31 December, 2015 and who fulfilled the inclusion criteria.

- Inclusion Criteria: All clients who had taken the medication for infertility management at least once, both sexes were included
- Exclusion Criteria: Those clients who visited the clinic for infertility management but didn't use fertility inducing drugs

3.4 Sample size determination and sampling technique

A. Quantitative study

A three year (1 January, 2013- 31 December 2015) patient charts were included in the study. Sampling frame was client's registration book.

The sample size was calculated using the formula for single population proportion with the following assumption.

Assumption:

Since the proportion of clients in the need of infertility treatment and their outcome is unknown in Ethiopia, 50% of population proportion was used to determine sample size. In addition, a 5% margin of error with 80% confidence level and 10% none -response rate were considered.

$$n = \frac{(Z\alpha/2)^2 p(1-p)}{d^2}$$

Where;

- ✓ N= total number of clients visiting the clinic for management of infertility
- ✓ Z α/2= 1.96(critical value at 80% confidence level certainty)
- ✓ P= the proportion of clients using fertility inducing agent(50% is preferred to obtain the largest sample size)
- ✓ D= margin of error between the sample and population, 5% marginal error is admitted
- ✓ n= the total sample size

Client charts were selected by simple random sampling using the list of client chart numbers as a sampling frame. The calculated sample size was found to be 384. When a10% contingency was added, the final sample size becomes 422. A total of 3, 245 clients had attended the clinic for management of infertility in the proposed study time. Among them 1,432 had treatment with FIDs at least once. A lottery was prepared for all the chart number of clients who had treatment for FIDs and the study subjects were identified by picking a lottery until the calculated sample size was reached.

B. Qualitative study

Key informants were selected based on purposive sampling technique to address issues related to drugs that induce fertility at FGAE special clinic. The sample involved two physicians and head of nurses. Data collection was performed until saturation of ideas was observed.

3.5 Variables

3.5.1 Dependent variables

- Outcomes of fertility inducing drugs

3.5.2 Independent variables

- Age
- Sex
- Educational status
- Marital status
- Economic status

3.6 Data collection and Management

3.6.1 Data Collection Instrument

Patient chart review was performed using structured data abstraction format (Annex 1). The abstraction format consisting of socio-demographic characteristics, clinical characteristics, types of infertility, fertility status of spouse and interventions taken, knowledge and practice of fertility period, semen analysis, substance abuse, fertility drugs, and outcomes of fertility inducing drugs.

An in-depth interview using a semi-structured questionnaire (Annex 2) was also used to key informants, which included prevalence of infertility and possible factors, current medicines that are used to treat infertility, available and accessibility of medicines, frequencies and doses of medicines used and outcomes of medicines. The questionnaire included open ended interview guide with flexible probing techniques that are related to fertility inducing drugs in order to extract detail information.

3.6.2 Data collectors

Two nurses working at FGAE were recruited as data collector and given a one day training prior to data collection on how to use the data abstraction format to gather information from patients' medication record.

3.7 Data quality Assurance

To maintain the quality of the data, a data collection checklist was prepared and pretest was done on 5 % of patients chart (21) randomly selected to ensure agreement of the data abstraction format and the structured questionnaire with the need of the study.

Any misunderstanding found during the process of pre-test was corrected and modification was made into the final version of the data abstraction format and the structured questionnaire. The data collectors were trained for one day before the process of data collection. Supervision and checking was made by the principal investigator to ensure the completeness and consistency of the collected data.

3.7 Data Entry and Analysis

Quantitative raw data collected using secondary data was organized and carried out right after the completion of data collection and data arranged categorically. Then it was entered in to computer, cleaned and analyzed using statistical package for social sciences (SPSS) version 20. Descriptive statistics such as frequencies and percentage was summarized and presented in the form of tables and graphs. Odds ratio and 80% confidence interval was used to check significant association between dependent & independent variables using bivariate and multivariate analysis by logistic regression model. Statistical significance was measured by p-values < 0.20 and adjusted odds ratio (AOR) with 80% confidence interval. The qualitative data was transcribed and categorized in to themes to identify the factors perceived by health workers.

3.8 Ethical Clearance

Ethical clearance was obtained from Addis Ababa University, school of pharmacy ethical review committee and official letter for co-operation was provided to FGAE head quarter. Permission was obtained from clinical director and head of the clinic to access medication records and to conduct the study. Informed consent was obtained from professionals for interview. The names of patients were replaced with codes to avoid individual identifiers and the nurses who work there were used as data collectors.

3.9 Operational Definitions

- Outcomes of fertility inducing drugs: in this study outcome of treatment includes any conception that end up in normal delivery or having some drawbacks associated with the treatment such as abortion, multiple pregnancies or ectopic pregnancies and other symptoms such as hot flashes, weight gain, and fatigue.
- Effectiveness of fertility inducing drugs: ability to conceive and give birth for healthy neonate, absence or minimal side effects

- Unwanted consequences: side effects of the drugs, such as multiple pregnancy, ectopic pregnancy, hot flashes, weight gain, and fatigue
- Primary infertility: a couple never conceived despite of having unprotected sex
- Secondary infertility: a couple has previously conceived but subsequently unable to do so despite of having unprotected sex.

4. RESULTS

4.1 Socio-Demographic Characteristics

During the study period, a total of 422 patient's charts were reviewed. The socio-demographic characteristics of the participants are shown in Table 1. Majority of the study participants were females (82.5%). The mean age was 33.7 (SD ±6.31) years ranging from 20 to 67 years. The greater proportion of them were married (94.3%), and live (83%) in Addis Ababa.

Table1: Socio-demographic Characteristics of Clients Attending FGAE Clinic, Addis Ababa, Ethiopia, 2013-2015

Characteristics	Frequency	Percent
Age(n=419)		
20-29	117	27.7
30+	302	72.1
Sex(n=422)		
Male	74	17.5
Female	348	82.5
Occupational Status(n=422)		
Governmental	116	27.5
House wife	132	31.3
Merchant	68	16.1
Other	106	25.1
Educational Status(n=407)		
Not read and write	35	8.3
Elementary(1-8)	19	4.3
Sec. and prep.	289	68.5
Diploma+	64	15.2
Marital status(n=421)		
Married	398	94.3
Single	23	5.5
Religion(n=422)		
Orthodox Tewahido	287	68.0
Muslims	93	22.0
Protestants	42	10.0
Addresses(n=422)		
Addis Ababa	350	82.9
Out of AA	72	17.1

4.2 Clinical Characteristics

4.2.1 Medical History

Regarding prior medical history, under 10% of patients had a history of HIV/AIDS and nearly 3% of them had STD and CVD (Table 2).

Table 2: Prior medical history of clients attending FGAE clinic, Addis Ababa, Ethiopia, 2013-2015

Variable	Frequency	Percent
Medical cases(n=417)		
Yes	156	33.0
No	261	61.8
HIV/AIDS	33	7.8
CVD	12	2.8
STD	48	3.3

CVD: cardiovascular disease; STD: sexually transmitted disease

4.2.2 Menstrual History

Majority of the women (98.9%) had dysmenorrhea. Less than a fifth of the women began menstruation at the age of ≤ 15 years and close to a third of them had irregular menstruation cycle (Table 3).

Table 3: Menstrual History of Clients Attending FGAE Clinic, Addis Ababa, Ethiopia, 2013-2015.

Menstrual History	Frequency	Percent
Dysmenorrhea (n=348)		
Present	344	98.9
Absent	4	1.1
Age of menarche(n=337)		
< 15 years	54	16.0
≥ 15 years	283	83.9
Menstrual regularity(n=331)		
Irregular	219	62.2
Regular	112	37.8

4.2.3 Trends of contraceptive use

From the 422 clients who visited FGAE special clinic, majority (68.5%) of them were contraceptives users, among them more than 59% used hormonal contraceptives, and the rest used non-hormonal contraceptives.

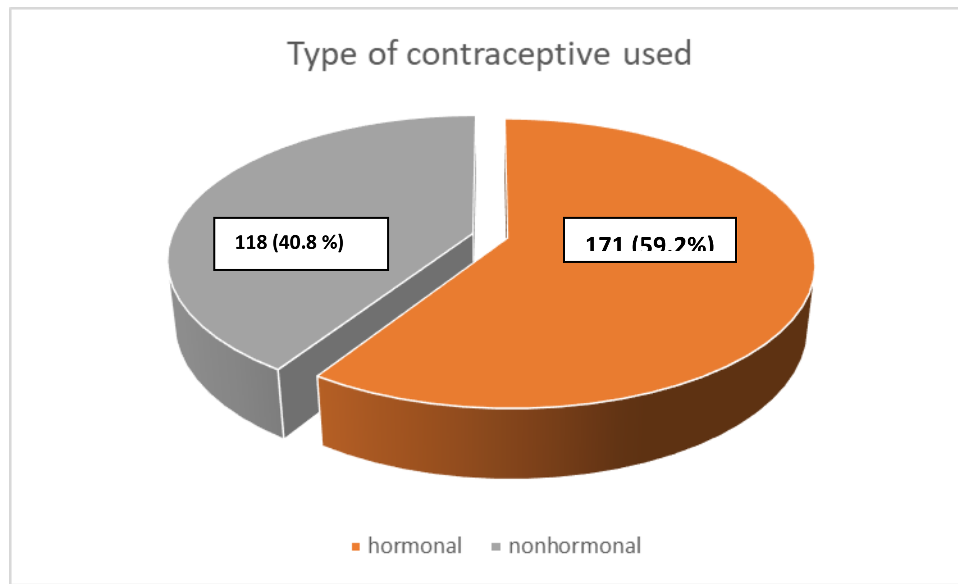

Figure 1: Trends of contraceptive use of clients attending FGAE Clinic, Addis Ababa, Ethiopia, 2013-2015

4.2.4 Types of Infertility

Regarding the type of infertility seen in the clients, about 40% were having primary infertility with the rest having secondary type.

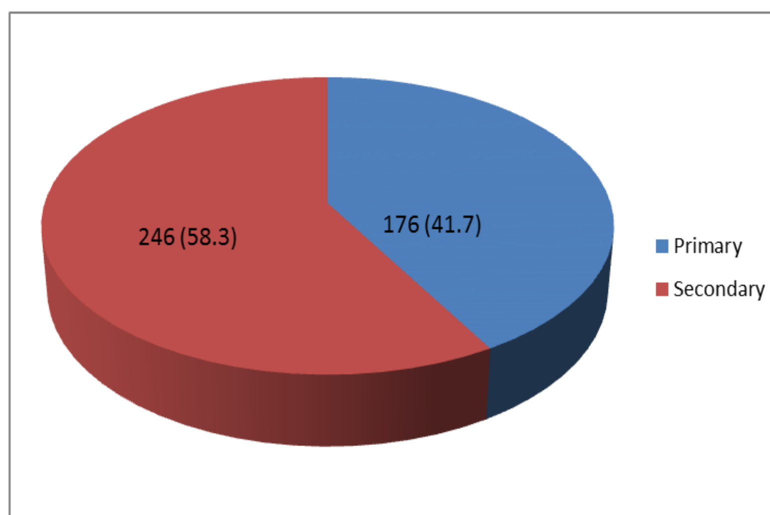

Figure 2: Types infertility of clients attending FGAE Clinic, Addis Ababa, Ethiopia, 2013-2015

4.2.5 Fertility Status of Spouse and Interventions taken

Majority (88%) of the spouse of these clients were infertile among them only 13.2% had taken fertility inducing drugs.

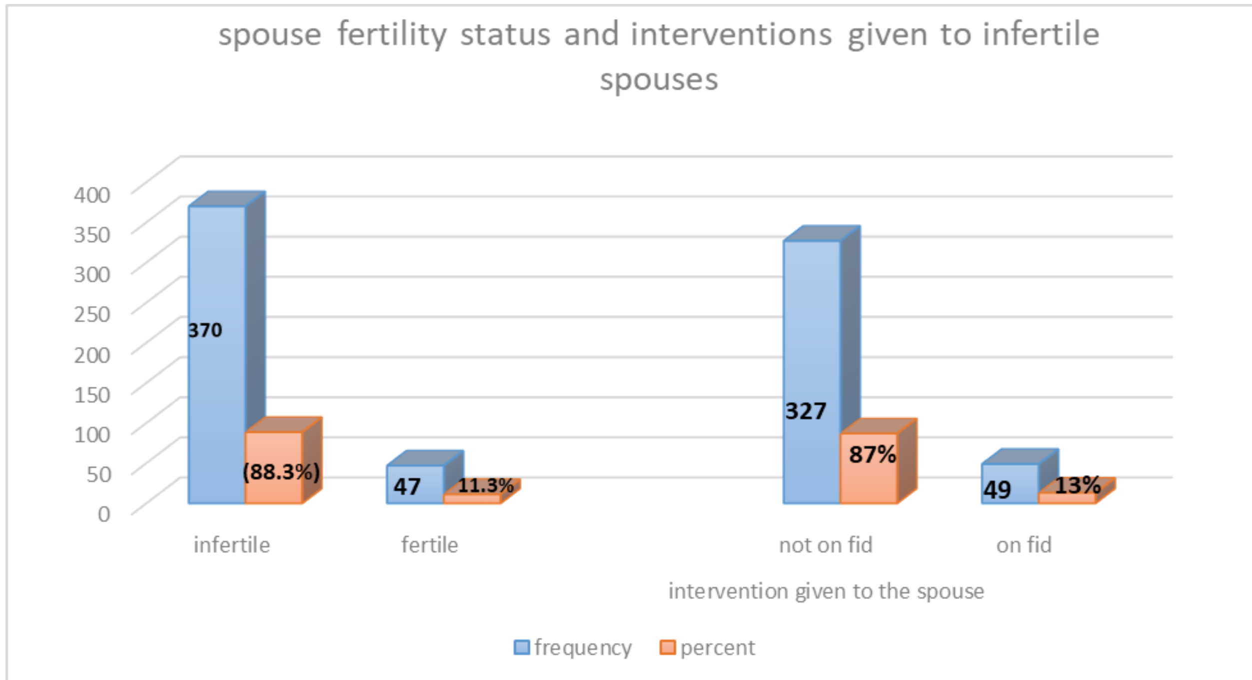

Figure 3: Fertility Status of Spouse and Intervention Taken on Clients Attending FGAE Clinic, Addis Ababa, Ethiopia, 2013-2015

FIDs: fertility inducing drugs

4.3 Knowledge and Practice on Fertility Period

The knowledge and practice on fertility period among the clients and their spouses was very low. Figure 3 shows that almost all clients didn't have any idea about fertility period.

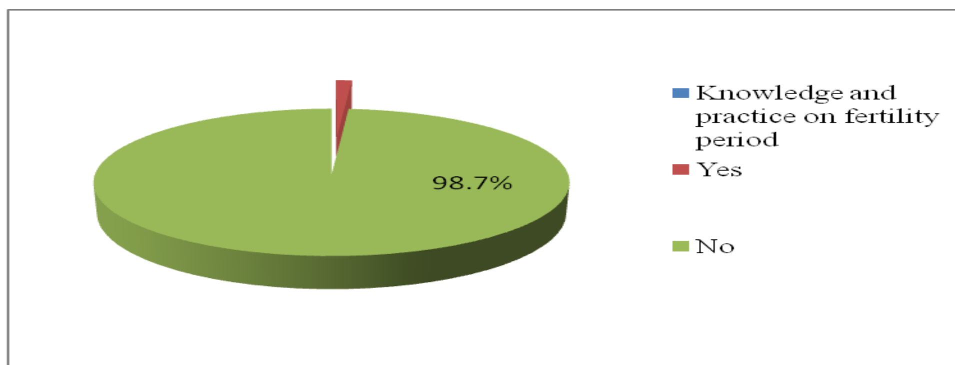

Figure 4: Knowledge and Practice on Fertility Period of clients attending FGAE Clinic, Addis Ababa, Ethiopia, 2013-2015

4.4 Semen Analysis

Semen analysis was performed as a part of the investigation of the infertile men using different semen parameters (Table 4). The analysis showed that the parameters were either adequate (for penile erection, sperm ejaculation, and semen volume) or normal (for semen count and sperm motility) for majority of the subjects.

Table 4: Semen Analysis of Male Infertile Clients Attending FGAE clinic, Addis Ababa, Ethiopia, 2013-2015

Semen parameters	Frequency	Percent	WHO Reference (WHO, MARCH 2014)
Status of Penile Erection (n=59)			
Adequate	41	69.5	
Inadequate	18	30.5	
Status of Sperm Ejaculation(n=74)			
Adequate	45	60.8	
Inadequate	29	39.2	
Semen Volume(mL) (n=58)			1.5 (1.4-1.7)
Adequate	52	89.7	
Inadequate	6	10.3	
Semen Count(X 10^6/ml) (n=36)			
Normal	33	91.7	
Abnormal	3	8.3	
Sperm Motility (%) (n= 39)			40 (38-42)
Normal	35	89.7	
Abnormal	4	10.3	

4.5 Substance Abuse

Concerning the use of psychoactive substances among the sampled clients, those who consumed alcohol and khat were under 10%. The habit of smoking was even very small, accounting for less than 2% (Table 5).

Table 5: Substance Abuse of Infertile Clients Attending EFGA Clinic, Addis Ababa, Ethiopia, 2013-2015

Alcohol consumption(n=412)	Frequency	Percent
Yes	31	7.3
No	381	90.3
Chat chewing habit(n=413)		
Yes	26	6.2
No	387	91.7
Cigarette smoking (n=409)		
Yes	7	1.7
No	402	95.3

4.6 Fertility Drugs

4.6.1 Types of fertility Inducing Drugs Used

The overall utilization of fertility inducing drugs group showed Primolut N to be the most commonly used single agent (44.3%). As shown in Table 6 majority of the clients were on monotherapy (60%), while the combination of primoult N and clomifene citrate was the most common combination drugs used (26.3%). There was also a trend of using alternative fertility drugs, i.e. using one drug in one month and another drug in other month, Primoult N/clomifene citrate was the most common modality used (0.7%).

Table 6: Fertility Inducing Drugs used among Infertile Clients Attending FGAE clinic Addis Ababa, 2013-2015

Drugs	Frequency	Percent

Monotherapy		
✓ Primoult N	187	44.3
✓ Clomifene citrate	60	14.2
✓ Proviron	3	.7
✓ Testosterone	3	.2
Combination Therapy		
✓ Primoult N & clomifene	111	26.3
✓ Proviron and Vit E	54	12.4
✓ Proviron and sildenafil	1	.7
Alternative Therapy		
✓ Primoult N/clomifene	2	.5
✓ Proviron/testosterone	1	.2

NB: Alternative= the client takes one drug in one month and another in other time

Qualitative responses from obstetrician and gynecologists providing the treatment also showed the provision of the FIDs with more or less similar frequency/ sequence as mentioned above. One of the obstetrician and gynecologist described his provision of the medications in the following sequence:

> *"I use primolut N before clomiphene to regulate menstruation, then the clients come back when their menstruation cycle get regulated. Sometimes the clients respond (pregnancy occur) after the use of primolut N or other oral contraceptives to regulate their menstruation without taking other FIDs". "There is no protocol of the institution or national guidelines. So we prescribe based on our experience."….. "There is also no way by which we evaluate the effectiveness of the drug. Thus we have no idea- whether the treatments induce ovulation or not. We do not use ultrasound findings or progesterone level measurements to adjust and we simply continue similar dose; On the other hand, we add the dose of CC without any investigation (for example, the mother may have tubal blockage, for which CC or other ovulation inducing drugs shouldn't be prescribed)"*

The other mentioned that even though they try to provide treatment in a stepwise manner, they don't have a guideline to be used as a base and an evaluation system to assess effectiveness of the treatment given.

> *Before they started the drugs, I educate the clients about timed coitus and observe its effect. When pharmacologic management began I initially treat them with clomiphene citrate starting with small dose (50mg) then increase the dose up to 200mg, Bromocriptine for clients who has prolactenemia, metformin for clients with PCOS, low dose of steroids, Vitamin E, antibiotics, such as doxycycline and erythromycin. Still I didn't use gonadotropins" said the other physician.*

The types and doses of fertility inducing drugs used for a specific client are decided on the preference of the gynecologists based on their previous experience and professional opinion. This is due to the absence of a well-designed guideline at country level. The need for such guideline was also emphasized as follows:

> *"There is no guideline. I used my clinical experience and different text books. Of course, the guideline is very important. Concerned bodies, such as Ethiopian Society of Obstetricians and Gynecologists (ESOG), Ethiopian Midwives Association (EMwA), and others should galvanize their effort with such guideline. I can volunteer to participate"*.

Adding on this the other gynecologist mentioned that:

> *There is no evaluation of the effectiveness of the drug whether they induce ovulation or not based on either ultrasound or progesterone level. Hence we didn't increase the dose based on the evaluation, simply we continue similar dose; Or, on the other hand, we add the dose of CC without any investigation(for example, the mother may have tubal blockage, for which CC or other ovulation inducing drugs didn't prescribed). From clients points of view, mother with menopausal period come, which increases the number of non-convinced ones. I am not sure too about whether the drugs are purchased and handled properly."*

4.6.2 Number of Cycles of Fertility Inducing Drugs Used

Regarding number of cycles, most clients used primolut N single dose as monotherapy. Proviron and Vitamin E once was commonest combination therapy.

Table 7: Number of Cycles of Fertility Inducing Drugs Used by Clients Attending FGAE clinic, Addis Ababa, Ethiopia, 2013-2015

Type of Drug(cycle)	Frequency	Percent
Monotherapy		
Primolut N three times	13	3.1
Primolut N twice	23	5.5
Primolut N once	158	37.4
Clomiphene three times	8	1.9
Clomiphene twice	20	4.7
Clomiphene once	42	10.0
Testosterone four times	1	0.2
Combination Therapy		
Primolut N and clomiphen three times	15	3.6
Primolut N and clomiphen twice	17	4.0
Primolut N and clomiphen once	34	8.1
Proviron and Vitamin E three times	1	0.2
Proviron and Vitamin E twice	10	2.4
Proviron and Vitamin E once	44	10.4
Testosterone and vitamin E twice	2	0.5
Primolut N three times and clomiphen twice	9	2.1
Primolut N twice and clomiphen once	6	1.4
Others	10	2.4

NB: The dose of fertility drugs: Primolut N is 5mg/d po for 5days, clomiphen citrate 50mg po/d for 5days, testosterone 750mg (3ml), vitamin E 200 IU, Sildenafil 50mg

4.7 Outcomes of Fertility Inducing Drugs Used:

Most of the clients need for fertility service was a secondary type of infertility (55.2%), the remaining were primary type.

Table 8: Outcomes of Fertility Inducing Drugs of Clients Attending FGAE clinic, Addis Ababa, Ethiopia, 2013-2015

Infertility type	Outcomes			
	Live birth	Abortion	Ectopic pregnancy	Remains infertile
• Primary	0	1	1	170
• Secondary	11	0	0	233

The factors that contribute for the low effectiveness of treatment were mentioned by the professionals working in the clinic during the qualitative interview. One of the gynecologists mentioned lack of adherence and slow effect of the drugs as factors. He had said about the issue in the following manner:

> *"Yes, there is adherence problem, because of affordability, accessibility of the drugs and some clients come from a distance . . ., so the clients didn't come again as per their appointments. Even clients from Addis Ababa appointed for two months, they return after three or six months, this may be because of stigma. Secondly, some clients had follow up from other health institutions and when they came to our clinic and they didn't see differences in services, they wouldn't return to our clinic."*

Another factor mentioned to contribute to the seemingly low effectiveness as mentioned by the same physician is that the women cease their follow up at the clinic once they get pregnant giving birth in other health institutions for reasons such as seeking better ANC follow up and keeping their privacy. As he put it in his words:

> *"Yes, of course, it is a big problem. Even I have document that lists down the number of clients who gave birth in other health institutions after they became pregnant in this clinic".*

Other factors mentioned include *"low achievement of fertility, that leads to discouragement (though, don't have any data that states about this, but from my personal experience, it needs about 3-4 cycles of treatment to conceive), inability to afford for diagnostic procedure and medicines as well as the absence of additional professional services such a well-organized counseling service for couples undergoing the infertility treatment."*

The nurse working closely with the clients coming to the clinic for infertility management commented as follows:

> *" the nature of infertility management is time consuming, which leads to fatigue, the other is the laboratory investigations that are requested to perform are not available here in our clinic, then they are obliged to seek other areas-which is either time consuming or costly".*

4.8 Factors Associated with Outcome of Treatment by Fertility Inducing Drugs

The effect of FIDs on fertility and other treatment related complications was analyzed using binary logistic regression method; the odds ratio was calculated to observe the relationship between each independent variable and the dependent variable using bivariate analysis revealing the Crude Odds Ratio (COR), once the independent variables having a relationship with the use of FIDs were observed, indicated by the odds ratio and having a P-value 0.2, the final predictor variable of the relationship was identified by using a multivariate analysis method and showing the Adjusted Odds Ratio (AOR) and p- value < 0.2.

The crude analysis revealed that age of the respondents (age > 35 years), menarche (> 15 years), semen motility and Chat chawing have a statistically significant association with the outcome of using FIDs showing a higher chance of remaining infertile even after the use of FIDs.

After adjusting for confounding variables a significant association was found between age and age at menarche of the respondents and outcome of treatment by FIDs. The chance of remaining infertile with the use of FIDs was higher among age groups > 30 years [AOR= 1.032, 80% CI (1.035, 7.617)] and a P< .185. Similarly, higher risk of remaining infertile was also observed among those female respondents whose age at menarche was >15 [AOR= 1.392, 80% CI (1.473, 10.989)] and a P< .076.

Table 9: Relationship between the independent variables and outcome of treatment by fertility inducing drugs, of Clients Attending FGAE clinic, Addis Ababa, Ethiopia, 2013-2015

Variables	Reference group	β	P-Value	Exp(β)	80% CI		Outcomes of FIDs (AOR, CI, P)
					Lower	Upper	
Age	<30	-1.17	0.058*	3.21	1.46	7.07	1.032 (1.035, 7.617) P= .185*
Sex	Male	-0.16	0.84	0.85	0.31	2.31	
Occupational status	Nongovernmental	0.16	0.79	1.18	0.54	2.58	
Educational status	Not read and write	-0.06	0.95	1.07	0.27	4.16	
Marital status	Single	-0.38	0.72	0.68	0.13	2.67	
Religion	Muslims	-0.06	0.93	0.94	0.40	2.22	
Address	Out of AA	0.13	0.87	1.14	0.42	3.10	
No of pregnancy	Null	0.49	0.64	1.63	0.42	6.30	
Birth status	Live birth	17.88	0.99	1.57	0.000	-	
Fertility type	Primary	-0.01	0.98	0.99	0.46	2.11	
Contraceptive use	No	-18.98	0.99	0.000	0.000	-	
Medical history	No	0.53	0.37	1.70	0.80	3.60	
STD	No	0.36	0.64	1.44	0.53	3.92	
STD type	Others	-18.81	1.0	0.000	0.000	-	

Age at Menarche	<15	-1.96	0.004*	0.14	0.06	0.34	1.392 (1.473, 10.989) P= .076*
Menstrual regularity	Regular	-0.14	0.85	0.87	0.34	2.25	
Dysmenorrhea	Absent	17.69	1.00	1.47	0.000	-	
Spouse status	Fertile	-0.37	0.64	0.69	0.25	1.89	
Interventions taken on infertile spouse	Not on FIDs	-0.60	0.57	0.55	0.14	2.11	
Knowledge of fertility period	Yes	17.74	1.00	50747899.83	0.000	-	
Penile erection status	Adequate	0.86	0.55	2.35	0.37	14.96	
Ejaculation status	Adequate	-.526	.714	.591	.094	3.720	
Semen volume	Adequate	-17.27	1.00	0.000	0.000	-	
Sperm count	Normal	17.74	1.00	504835	0.000	-	
Sperm motility	Normal	2.43	0.11*	11.33	1.58	81.26	
Cigarette smoking habit	No	-17.80	1.00	0.000	0.000	-	
Alcohol consumption	No	0.03	0.98	1.03	0.24	3.98	
Chat chewing habit	No	1.05	0.19*	2.85	1.03	7.91	
Type FIDs used	Others	-0.60	0.33	0.54	0.25	1.20	

5. DISCUSSION

Various demographic characteristics affects infertility, among them age was found to have relationship with infertility in this study. More than half (57.1%) of the respondents in this study are in the age group between 30-39 years, followed by age groups 20-29- (27.7%). This figure showed how infertility increases as the age of the respondent advances. According to this study the rate of infertility increases with age from 27.7% among age groups 20-29 to 57.1% among 30-39 age groups, showing a 29.3% increment as the clients' age increases. This finding is in agreement with a study conducted in Iran where age groups from 18-30 was 28.9% and from 31-41 was 47.1% of the study subjects. An Indian study also showed that as the respondents' age increases from 25 to 35, their infertility increases from 7.2% to 8.7%. On the contrary, on this study the percentage of those above 40 years old who were on treatment for infertility was lower (14.1%), the same was true in the Iranian study where infertility status decreases to 24% among those above 40 years. This finding is in line with a study on the prevalence and risk factors of infertility in Turkey in 2017 showed that the risk of infertility was significantly higher among women aged between 35 and 49. This may be due to cessation of follow up after long term trial, due to the economic burden of treatment and consideration of their age particularly the upcoming menopause in case of females. In this study it was also observed that age > 30 years was having a higher risk of remaining infertile even with the use of FIDs [AOR= 1.032, 80% CI (1.035, 7.617)] and a P< .185. Advanced age is also common demographic factor associated with female infertility in other studies. Percentage of first-time mothers who are > 30 years of age increased steadily from 11% in 1987 to 26% in 2005. During the same period, there was a significant rise in first-time mothers > 35 years of age, from 4% in 1987 to 11% in 2005, and a corresponding decrease in the group who are < 25 years. Similar trends have been seen in other parts of the world (Maher and Macfarlane, 2004; Statistics Canada, 2008). There can also be a relationship between advanced education and infertility as perusing more educational and work achievements among women can push up their age of starting mother hood.

In this study it was observed that people with illiterate status and those with elementary school level were less infertile (8.3% and 4.3% respectively) in comparison with those at secondary and preparatory level (68.5%) and those attended higher education (15.2%). Studies in Iran and India where the prevalence of infertility was 8.3% and 9% respectively among the illiterate. However,

this similarity was not maintained for the rest of the groups as the prevalence of infertility was very high (48.9%) in Iran in contrast with 4.3% in this study for elementary school (grade 1-8), it was also 68.5% in this study and 32.8% in Iran among grade 9-12. These differences might have been contributed by the cultural and economic differences in delaying fertility in the two population groups. Though the Indian study showed a slight decrement in the prevalence of infertility as educational status increases: 9%, 8.1% and 6.67% for no schooling, less than 10 and greater than 10, respectively (Rostami Dovom *et al.,* 2014; Sarkar and Gupta , 2016), but the overall prevalence of infertility didn't show that much difference across different educational statuses and was lower when compared with this study's and the Iranian study's findings, probably due to natural as well as cultural reasons.

Concerning the causes of infertility, sexually transmitted diseases (STD) was seen in 3.3% of the clients in this study. A study of 5800 couples in 33 WHO centers in 25 countries showed that almost 50% of the African couples and 11–15% of other patients in other parts of the world had infectious tubal disease (Sciarra, 1994). There was also study in Germany that revealed *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections and untreated women results in tubal factor infertility in 10%–40% of the cases (Apari *et al.,* 2014). Another study by Gerais and Rushwan, (1992) suggest that in Africa, over 85% of women had an infertility diagnosis attributable to an infection compared with 33% of women worldwide. In another study from sub Saharan Africa, a history of STDs was reported by 46% of participating men (Gerais and Rushwan, 1992).

This study had shown 68.5% of clients used contraceptives, among them 58%were hormonal contraceptives. But a study in UK showed that previous prolonged oral contraceptive usage was statistically significantly associated with a decreased risk of delayed conception. Prolonged use of oral contraception was also associated with improved fecundity independent of other factors (Farrow *et al*., 2002), but temporary delays in conception compared with other methods of contraception have been reported.

Around 40% of respondents in this study had primary infertility. This finding was higher in comparison with findings in India where, the burden of primary infertility among couples ranged between 4 to 17%. This difference might have been contributed by the recent trend of raising age of first child delivery due to giving more emphasis for educational and work achievements while delaying fertility in our country (Unisa, 1999; Rutstein and Iqbal, 2004).

One of the factors identified to affect the effectiveness of treatment by FIDs in this study was age at menarche of the respondents those >15years at menarche had a higher risk of remaining infertile after treatment by FIDs [AOR= 1.392, 80% CI (1.473, 10.989)] and a P< .076.

Another similar findings were seen on a study conducted on the relationship between age at menarche and infertility among Chinese rural women, where almost a linear, trend of prevalence rate of infertility with increasing age at menarche (P <0.001). 1.57 (95% CI: 1.20, 2.04), 1.41 (95%CI: 1.00, 1.99) and 1.73 (95%CI: 1.18, 2.52) for age groups 16, 17 and 18 (Chen *et al*, 2015). In contrast to the findings in this study early menarche was also associated with decreased fertility. A study conducted in Denmark, Aarhus university hospital, indicated that the onset of menarche at 15years or later is associated with subfecundity and infertility (Guldbrandsen *et al,* 2014).

Both early and late AOM may be associated with adverse pregnancy outcomes (Chen *et al*, 2015) such as spontaneous abortions (Liestol, 1980; Martin et al., 1983; Wyshak, 1983) and ectopic pregnancies (Sandler et al., 1984).

Common causes of male infertility identified in this study were inadequate penile erection 30.5%. Inadequate sperm ejaculation 39.2%, low semen volume 10.3%, low sperm count($x10^6$/ml) 8.3% and inadequate sperm motility 10.3%. These findings have similarity with the results of previous studies. A low sperm count or quality is thought to contribute to infertility in 19% of couples (Rowe, Comhaire, 2000). A study in Nigeria showed that 53.2% of male infertility accounts to a problem of sperm motility of less than 50% (Loto, 2004). Unexplained abnormalities in sperm parameters including low sperm concentration ($\leq 15 * 10^6$ per mL), reduced sperm motility (≤ 40%), and abnormal sperm morphology (≤ 4% normal forms) (Jungwirth , Diemer , Dohle , *et al*., 2012).

This study showed only 3.3% fertility rate with the use of FIDs, but many studies showed that fertility rate after using FIDs were high (20-97%). This may be due to that in my study, the most frequently prescribed drug was Primolut N and the cycle was three. Primolut N is used as a contraceptive agent and is not included in a guideline as a fertility enhancing drugs (ASMR, 2012; National Collaborating Centre for Women's and Children's Health, 2004; United Health Care Commercial Medical Policy, 2017). A study in Ghana showed that, of the two hundred and twenty (220) users interviewed, 94% demanded primolut N for pre-coital contraception (Opare-

Addo *et al.*, 2011). Actually it is indicated for use in conditions such as dysfunctional uterine bleeding (DUB), primary dysmenorrhoea, endometriosis, premenstrual syndrome and progesterone challenge test as in secondary amenorrhoea (Mishel, 2001, Malahyde Information System, 2004). As observed from both the quantitative as well as the qualitative responses FGAE's clinic uses this drug as a first line drug of fertility inducing drugs that is majority of the clients, 44.3% used primolut N.

Clomiphene citrate was the second most common drug used by 16.6% of the respondents in this study. Seyedoshohadaei *et al* (2012) identified that it is the first-line therapy for ovulation induction. The dose of clomiphene citrate in this study is 50mg po per day for five days. It was also shown in other studies that the standard dosage of clomiphene citrate is 50 -100 milligrams (mg) per day for five consecutive days (ASRM, 2012). The dose can increase as high as 200mg and the cycle also increase to six even up-to 10 and 12 cycles. In other many studies, administration of clomiphene citrate can induce pregnancy for about 40% of women (Richard *et al.*, 2005), Pregnancy rate per cycle was 10-20%, 60% after six cycles and 97% after 10 cycles (Messinis, 2005; (Richard *et al.*, 2005; ASRM, 2012).

A well designed guideline on the treatment plan is not available in our country, therefore, the gynecologists are forced to use only their prior experience and professional opinion as a base for treatment (as well expressed in their qualitative response). This lack of guideline is affecting their treatment schedule as they tend to use the medication as the trend better for the individual case rather than moving stepwise based on a given protocol, this with the other factors also can reduce the effectiveness of the medications and finally resulting in ineffectiveness of treatment.

Regarding management of male infertility, FGAE clinic experience showed that a combined drug therapy was given using proviron and Vitamine E or testosterone and sildenafil. Similarly combinations of different hormonal therapies and anti-oxidants have been studied as potential empirical treatments for idiopathic male infertility (Safarnavadeh and Rastegarpanah, 2011).

6. LIMITATIONS OF THE STUDY

Since this study was conducted in one institution it might be difficult to generalize for the general population. Patient charts were incomplete and illigble to collect the necessary data. Most clients didn’t complet the whole course of treatment and their antenatal care followup, hence it is difficult to conclude the outcomes of fertility inducing drugs.

CONCLUSION

Effectiveness of fertility inducing drugs in family guidance association clinic is 3.3%. There was one abortion and one ectopic pregnancy. HIV/AIDS, CVD and STD were common medical finding of clients those attained FGAE for infertility service. The frequently used fertility inducing drugs were found to be primolut N followed by clomiphen citrate, proviron and vitamin E. Majority of the clients were on monotherapy. Primolut N and clomiphene citrate were commonly used alternative therapy. The alternative therapy didn't follow regular schedule. Most of the drugs were not available and they were costly. Poor adherence to FIDs treatment and lack of treatment guideline were the main contributing factors hindering effectiveness of infertility treatment identified in the study.

RECOMMENDATIONS

To ensure the effectiveness of fertility inducing drugs on patients attending the EFGA clinic, it is recommended that:

- EFGA clinic and concerned bodies like ministry of health, professional associations (ECOG, EMwA) should prepare and uses institutional and nationwide guidelines
- Fertility inducing drugs should be available and affordable
- Increase the dose and cycle of fertility inducing drugs based on international guidelines
- Assess adherence to medications and provide counseling accordingly
- FMHACA should include fertility inducing drug in national drug formulary lists

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ANNEXES

Annex I : Data abstraction format

- Card No:-----------------
- Age:----------------------
- Sex: □ male □ female
- Educational status: □ not read and write □ elementary school(1-8) □ high school and preparatory □ diploma+
- Marital status : □ married □ single □ divorced □ widowed
- Religion: □ Orthodox □ Muslim □ protestant □ others
- Address: □ Addis Ababa □ out of Addis Ababa
- No of pregnancies: □ para I □ para II □ para III and above
- Status of birth: □ live birth □ still birth □ abortion
- Type of infertility: □ primary □ secondary
- Contraceptives used: □ yes □ no
- Types of contraceptives used: □ hormonal □ non hormonal
- Any medical history: □ yes □ no
- Type of medical history: □ HIV/AIDS □ CVD STD □ others
- Menstrual regularity: □ regular □ irregular
- Dysmenorrhea: □ absent □ present
- Infertility status of Couples: □ fertile □ infertile
- Interventions taken for infertile couple: □ FIDs □ not on FIDs
- Knowledge &use of fertility periods: □ yes □ no
- Status of penile erection: □ adequate □ inadequate
- Status of ejaculation: □ adequate □ inadequate
- Semen volume: □ normal □ abnormal
- Semen count: □ normal □ abnormal
- Sperm motility: □ normal □ abnormal
- Alcohol consumption: □ Yes □ No
- Chat Chewing habit: □ Yes □ No
- Cigarette smoking: □ Yes □ No

Annex II: Questionnaire

Interview guideline for key informants:

- Physician/s

1. How do you describe the prevalence of infertility and possible factors?
2. What are the current, effective medicines that are used to treat infertility? Are they available in our country/FGA's clinic/? If not what would be the possible factors?
3. In your practice, how often does this treatment result in pregnancy?
4. Do you think that the medical treatment is effective?
    - Is adherence a factor in fertility treatment/ what are the possible causes of adherence/non-adherence? The number of clients that have a child after the treatment is not significant, what do you think are the possible reasons?
5. The number of clients that have a child after the treatment is not significant, what do you think the possible reasons? Do you have any evidence that client/s that conceived but not give live birth? And is there/ are there women that were pregnant using fertility inducing drugs here in your clinic and they follow other clinic/hospital?
    - What are the problems you faced in related to fertility inducing drugs? Could you mention the possible solutions?
    - Any other comments.

- Managers

  What are the possible factors that affect/s the effectiveness of fertility inducing therapies?

    - Drug related
    - Client related
    - Professional related
    - Institutional related (if there is unfulfilled materials, drugs, professionals, …)
    - Other concerning body/ies
    - Is there anything to improve the service?