CLINICAL CHARACTERISTICS AND EARLY OUTCOMES OF IN VITRO FERTILIZATION TREATMENT AMONG WOMEN ATTENDING A PRIVATE FERTILITY CENTER IN ELDORET,KENYA.

BY

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A research thesis submitted in partial fulfilment of the requirement for the award of the Degree of Master of Medicine in Reproductive Health, School of Medicine, Moi University.

DECLARATION

I hereby declare to the best of my knowledge that this is my original work and has not been presented for any award of degree or any academic credit in any other institution and has never been published anywhere.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Assisted Reproductive Techniques or Technology
FSH	Follicles Stimulating Hormone
GIFT	Gamete Intrafallopian Transfer
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
ICPD	International Conference on Population and Development
ICSI	Intracytoplasmic Sperm Injection
IREC	Institutional Research Ethics Committee
IUI	Intrauterine Insemination
IVF	In vitro Fertilization
IVF-ET	In vitro Fertilization and Embryos Transfer
IVM	In vitro Maturation of oocytes
LH	Luteinizing Hormone
LMICs	Low- and Middle-Income Countries
MESA	Microsurgical Epididymal Sperm Aspiration
PGD	Preimplantation Genetic Diagnosis
STDs	Sexual Transmitted Diseases
TESE	Testicular sperm Extraction
TFTs	Thyroid Function Tests

UN-ICPD	United Nations International Conference on Population and Development
WHO	World Health Organization
ZIFT	Zygote Intrafallopian Transfer

OPERATIONAL DEFINITION OF TERMS

Assisted Reproductive Technology: Refers to all techniques involving direct manipulation of oocytes or embryos outside of the body.

Clinical characteristics: Refers to the demographic, clinical and etiological factors presented by women undergoing IVF treatment. These include maternal age, donor age, BMI, Number of ART interventions, type of infertility, and co morbidities.

Gamete Intrafallopian Transfer: Placement of human ova and sperm into the distal end of the oviduct.

Infertility: Inability to achieve conception after twelve months of unprotected intercourse with adequate frequency per week (3 times).

Intracytoplasmic Sperm Injection: Technique by which a single spermatozoon is injected into the cytoplasm of an ovum.

In Vitro Fertilization: Fertilization of human ova by sperm in a laboratory environment.

Unexplained Infertility: Refers to the diagnosis of an infertile couple when ovulation and tubal patency as well as a normal semen analysis, are all present.

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ABSTRACT

Background: Infertility has been identified as a global reproductive health concern with a greater burden in countries with limited resources. It is also a major cause of marital instability and affects the quality of life and wellbeing of the affected. Although in-vitro fertilization (IVF) has been considered a definitive treatment of infertility, not all post-IVF outcomes are favorable. This could be attributed to procedural issues as well as the patient's sociodemographic and clinical characteristics. However, there is limited local data addressing the clinical characteristics that affect early IVF outcomes among women seeking the services.

Objectives: This study aimed to determine clinical characteristics and early outcomes among women undergoing in-vitro fertilization treatment at Mediheal Hospital and Fertility Center in Eldoret, Kenya.

Methods: This was a one-year prospective cohort study involving 153 women undergoing in-vitro fertilization as a definitive treatment for infertility at Mediheal Fertility Centre. The participants were sampled consecutively over a nine-month accrual period and followed up at 2, 6, and 12 weeks of IVF treatment. Sociodemographic characteristics were collected using an interviewer-administered questionnaire. Pregnancy tests, first and second (obstetric ultrasound was done on the 2^{nd}, $6^{th,}$ and 12^{th} week after IVF treatment to determine early clinical outcomes. Data analysis conducted using R statistical computing software (R Core Team, 2017). Pearson Chi-Square test and independent samples t-test were used to compare Clinical and Sociodemographic Characteristics and early clinical outcomes. Logistic regression model was used to assess the determinants of IVF success (critical value ≤ 0.05). Odds Ratios were computed at 95% confidence interval.

Results: A total of 153 women with a mean age of 36.2 (± 5.7) years were enrolled. Majority, 140 (91.5%) were married, 132 (86.3%) had a tertiary level education and 109 (71.2%) had health insurance and a median body mass index was 26.2 IQR: 23.5, 29.1) kg/m^2. Primary infertility was reported among 83 (54.2%) women, 120 (78.4%) had regular menstrual cycle, 71 (46.4%) had regular coitus (>4 times a month) while 112 (73.2%) had reproductive disorders. On the first follow-up visit (2 weeks post IVF) 8 women were lost to follow-up hence pregnancy tests was done on 145 women of which 75 (49%) were positive and 70 (45.8%) were negative and were dropped from the study. On the second visit (6 weeks post IVF) 5 women were lost to follow -up leaving 70 women for an obstetric ultrasound of which 61(39.9 %) were normal pregnancies with 3 (4.3%) ectopic pregnancies and 6 (8.6%) miscarriages. At the third visit (12 weeks post IVF), all the 61 women returned for an obstetric ultrasound, with 52 (34%) being normal while 6 (9.8%) had miscarriage, 2 (3.3%) had vanishing twins and 1 (1.6%) had blighted ovum. Although majority of the assessed characteristics were not associated with early IVF outcomes, women with a regular menstrual cycle (AOR=1.089; 95% CI: 0.741, 1.599) and primary infertility (AOR=1.051; 0.748, 1.477) were more likely to have positive pregnancy tests on the first follow-up visits. A normal BMI (AOR=2.216; 0.663, 7.405) and regular menstrual cycle (AOR=1.406; 0.398, 4.973) increased the likelihood of normal pregnancy after 12 weeks following IVF treatment. Previous infertility treatment was significantly associated (p=0.032) with normal pregnancy outcomes after 12 weeks of IVF treatment.

Conclusions: Majority of the women who seek IVF treatment are married for five or more years, have a tertiary level of education, formally employed with health insurance and reproductive disorders. The overall pregnancy success rate 12 weeks after IVF treatment at Mediheal fertility centers is 34%. Previous infertility treatment is significantly associated with favorable early clinical outcomes of IVF treatment.

Recommendations: More women should seek health insurance as a way of financing IVF treatment. Previous fertility treatment should be encouraged prior to IVF treatment to improve early clinical outcomes. Future studies should assess reasons for loss to follow-up and validate this study's findings in a public healthcare facility.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Infertility is defined as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Houschild et al., 2017). This could be attributed to anomalies in the male and female reproductive systems (Benksim et al., 2018; Podolska & Bidzan, 2011). In some cases, the cause of infertility is unexplained. Infertility is either primary or secondary (Zegers-Houschild et al., 2017). Primary infertility – occurs among those who have never achieved clinical pregnancy while Secondary Infertility – are among those who have achieved at least one clinical pregnancy but are unable to subsequently become pregnant.

The World Health Organisation (WHO) estimates that over 180 million couples in countries with developing economies suffer from either primary or secondary infertility (Ombelet, 2011). It recognizes infertility as a global health problem (Asemota and Klatsky, 2015). This led to the establishment of universal access to reproductive healthcare as one of the United Nations Millennium Development Goals of 2015 (Asemota and Klatsky, 2015). In resource limited healthcare settings within countries with developing economies, infertility is often overlooked despite it being a global health problem. There are also fewer resources dedicated to infertility care within Sub-Saharan Africa (Njagi *et al.,* 2020). This has led to a diagnosis of infertility to cause negative psychological, sociocultural and economic consequences among couples in low-income countries. This situation overly affects the wellbeing of those affected.

Emergence of assisted reproductive technologies (ARTs) such as in-vitro fertilization (IVF) could help in the definitive treatment of infertility. However, because of the low socioeconomic status of couples in Sub-Saharan Africa, this could be so costly if not financed by either national or private health insurance schemes. Making access to IVF care varied and often accessible to the wealthy visiting private healthcare setups. This high cost increases the stakes for desirable pregnancy outcomes among those who opt for IVF. This study determined the early clinical outcomes of IVF treatment and its associated clinical and sociodemographic factors in two private fertility centers in Kenya.

1.2 Problem Statement

Infertility has been identified as a global reproductive health concern with greater burden in countries with limited resources (Gerrits et al. 2017). This is because it is a major cause of marital conflict and influences the quality of life of couples and their wellbeing (Schmidt et al. 2012). One of the major causes of infertility in sub-Saharan Africa is infection-related to the tubes (Ombelet and Onofre 2019). One of the definitive treatments for infertility (Khairy et al. 2007) is assisted conception through in-vitro fertilization (IVF). Despite this mode of therapy being available, not all patients who receive IVF treatment have favorable desirable clinical outcomes due to multiple underlying patients and procedural characteristics (Shah et al. 2011). Several infertility centers have lately been established in Kenya (Noreh, Tucs, and Noreh 2009) including those at Mediheal group of Hospitals. The patient characteristics and operational factors affecting IVF treatment outcomes in these fertility centers ~~is~~ not adequately documented. This necessitates a local study on the early clinical outcomes of IVF treatment in these facilities such as Mediheal Fertility Centers in Kenya.

1.3 Justification

Assisted reproductive technologies have been fraught with lots of erroneous and incomplete information raising moral questions on the technique (Shenfield et al. 2002; Chemaitelly et al. 2019; Njagi et al. 2020). This is despite more than 40 years of IVF treatment and previous scientific publications on its efficacy as a definitive treatment for infertility (Diedrich and Bauer 1992; Andersen et al. 2009; Ombelet and Onofre 2019). The primary objective for IVF treatment is conception and ultimate parturition and this creates a need to determine the influence of patient characteristics on the clinical outcomes for IVF treatment. This will inform better understanding of predictors of IVF success and factors that interfere with desirable treatment outcome.

1.4 Research Questions

- What are the sociodemographic and clinical characteristics of women undergoing in-vitro fertilization treatment at Mediheal Hospital and Fertility Center in Eldoret, Kenya?
- What are the early clinical outcomes of IVF treatment among women at Mediheal Hospital and Fertility Center in Eldoret , Kenya?
- Is there an association between sociodemographic and clinical characteristics versus early clinical outcomes of women undergoing IVF treatment at Mediheal Hospital and Fertility Centers in Eldoret, Kenya?

1.5 Objectives

1.5.1 Broad Objective

To determine the early clinical outcomes and its associated clinical characteristics among women undergoing in-vitro fertilization treatment at Mediheal Hospitals in Eldoret, Kenya.

1.5.2 Specific Objectives

1. To determine the sociodemographic and clinical characteristics of women undergoing IVF treatment at Mediheal Hospital and Fertility Center,Eldoret.
2. To determine the early clinical outcomes of IVF treatment among women at Mediheal Hospital and Fertility Center,Eldoret.
3. To test the association between sociodemographic and clinical characteristics and early clinical outcomes of women undergoing IVF treatment at Mediheal Hospital and Fertility Center,Eldoret.

1.6 Conceptual Framework

This study hypothesized that clinical characteristics (independent variables) could predict the likelihood of a good pregnancy outcome (dependable variable). This relationship between clinical characteristics and early pregnancy outcomes could be influenced by the participants sociodemographic characteristics.

CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

This chapter describes and compares findings of studies on infertility and in-vitro fertilization. Specifically, it will address the global, regional and local epidemiology of infertility, sociodemographic and clinical characteristics of patients undergoing invitro fertilization and early (first trimester) outcomes of in-vitro fertilization treatment.

2.1 Epidemiology of Infertility

Infertility is defined as the lack of conception after 1 year of unprotected intercourse of reasonable frequency of approximately four to five times a week (Ombelet and Onofre 2019; Swift and Liu 2014). This is despite the fact that fertility is not determined by intercourse frequency but male and female factors.

The World Health Organization (WHO) defines infertility as failure to achieve a clinical pregnancy after twelve months or more of regular unprotected sexual intercourse (Asemota and Klatsky 2015). In clinical studies, the cut-off timeline for infertility is one-year. However, demographic studies define infertility as inability to conceive despite desire for fertility over a five-year period. The WHO identifies infertility as a disease that generates disability and impairs of function (Zegers-Hochschild et al. 2017). Majority (> 186 million) of the people around the world suffer from infertility with many of them living in the countries with developing economies (Inhorn and Patrizio 2015). In the United Kingdom, approximately one in seven couples (14%) experience conception difficulties (Wilkes et al. 2009). This finding is comparable to other countries with developed economies at 8-20% (Wilkes

et al. 2009). The common causes of infertility reported in the United Kingdom include male infertility (19-57%), ovulatory disorders (21-32%), tubal disorders (14-26%) and endometriosis at 6% (Wilkes et al. 2009).

Infertility can be classified as either primary or secondary. Primary infertility is where a woman has not previously conceived while secondary infertility occurs following at least one conception independent of the outcome. In Iran, the infertility rate was estimated at 13.2% with a primary infertility proportion at 11.9% while secondary infertility was 1.3% (Esmailzadeh et al. 2019). Overally, secondary infertility attributed to reproductive tract infections is more common than primary infertility (Borght and Wyns 2019). The occurrence of secondary infertility has also been significantly associated with intrauterine contraceptive device (IUCD) use, tubal sterilization, partner's sterilization, tubal and pelvic surgery as well as endometriosis (Bhattacharya et al. 2009). In Northeast Scotland, there were higher proportions of primary (9.5%) compared to secondary infertility at 4.9% (Bhattacharya et al. 2009). The three major factors influencing the spontaneous probability of conception are the time of unwanted non-conception, the age of the female partner and the disease-related infertility.

Infertility and sub-fertility have been found to be prevalent within high fertility zones in Africa such as Gabon, Central African Republic, Democratic Republic of Congo, Chad and Cameroon (Araoye 2003). Regions in countries within central and southern Africa have been described to have "the infertility belt" (Inhorn and Patrizio 2015). Although the proportion of infertility within East Africa has been reported to be lower than other sub-Saharan Africa regions, there are still higher proportions of infertility compared to other countries with developed economies (Ombelet and Onofre 2019; Inhorn and Patrizio 2015).

Childlessness among African women is a major cause of isolation, stigmatization and ostracization that could lead to neglect and being disinherited by the entire family and the local community (Gerrits et al. 2017). Infertility therefore affects the health and social wellbeing of the childless couples. It not only affects marital harmony of the couples but also their overall wellbeing. Childless women have been linked to a higher likelihood for anxiety, depression, suicide (Shani et al. 2016) isolation, loss of control, violence, marital breakdown and divorce (Araoye 2003). Because of this, there is need to treat infertility using alternative approaches such as assisted conception. The most common techniques for assisted conception include intrauterine insemination and in-vitro fertilization (van Loendersloot et al. 2014). In-vitro fertilization treatment is often offered alongside IUI (Andersen et al. 2009).

2.2 In Vitro Fertilization

In-vitro fertilization (IVF) gained prominence in 1978 with the birth of Loise Brown who had been conceived using the technique (Andersen et al. 2009; van Loendersloot et al. 2014). Since then, access to IVF has improved across countries in various continents (De Geyter et al. 2018; van Loendersloot et al. 2014). Despite this IVF cycles increase globally, little attention was paid to subfertility prevention and treatment in many African countries (except for Egypt and South Africa) prior to 2001 (S. J. Dyer and Kruger 2012; S. Dyer et al. 2016; Zegers-Hochschild et al. 2017). That is why the World Health Organization (WHO) commissioned the "Medical; Ethical and Social Aspects of Assisted Reproduction" committee in 2001 that recognized infertility as a global public health problem whose treatment should be integrated into National Reproductive Healthcare Programmes (Ombelet and Onofre 2019). Furthermore, the WHO recommended that assisted reproductive

technologies (ART) should be complementary to other ethically acceptable sociocultural solutions to infertility (Rutstein and Shah 2004). The process of in-vitro fertilization begins with ovarian stimulation, oocyte (egg) retrieval,sperm retrieval, embryo culture (fertilization) and ends with embryo transfer.

2.2.1 Patient history and investigation

Prior to in-vitro fertilization, standardized investigations for the couple is done at the fertility centers. This begins with screening for infections (including sexually transmitted diseases) since tubal obstruction resulting from previous pelvic infections has been attributed to infertility among many women in Africa. Hysterosalpingography, hysterosalpingogram (contrast-sonography) and the standard gynecological and fertility ultrasound scanning of the uterus and the ovaries is also ordered for. These techniques are combined with an accurate medical history to identify women's infertility causes (such as ovulatory disorders, uterine malformations and tubal infertility). Hysteroscopic investigations of the uterine cavity is important to investigate intrauterine abnormalities such as Ashermans syndrome, intrauterine polyps and myomas. Male factors for infertility are evaluated using semen analysis technique. The medical results and conclusions from all the examinations are then discussed with the couple on that same day to propose a management strategy.

2.2.2 Ovarian Stimulation

Ovarian stimulation (agonist and antagonist) protocols have been described previously (Bodri et al. 2006). In the antagonist protocol, ovarian stimulation begins with the administration of 225 international units (IU) of recombinant follicle stimulating hormone (FSH) from the second day of their menstrual cycle while a gonadotropin releasing hormone (GnRH) antagonist at 0.25 mg per day is introduced

on the sixth day after FSH stimulation according to a multiple-dose, fixed protocol (Bodri et al. 2006).

The agonist stimulation protocol begins with the administration of the GnRH agonist at 0.1 mg per day from the second day of their menstrual cycle followed by 187.5 IU recombinant FSH from the fourth day of their cycle. This lower initial dose is chosen to avoid adverse events (initial flare-up) of hyperstimulation of the ovaries.

Ultrasonography and serum estradiol laboratory assay is then performed after five days from the day of the stimulation. A subsequent daily dose of FSH is adjusted individually according to the ovarian response. Recombinant human chorionic gonadotropin (rHCG) is administered when at least three follicles of 18 mm or more are present. No previous treatment with oral contraceptives is used for oocyte donors. When less than four follicles are observed during the ultrasonography and /or the serum estradiol levels are way below the expected range the cycles are cancelled for low response. Coasting is then initiated in the event that the estradiol levels are more than 6000 pg/ml while more than 20 large follicles are observed before HCG administration. Cycles were also cancelled if coasting procedure lasted more than four days or if extremely high estradiol serum levels were observed during stimulation.

2.2.3 Oocyte retrieval

A single dose of 1 gramme of azithromycin is administered as a prophylactic antibiotic on the evening before the intervention. Oocyte retrieval is then performed using the transvaginal ultrasound-guided approach with a 17-gauge ovum-aspiration needle. The ultrasound probe is thoroughly disinfected before and after use and covered with a sterile plastic sheet. The vagina is then disinfected with chlorhexidine and thereafter abundantly rinsed with isotonic saline solution. The patient is covered

with sterile surgical sheets and the gynecologist performing the procedure wears sterile surgical gloves. Oocyte retrieval is performed under general anaesthesia by an anesthesiologist using intravenous alfentanil and propofol as well as assisted mask ventilation with oxygen and an inhalatory anaesthetic. At the end of the procedure, the vagina is thoroughly examined with a speculum and if necessary local compression is applied to allow hemostasis. Oocyte donors are observed in a post-operative recovery unit for two hours following the procedure while those with complications, donors were admitted to a tertiary university-affiliated center.

2.2.4 Intrauterine insemination

Intracytoplasmic sperm injection was performed in all participants, in order to reduce the possibility of fertilization failure.

2.2.5 Embryo culture (Fertilization)

Successful fertilization is defined as the presence of two clear pronuclei after 18–20 hours of insemination. Embryos are assessed and graded depending on the number, regularity of the blastomeres, and embryonic fragmentation according to the criteria established by the Istanbul consensus workshop (Magli and Sige 2011). All embryos are then cryopreserved by vitrification on the third day after oocyte retrieval (Harper et al. 2012).

2.2.6 Embryo Transfer

An artificial cycle is used for endometrial preparation in frozen embryo transfer (Zheng et al. 2015) which is done under transabdominal sonographic guidance. Daily progesterone (Crinone 8% gel and Duphaston 4 mg) are administered for luteal phase support. A pregnancy test is performed 14 days after embryo transplantation. In the event of a positive pregnancy test, progesterone administration continues until 8

weeks of gestation. Clinical pregnancy is defined as a visible fetal heartbeat in an intrauterine gestational sac by transvaginal ultrasound conducted 6 weeks and 12 weeks following in-vitro fertilization treatment. Ongoing pregnancy is determined by the presence of a fetal heartbeat beyond 20 weeks of gestation while cancellation was a cycle with incomplete ovarian stimulation or no retrieved oocyte (Hong et al. 2018; Lee et al. 2018; Lensen et al. 2019).

2.3 Early Outcomes of In Vitro Fertilization

The primary objective of in-vitro fertilization is clinical pregnancy that eventually leads to a live birth. Many factors could influence the likelihood of a clinical pregnancy and live birth. These include the type of oocyte used (self or donor), whether or not it was freeze-thawed or fresh oocyte. The overall global clinical pregnancy rate (CPR) following IVF treatment has been estimated at 23.4% to 54.2% while live birth rates (LBR) 14.2% to 44

In a prospective study conducted in India, the clinical pregnancy rate was higher among women who underwent fresh embryo transfer cycles using donor oocytes (50.2%) compared to their own freeze-thawed oocyte (42.9%) and fresh oocytes (40.8%). According to the Society for Assisted Reproduction Technologies (SART) registry of 2013 across 467 clinics in the United States of America, women who underwent fresh embryo transfer using their own oocytes had a clinical pregnancy rate of 54.3% (among women younger than 35 years), 47.3% (35 – 37 years), 38.3% (38 – 40 years), 27.3% (41-42 years), 15.9% (43-44 years) and 6.9% among those older than 44 years. Among women who received donor oocyte transfer, 66% of them had a clinical pregnancy compared to frozen-thawed embryo transfer at 50.1% (SART 2013).

Fresh embryo transfer was associated with a complete pregnancy rate of 48.2% and a multiple pregnancy rate (MPR) of 32.2% (Shen et al. 2014. For the frozen-thawed cycle, CPR was 36.5% while MPR was 29.3% (Shen et al. 2014). The overall CPR reported in a retrospective study conducted in Virginia-USA was 47% while MPR stood at 35% (Mirkin 2003).

2.4 Alternatives of In-Vitro Fertilization

2.4.1 Gamete Intra-fallopian Transfer (GIFT)

In-vitro fertilization and embryo transfer were originally designed for the treatment of infertility patients who had severely damaged, blocked, or absent fallopian tubes. This was later extended to treat infertility caused by various etiological factors which include anatomically patent fallopian tubes. Gamete intra-fallopian transfer (GIFT) was introduced as a method for the treatment of non-tubal infertility. The technique entails the laparoscopic aspiration of oocytes and their insertion into the fallopian tube with washed sperms. It has been widely used in the treatment of infertility caused by poor sperm fertilizing ability, impairment in tubal sperm transport, failure of ovum release, or failure of ovum pickup at the fimbria. Other indications of the GIFT procedure include unexplained infertility, endometriosis, and immunological factors (Kelada & Craft, 2014).

In a study by Abel et al (2007) whereby the GIFT procedure involved laparoscopic follicle aspiration done under general anesthesia. 100% CO2 was used to create a pneumoperitoneum. Aspirated oocytes were then evaluated for maturity and classified as either being metaphase I or II. Random selection of oocytes was done on completion of follicle aspiration. The participants whom less than 3 oocytes were obtained during aspiration were excluded from the study. The oocytes were loaded

into a transfer catheter together with 100, 000 sperm. The number of sperm was then increased to 500,000 if the male partner had a morphology of less than 14% normal forms on semen analysis. The loaded catheter was then passed through the cannula used for aspiration and inserted into the fallopian tube to a distance of 2cm from the fimbrial opening, where the gametes were deposited.

In the prospective randomized controlled study, the mean age of the female partners was 34 years (22-40). A total of 44 women were involved and a total of 45 cycles were attempted. The rate of Conception achieved by GIFT was 53.3% (24/45). The ongoing pregnancy rate per cycle was 35.6% (16/45). There were 23 intrauterine pregnancies and 1 tubal pregnancy. The intrauterine pregnancies had 3 sets of twins and 13 singletons. The rate of twinning was 12.5% (3/24). The rate of miscarriage was 19.17% (7/24) and the rate of tubal pregnancy 4.17% (1/24) (Abels et al., 2007)

2.4.2 Zygote Intra-fallopian Transfer (ZIFT)

One of the major challenges following in-vitro fertilization is repeated implantation failure (RIF). Zygote intra-fallopian transfer (ZIFT) is reported to help improve the rate of success after RIF. Some of the mentioned advantages of ZIFT include; an ideal and natural intra-fallopian milieu that results in a better synchronization between embryonic and endometrial development, a rapid scheduling causing alleviation of patients' stress, and a simple culture of human zygotes avowing the extended culture's disadvantages that include the fragmentation and complete block of development (Shahrokh Tehraninejad et al., 2015). The procedure prevents intrauterine manipulation and the possible consequent embryo expulsion secondary to sub-endometrial and myometrium contractions (Gat et al., 2014). However, some of the reported disadvantages of the ZIFT procedure include the need for general anesthesia, laparoscopy, and an increased risk of ectopic pregnancy.

A study by Gat et al. (2014) evaluated 47 patients undergoing their first ZIFT cycle. The patients had undergone their 10.2 ± 2.9 IVF cycle attempts during the study cycle (range, 6-19). The mean age of the patients was 33.6 ± 4.9 years. 12 clinical pregnancies were recorded following the ZIFT cycle as compared to none in the previous IVF cycle (a clinical pregnancy rate of 25.5%). However, the increased pregnancy rate in the ZIFT cycle was biased owing to the study design that offered the approach to patients with repeated implantation failure who had failed previous in-vitro fertilization attempts. It was shown that patients who may benefit from ZIFT are majorly young patients (<31 years) who have undergone ≤ 6 cycle attempts yielding over eight 2 pronuclear embryos with a low (≤ 0.4) ratio of the number of top-quality embryos to a total 2 pronuclear embryos.

2.4.3 Intracytoplasmic Sperm Injection (ICSI)

Intracytoplasmic Sperm Injection involves the injection of a single sperm directly into the cytoplasm. The treatment capabilities of this treatment modality range from the utilization of spermatozoa with poor progressive motility to those gametes microsurgically collected from the epididymis of the testes of azoospermic patients (Pereira & Palermo, 2018). ICSI is also very useful in the fertilization of oocytes that were previously cryopreserved. Cryo-stress usually leads to the premature exocytosis of the cortical granules and zona hardening, which hinders spermatozoa from natural penetration. ICSI is also the preferred method of insemination to avoid polyspermy, fertilize a high number of oocytes, and generating a maximal cohort of embryos. The selection of a single spermatozoon results in a significant reduction in the transmission of diseases such as HIV, HBV, and HCV (Boulet et al., 2015). ICSI is also advantageous in that it is not affected by the immaturity of the male gamete such as the spermatozoa that are retrieved directly from the epididymis or the testis that is

often characterized by an incomplete flagellum and an underdeveloped cell membrane (Pereira & Palermo, 2018).

The use of ICSI in cases of assisted reproductive technology (ART) within Australia and New Zealand increased from 59.1% in 2008 to 63% in 2015. There has been a similar pattern in the USA, whereby the proportion of cycles using ICSI rose from 36.4% to 72.6% between 1996 and 2012 (Boulet et al., 2015). A cross-sectional survey of ART procedures performed by the International Committee for Monitoring Assisted reproductive technologies (ICMART) reported that 63.0% (455,845 of 723,855) of all cycles performed in 60 countries in 2010 utilized ICSI. The prevalence ranged from 58.4% in Asia to a virtual totality of 98.4% in the Middle East (Pereira & Palermo, 2018).

2.5 Pregnancy Outcomes among Women Undergoing ARTs

A prospective and descriptive cross-sectional study by Lucas et al. (2021) was evaluated women visiting Cape Windhoek Fertility Clinic in Namibia. The study incorporated 178 patients classified as ‘infertile women’ visiting the clinic for ART treatment. Of the 178 women, 96 were infertile, while the remaining 82 were sub-fertile. The classification as infertile (0 children) or sub-fertile (1 or more children) was based on the gravida-para status of the women. The women enrolled in the study ranged from 25 to 50 years of age, the majority of the participants (n=145; 81.5%) were married. Most of the women (n= 97; 54.5%) seeking infertility treatment were in the age group of 30 to 39 years. Of the 178 infertile women, 96 cases (53.9% suffered from primary infertility and 82 (46.1%) of the women suffered from secondary infertility. Of those who presented with secondary infertility, most (40; 22.5%) already had 2 children (Lucas et al., 2021).

In the study by Lucas et al. (2021) the predominant cause of complications for infertility was defective ovulation in 51 women (28.7%) and the most common ART treatment method administered was split In-Vitro Fertilization/ Intracytoplasmic Sperm Injection (IVF/ICSI) (93;52.2%). The total number of ART cycles performed was 247, the oocytes retrieved: 1352, oocytes fertilized: 1060, embryos implanted; 480, biochemical pregnancies achieved: 59, embryos transferred (fresh: 424, thawed: 53).

Among the 178 patients, 10.1% tested positive for HIV, 7.3% for HBsAg, 1.1% for syphilis while all the patients tested negative for HCV. A majority reported to be non-smokers (177; 99.4%) and did not consume alcohol (143: 80.3%). A majority of the women, 130 (73.1%) received only one ART treatment cycle. Only 33.1% of the women undergoing ART treatment (59/178) eventually conceived. A majority (119/178; 66.9%) did not respond favorably to treatment. There was no correlation between the pregnancy outcome and HIV ($p = 0.986$) or syphilis ($p = 0.611$) status. However, there was a correlation between the pregnancy outcome and the patient's HBsAg status ($p = 0.024$) (Lucas et al., 2021. The study noted 100% successful pregnancy outcomes after ART treatment in women in the age group >49 years. However, there was no correlation between the age of the patient and the pregnancy outcome (chi-square; p-value = 0.077). The younger women (20 -29 years) had the 2nd highest (44.4%) pregnancy success rate. This was attributed to the ovarian reserve given their age.

A retrospective, hospital-based cohort study in couples who underwent in-vitro fertilization treatment at Beijing Obstetrical and Gynecology hospital evaluated the differences in maternal characteristics and the pregnancy outcomes of Chinese women with different causes of infertility. Among the singleton pregnancies, in comparison

with spontaneous pregnancies, IVF pregnancies were correlated to an increase in the rates of the following: in the group with ovulation disorder, gestational diabetes mellitus (aOR 1.76 [95% CI 1.33-2.33]), preeclampsia (2.60 ‘1.61-4.20]), preterm preeclampsia (4.52 [2.03 -10.06]), post-partum hemorrhage (1.57 [1.04 -2.36]), intrahepatic cholestasis of pregnancy (3.84 [1.06 -13.94]), preterm premature rupture of membranes (2.11 [1.17 -3.81]), preterm birth (1.91 [1.26 -3.01]), low birth weight (1.90 [1.13- 3.20]), macrosomia (1.53[1.03 -2.27]), and admission to neonatal intensive care unit (1.69[1.22 -2.34]) (Wang et al., 2021).

In the group classified as having tubal disease; gestational diabetes (aOR1.50 CI [1.21 -1.86]), Placenta Previa (2.70[1.59 - 4.59]), placenta accreta (1.78 [1.10 – 2.89]), post-partum hemorrhage (1.61 [1.19- 2.18]), macrosomia (1.60 [1.21 -2.13}) and a 5 minute APGAR score <7 (4.09[1.04-16.080 (Wang et al., 2021). Within the endometriosis group; placenta previa (9.33 [4.22-20.62]), small for gestational age (2,29 [1.04 – 5.08]), macrosomia (2.00 [1.02 – 3.95]) and admission to the neonatal intensive care unit (2.35 [1.35 -4.09]). In the group that had male infertility; Placenta Previa (4.14 [2.23 – 7.68]) and placenta accreta (2.05 [1.08 -3.87). In the mixed infertility group, there were significant increases in placental abruption (3.39[1.20 -9.56]), chorioamnionitis (2.93 [1.04 -8.26]) preterm birth (2.69 [1.41 – 5.15]) and a 1 minute APGAR score <7 (4.48 [1.62 – 13.52]). The significant differences in singleton pregnancies were less extensive in multiple pregnancies or had disappeared (Wang et al., 2021).

2.6 Predictor Factors for Success and Pregnancy Outcomes in IVF

2.6.1 Duration of Subfertility

Various studies established a correlation between the duration of subfertility and pregnancy. A study by Ottosen et al. (2007) subdivided the duration of subfertility into six categories.It was reported that women with a duration of subfertility exceeding twelve months had a lower chance of pregnancy as compared to women with a duration of subfertility of less than twelve months. The duration of subfertility was evaluated as a continuous measurement and data could be pooled. The rate of pregnancy per woman was lower with increasing duration of subfertility. With 1077 patients, the OR of the study was 0.99, (95% CI: 0.98 -1.00) (Van Loendersloot et al., 2015).

2.6.2 Type of subfertility

There have been reported associations between the types of subfertility (primary versus secondary subfertility with pregnancy. Women with a previous clinical pregnancy had lower chances of pregnancy after in-vitro fertilization. However, women who previously had given birth had higher chances of pregnancy after in-vitro fertilization. Pooling of data was done with a sample of 1077 cycles, whereby the summary OR was 1.04 (955 CI: 0.65 -1.43) (Van Loendersloot et al., 2015).

2.6.3 The Indication for In-Vitro Fertilization

Several studies have reported an association between pregnancy and the indication for in-vitro fertilization. This predictor has been evaluated based on categories including unexplained infertility, male infertility, and tubo-peritoneal disease. Women with tubo-peritoneal disease and those in the category of male infertility had lower chances of pregnancy as compared to those with unexplained infertility. Women with either male subfertility, subfertility due to endometriosis or tubal subfertility had lower

chances of pregnancy as compared to women with unexplained infertility. Women with tubal subfertility have significantly lower chances of pregnancy after in-vitro fertilization. Women with an indication for In-vitro fertilization being endometriosis, unexplained subfertility, male subfertility, and hormonal factors had higher chances of pregnancy though not significant (Van Loendersloot et al., 2015).

2.6.4 Basal Follicle Stimulating Hormone (FSH)

Studies by Ebbesen et al (2009) and Sabatini et al. (2008) dichotomized basal FSH into 0-10 IU and >10 IU categories. Both studies depicted the chances of pregnancy being significantly higher in women with FSH <10 IU than in women with concentrations of FSH >10 IU. The summary OR showed that increasing basal FSH values was associated with a lower rate of pregnancy rates after in-vitro fertilization (OR 0.94; 95% CI: 0.88 -1.00).

2.6.5 Number of Oocytes Retrieved

There is a correlation between the numbers of Oocytes retrieved with chances of pregnancy. Ottosen et al. (2007) categorized the number of oocytes as; 1-5 oocytes, 6-10 oocytes, and 11 or more oocytes. It was determined that women with more oocytes had increased chances of pregnancy after in-vitro fertilization with an OR of 1.04 (95% CI: 1.02 -1.07).

2.6.6 Method of Fertilization

There is a reported association between the method of fertilization used (in-vitro fertilization or intracytoplasmic sperm injection) with the chances of pregnancy thereafter. There were reported lower chances of pregnancy with intracytoplasmic sperm injection compared to in-vitro fertilization (OR 0.95, 95% CI; 0.79-1.14), even

though the chances were not significant between the two methods (Van Loendersloot et al., 2015).

2.6.7 The number of Embryos Transferred.

There is a correlation between the number of embryos transferred and the chances of success after in-vitro fertilization. These were categorized into either more than 2 or less than 2 embryos transferred. It was elicited that women who had more than two embryos transferred had significantly higher chances of pregnancy (Van Loendersloot et al., 2015).

2.6.8 Embryo Quality

Hunault et al. (2008) classified embryo quality based on two separate factors. The evaluation for the best and the second-best embryo was based in terms of developmental stages and the morphology score. The stage of development was described into three categories; delayed, appropriate and advanced stage. With advanced-stage being used as a reference category, women whom either the best or second-best embryo had a delayed or appropriate development stage had lower chances of pregnancy compared to women who had either the best or second-best embryo with an advanced development stage. Lower morphology scores were also associated with lower chances of pregnancy. Van Loendersloot et al. (2015) reported the use of predictors such as the number of good quality embryos available, the number of good quality embryos transferred and the number of embryos suitable for freezing was associated with increased chances of pregnancy.

2.6.9 Quality of Life

The process of Assisted Reproductive Therapy (ART) especially in-vitro fertilization (IVF) is psychologically and emotionally stressful for many patients. There is a huge possibility of perceived stress, anxiety, and depression before, during, and/or after the IVF treatment (Wu et al., 2020). In addition to the fear of not getting pregnant, the treatment stresses out women due to the cost of treatment, the daily injections, the required procedure, and a possibility of failure at any stage within the treatment process. These factors could negatively impact the patient's quality of life (Rooney & Domar, 2016).

The longitudinal study by Wu et al. (2020) investigated the prospective association between quality of life and pregnancy outcomes in Assisted Reproductive Technology. It was shown that the emotional quality of life measured before embryo transfer was a significant predictor for pregnancy positive outcomes for in-vitro fertilization treatment (Rooney & Domar, 2016). The fertility quality of life (FertiQol) tool, which is a gold standard tool, was used to capture the quality of life of the women undergoing treatment for fertility problems. FertiQol covers different aspects of the women receiving infertility treatments such as the treatment module, treatment environment, and their tolerability domains (Boivin et al., 2011). The study by Wu et al. (2020) established a significant association between the emotional Quality of life scores with In-vitro fertilization outcomes. A one-unit increase in the quality of life score was associated with significantly increasing the probability of ongoing pregnancy ad live birth rate by 2.4% and 2.6% 9p<0.05) respectively.

Mental health has both direct and indirect effects on physical health. It is therefore possible that poor emotional quality of life lowers the physical condition of infertile women which consequently affects their outcomes in pregnancy (Rooney & Domar,

2016). There is a prospective relationship between emotional quality of life and pregnancy outcomes among women receiving in-vitro fertilization treatment. This shows that psychological consultation and support which can help improve the emotional state of women undergoing in-vitro fertilization can increase the possibility of a successful pregnancy (Wu et al., 2020). There is an opportunity to improve in-vitro fertilization pregnancy rates by decreasing the impact of infertility treatments on the emotional health of the patients.

2.7 Factors Affecting Pregnancy Outcomes Post IVF

2.7.1 Maternal Age

In a study conducted by Khadra et al. (2017) that involved 1,025infertile couples. The cause of infertility was mainly due to the male partner (35 %), a female factor (33%) and both partners combined were responsible for 11% of the infertility cases. 21% were unexplained infertility. The female infertility factors included tubal factor (40%), anovulation (39%), endometriosis (6%), and other causes such as uterine fibroids and congenital uterine abnormalities (15%). The main outcome measure included in the study was live birth per embryonic transfer (LBR). The analysis was also done for a positive pregnancy test on day 14 per embryonic transfer performed. The evidence of conception was based on positive hCG (>20IU) (Khadra et al., 2017).

44.3% of the couples had a positive pregnancy test. The positive pregnancy rate (PPR) and LBR in women younger than 35 years was 47.5% and 33.5% respectively. In women between the ages of 35 and 39 years, the PPR was 27.6% and LBR was 15.6%. For women older than 40years the PPR was 10.9% and LBR was 4.7 %. The highest rate of pregnancy tests (51%) was in the group aged 20 to 24 years. The highest rate of live birth (42.5%) was in the age group between 25 to 29 years. For

women older than 35 years, there was a sharp decline in both PPR and LBR. Female age was established as the main factor affecting both LBRs and PPR (Khadra et al., 2017).

A study by Kim et al. (2017) incorporated data from 2,362 IVF cycles that were subdivided by 1 year maternal age increment at age 40 and over. There was a noted cancelation rate increase from 7.8& at the age of 40 years to 22% at the age ≥ 45 years during controlled ovarian hyper-stimulation. The total rate of cancellation in both controlled ovarian hyperstimulation and embryo transfer was as high as 30.1% at the age of 40 years and 50 % at the age ≥ 45 years. The rate of clinical pregnancy was shown to decrease from 22.3% at age of 40 years to 2.7% at age ≥ 45 years. The live birth rate decreased from 12.9% at the age of 40 years to 0.7% at age ≥ 45 years. The rates of clinical pregnancy and live births in women ≥ 40yeras decreased significantly each year ($P<0.001$) (Kim et al., 2017).

A comparison of IVF parameters between women aged ≥40 years who had a live birth (n – 102) versus those who did not have a live birth (n = 1430), the group with live births had a significantly lower maternal age (40.9 ± 1.2 years versus 42.0 ± 1.9 years, $p <0.001$). an analysis of the cumulative live birth rate based on the number of IVF cycles attempted for each age depicted a gradually increasing trend in the cumulative live birth rate for up to 11 cycles for those aged 40 years, up to 7 cycles (19% for those aged 41 to 42 years, and up to 4 cycles (3%) in those aged between 43 and 44 years. However for those aged 45 years and above, repeated attempts didn't result in any increased cumulative live birth rate (Kim et al., 2017).

2.7.2 Underlying Medical Conditions, Diet, and Habits

Before the initiation of in-vitro fertilization treatment or any other Assisted Reproductive technologies, a complete medical evaluation for the optimization of the patients' health is essential. Some maternal conditions are known to limit the physiologic support a woman can provide to a pregnancy, which could pose a risk to the life of the woman, or affect the pregnancy outcome post-IVF (ACOG, 2020). A history of preexisting cardiopulmonary disorder for example Marfan or Turners syndrome could lead to significant cardiopulmonary compromise due to increased cardiopulmonary demands of pregnancy. The patient should therefore undergo evaluation and risk counseling. For more common illnesses such as hypertension, obesity, epilepsy, or diabetes mellitus, the optimization of weight, maternal medicals status, treatment regimen, and other care aspects have integral effects on becoming pregnant and the pregnancy outcomes (ACOG, 2020).

A study by Sazonova et al. (2016) linked various maternal conditions, habits, and characteristics to different pregnancy outcomes post-IVF. The study analyzed four major pregnancy outcomes: very preterm births (<32 weeks), small for gestational age (SGA), Placenta Previa, and placenta abruption.

The outcome of very preterm births post-in-vitro fertilization had a significant association with primi-parity (AOR 2.52; 95% CI; 1.51-4.20), maternal smoking (AOR 1.71; 95% CI 1.02 -2.85), and BMI (AOR 1.05; 95% CI 1.01 -1.10). The outcome of small for gestational age post-IVF was associated with maternal age (AOR 1.04; 95% CI 1.10 -1.107), primi-parity (AOR 1.99; CI 95% 1.43- 2.75), maternal smoking (AOR 1.57; 95% CI 1.06-2.34) and the years of infertility (AOR 1.07; 95% CI 1.02 -1.13) (Sazonova et al., 2016). High as well as low BMIs were found to be correlated with increased risk of small for gestational age as compared to

a normal BMI (20-25kg/m2) in patients who had undergone in vitro fertilization. Smoking was the only variable significantly associated with placental abruption in patients post-IVF (AOR 1.94; 95% CI 1.02 -3.67) (Sazonova et al., 2016).

Lifestyle factors including diet, exercise smoking, and stress affect the reproductive performance following in vitro fertilization (Hornstein 2016). Both preconception and post-IVF dietary habits influence pregnancy outcomes. The Mediterranean diet, a diet rich in fruits vegetables, whole grains, legumes, nuts, and olive oil, and low in red meat seems to be the most promising on human health (Braga et al., 2015). A study by Karyannis et al. (2018) on 244 women who had received in-vitro fertilization treatment assessed their dietary pattern 45.9% of the women reported using dietary supplements, mainly multivitamins and folate. 56.5% (138) of the women had successful implantation and 42.6% (104) attained clinical pregnancy and 40.5% (90) had a live birth. The women with live births did not differ in age, smoking habits, physical activity BMI or stress levels. The rate of clinical pregnancy and live birth was established to be significantly lower in women with the lowest compared to women with the highest tertile of the Mediterranean diet score (29.1 versus 50.0%, p = 0.01 and 26.6 versus 48.8%, p = 0.01, respectively) (Karayiannis et al., 2018).

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Setting

The study was carried out at Mediheal Hospitals and Fertility Center Eldoret, which operates one fertility clinic. IVF procedures are done every other month by a team made up of one consultant fertility specialist assisted by a resident consultant obstetrician and gynecologist,One embryologist, two fertility trained nurses and two laboratory technologists.

The facility has developed an innovative approach to healthcare provision in the region and it is the only center offering assisted fertility, using ARTs and IVF in Western Kenya. This center has a limited number of equipment for its operation: These include USG machines, mobile heating plates, incubators, spermfuges and microscopes. It has a contract partnership with a Nairobi based biomedical engineering company which maintains and services these machines at regular contracted period. Mediheal hospital serves a catchment population of approximately 16 million in Western Kenya and approximately 25 million in Nairobi and its environs.

3.2 Study Design

This was an observational prospective study that involved a three months' follow up of infertile women that had undergone IVF fertility procedures at the Mediheal hospital fertility centers. During the three months follow up period, each IVF treated case was contacted and examined for IVF treatment outcomes at three intervals as per their appointment schedules/dates provided to them by their fertility specialists and normally this happens during the second week, the sixth week and at the twelfth week post initiation of IVF treatment.

3.3 Study Population

The target population consisted of infertile women diagnosed and confirmed to have primary or secondary infertility who were treated at Mediheal facility centers. The study population consisted of infertile women undergoing IVF at the Mediheal Hospital and Fertility Center who met the eligibility criteria.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

All infertile women undergoing IVF at Mediheal Hospital and Fertility Centre

Those who provided informed consent to participate in the study.

3.4.2 Exclusion Criteria

Women who underwent IVF elsewhere, but chose Mediheal Hospitals and the Fertility Center for follow-up.

3.5 Sample Size Estimation

According to a study by Dyer et al in South Africa the pregnancy rate of IVF was 33.6%. Thus, to be 95% sure that we report this proportion within plus or minus 5% margin of error we determined the sample size using the formula by Cochran (Cochran, 1963).

$$n = \left(\frac{Z_{1-\alpha/2}}{d}\right)^2 \times P \times (1-P)$$

$$= \left(\frac{1.96}{0.05}\right)^2 \times 0.336 \times (1-0.336)$$

$$= 342$$

Where P is the postulated success rate of IVF, Z_c is the quantile of the standard normal distribution corresponding to c x 100% percentile, c = (1 – a / 2), a is the type I error rate, d is the margin of error.

In Mediheal facilities IVF was performed in alternate months with an average of 48 women undergoing the procedure every alternate month in the previous year with 216 women having undergone IVF. The study duration for the study was one year with nine months accrual period. This implied that during this period we anticipated to see an average of 216 infertile women undergoing IVF.

Adjusting for finite population

$$n' = \left(\frac{n}{1 + \frac{n-1}{N}} \right)$$

$$= \left(\frac{342}{1 + \frac{341}{216}} \right)$$

$$= 130$$

Adjusting for a 15% loss to follow up rate we thus need a minimum of 153 participants

3.6 Sampling technique

Consecutive sampling was used whereby patients who were undergoing IVF and were willing to participate in the study were recruited into the study until the desired sample size was achieved.

3.7 Enrollment and Data Collection

The participants who met the study inclusion criteria were recruited until the desired sample size was attained. Data was collected from each patient prospectively at specific intervals and relevant information captured into a structured questionnaire. Data was collected by the principal investigator and a trained research assistant and entered into a structured questionnaire and later a window access database.

3.8 Data Management

Data collected using structured questionnaires was entered in an electronic Microsoft access database. Prior to entry the data was stripped of the patient identifiers for confidentiality reasons. The database was encrypted to enhance the security and confidentiality of the patient data. The password was made accessible to the principal investigator alone. Backup for the data was done using memory sticks and external drives to cushion against data loss. After data entry, the questionnaires were then kept in a safe cabinet under a lock and key kept by the principal investigator. They will be destroyed five years after publication of the results from this study.

3.9 Quality Control

- Research assistants were trained by the principal investigator and were routinely monitored to assure the consistency and quality of the interviewing process;
- Pre-testing daily the questionnaires and checking for their completeness;
- Back up of the data and filled questionnaires were stored in a safe place under lock and key;
- Meetings with research assistants were done to sort out data collection problems.

3.10 Study Procedure

The researcher approached the records department to identify potential participants who were scheduled for the invitro fertilization treatment after all the initial screening had been done. One-hour post IVF treatment, the potential participants were approached and informed of the study's objectives, procedures and potential benefits. Those who agreed to the study were consented by a research assistant in the private recovery room. They were informed on how their privacy and confidentiality will be

maintained, what will happen at each follow-up visit and the importance to come for all the scheduled visits. For the women who consented, data on their sociodemographic and reproductive characteristics were collected. In the event some information were missing, these were retrieved from the medical records. Each participant was followed-up for 12 weeks from the day of enrollment.

On the first visit (2 weeks post IVF), pregnancy tests were conducted in the hospital's medical laboratory using blood samples. Those who tested positive were encouraged to come for the second visit (6 weeks post IVF) while those who were negative stopped follow-up. On the second visit, obstetric ultrasonography was conducted to assess clinical pregnancy. Those who had a normal clinical pregnancy proceeded to the third visit (12 weeks post IVF). Abnormal pregnancy outcomes for the sixth week visit were recorded on the data collection form.

On the final visit, a confirmatory obstetric ultrasound was performed (at week 12 post IVF) and pregnancy outcomes recorded. The participants were thanked for their participation and promised to be disseminated to the study's findings.

3.11 Data Analysis

Descriptive statistics such as frequencies was used to summarize categorical variables and mean and standard deviation as well as the median and the inter quartile range was used to summarize the continuous variables. Inferential statistics such as the Pearson Chi Square test was used to compare and infer from the data. Measures of association, specifically the odds ratios and the corresponding 95% confidence limits, was used to assess the magnitude and direction of the effect of determinants of success of IVF. Logistic regression model was used to assess the determinants of IVF

success. Data analysis was done using R: A language and environment for statistical computing (R Core Team, 2017).

3.12 Ethical Considerations

This study got ethical clearance from the Institutional Research and Ethics Committee (IREC) of Moi University School of Medicine and Moi Teaching and Referral Hospital. Permission to conduct the study was obtained from the management of Mediheal Hospital and Fertility Center. A written informed consent was sought from each participant prior to enrollment. Consenting was done in a private room where the study's objectives, procedures, risk and benefits were properly explained to the potential participants. They were not coerced or offered incentives to participate, while also offered the freedom to withdraw participation at any time.

After enrollment, their privacy and confidentiality ensured through deidentification of personal information and restricted access to electronic databases through password protection. Similar care was offered to patients irrespective of their study participation status. The study's findings will be disseminated to the participants, hospital management, other stakeholders and publication in peer reviewed scientific journals.

CHAPTER FOUR

4.0 RESULTS

4.1 Recruitment and Follow-up

This study enrolled 153 participants all who were consented after the in-vitro fertilization procedure. Of these, 8 were lost to follow-up and did not return to the clinic for blood pregnancy test conducted 14 days after invitro fertilization treatment. Among the 145 who had a pregnancy test, 75 tested positive and were advised to return to the fertility center after four weeks. Despite the advice, 5 participants were lost to follow-up and did not return to the clinic six weeks after IVF treatment. This left only 70 participants who had a week 6 obstetric ultrasonography done. Of the 70 who had the obstetric ultrasonography, 61 had a normal pregnancy and were advised to come 6 weeks later for a repeat obstetric ultrasound. All the 61 participants returned 12 weeks after IVF treatment for the repeat ultrasound, of which 52 had a normal pregnancy (Figure 4.1). The overall loss-to-follow-up was 13 (8.5%).

4.2 Sociodemographic characteristics

The mean age of the women enrolled was 36.2 (±5.7) years with more than half being aged 35 years or more. Majority 140 (91.5%) were married, 132 (86.3%) had a tertiary level education and 109 (71.2%) had health insurance.

Table 4.1: Sociodemographic characteristics of the study participants

Variable	**(N=153)**
	Frequency (%)
Age in categories	
<=35 years	75 (49.0%)
>35 years	78 (51.0%)
Marital status	
Married	140 (91.5%)
Other	13 (8.5%)
Length of Marriage	
< 5 years	48 (31.4%)
≥5 years	105 (68.6%)
Health Insurance	
No	44 (28.8%)
Yes	109 (71.2%)
Employment n= 119	
Employed	60 (50.4%)
Self employed	59 (49.6%)
Education level	
Secondary and below	21 (13.7%)
Tertiary	132 (86.3%)

4.3 The clinical characteristics of infertile women.

Their median body mass index was 26.2 (IQR: 23.5, 29.1) with the majority of them having been married 105 (68.6%) and tried to have children 95 (62.1%) for five or more years. Primary infertility was among 83 (54.2%) women, 120 (78.4%) had regular menstrual cycle, regular coitus (>4 times a month) was in % 71 (46.4%) and 112 (73.2%) women had reproductive disorders.

Table 4.2: Clinical characteristics of the study participants

Variable	Median (IQR)/ Freq (%)
BMI	26.23 (23.51, 29.14)
Duration been trying to get pregnant.	
≥5 years	95 (62.1%)
1-4 years	58 (37.9%)
Infertility Type	
Primary	83 (54.2%)
Secondary	70 (45.8%)
Frequency of Coitus per week	
1-2	30 (20%)
3-4	52 (34%)
>4	71 (46%)
Menstrual Cycle	
Irregular	33 (21.6%)
Regular	120 (78.4%)
Alcohol intake	
No	145 (94.8%)
Yes	8(5.2%)
Reproductive Disorders (73.2%)	
Pelvic Surgery	45 (40.2%)
PCOS	25 (22.3%)
Endometriosis	12 (10.7%)
Pelvic Infections	30 (27.8%)

4.4 Early clinical outcomes post IVF treatment

Pregnancy tests were done on 145 women during follow up at 2 weeks where 75 (49%) were positive. On the week 6 visit, 70 women had an obstetric ultrasound done; 61 of which were normal pregnancies. At 12th week visit, all the 61 women returned for an obstetric ultrasound, with 52 being normal. The overall pregnancy success rates at weeks 2, 6 and 12 were 49%, 39.9% and 34 respectively.

Table 4.3: Early clinical outcomes post IVF treatment

Visit	Number of Participants	Outcome	Adverse Outcomes
Week 2 (Pregnancy Tests)	145	Positive (n=75)	
		Negative (n=70)	
Week 6 (Ultrasound)	70	Normal pregnancy (n=61)	
		Abnormal pregnancy (n=9)	Ectopic (n=3)
			Miscarriage (n=2)
			Abnormal Gestational sac (n=4)
Week 12 (Ultrasound)	61	Normal pregnancy (n=52)	
		Abnormal pregnancy (n=9)	Missed Abortion (n=2)
			Abortion (n=4)
			Vanishing twins (n=2)
			Blighted ovum (n=1)

4.5 Association between clinical characteristics and early pregnancy outcomes

Majority of the patient characteristics assessed were not associated with early clinical outcomes of IVF treatment, women with a regular menstrual cycle (AOR=1.089; 95% CI: 0.741, 1.599) and primary infertility (AOR=1.051; 0.748, 1.477) were more likely to have positive pregnancy tests on the first follow-up visits. A normal BMI (AOR=2.216; 0.663, 7.405) and regular menstrual cycle (AOR=1.406; 0.398, 4.973) increased the likelihood of normal pregnancy at 12 weeks after IVF treatment. However, none of these relationships was statistically significant (Table 4.4)

Table 4.4: Association between clinical characteristics and Week 2 Pregnancy outcomes

Variable	Negative (N=70) Freq (Row%)	Positive (N=75) Freq (Row%)	p value
Age in categories			0.220
<=35	37 (53.6%)	32 (46.4%)	
>35 years	33 (43.4%)	43 (56.6%)	
Marital status			0.566
Married	65 (49.2%)	67 (50.8%)	
Other	5 (38.5%)	8 (61.5%)	
Education level			0.807
Secondary and below	10 (52.6%)	9 (47.4%)	
Tertiary	60 (47.6%)	66 (52.4%)	
Alcohol			0.278
No	68 (49.6%)	69 (50.4%)	
Yes	2 (25.0%)	6 (75.0%)	
Trying to get pregnant			0.930
>=5 years	49 (48.5%)	52 (51.5%)	
1-4 yrs	21 (47.7%)	23 (52.3%)	
Outcome of pregnancy			0.175
Abnormal	9 (33.3%)	18 (66.7%)	
Never been pregnant	39 (49.4%)	40 (50.6%)	
Term/preterm pregnancy	22 (56.4%)	17 (43.6%)	
Period monthly			0.672
No	17 (51.5%)	16 (48.5%)	
Yes	53 (47.3%)	59 (52.7%)	

Secondary infertility was statistically associated (p=0.039) with having a normal week-6 obstetric ultrasound result. None of the other reproductive disorders significantly affected pregnancy outcomes at the sixth week of follow-up (Table 4.5).

Table 4. 5: Association between clinical characteristics and Week 6 Pregnancy outcomes

Reproductive Disorder		Week 6 Outcome		Total	p-value
		Normal	Abnormal		
Endometriosis	Yes	5	0	5	0.373
	No	56	9	65	
Pelvic infection	Yes	9	0	9	0.217
	No	52	9	61	
Pelvic surgery	Yes	18	2	20	0.652
	No	43	7	50	
PCOS	Yes	11	1	12	0.607
	No	50	8	58	
BMI	Normal	22	3	25	0.873
	Abnormal	39	6	45	
Length of Marriage	≤4 years	21	1	22	0.360
	>4 years	40	8	48	
Duration Trying to get Pregnant	≤4 years	22	3	25	0.914
	>4 years	39	6	45	
Menstrual Cycle	Regular	45	9	54	0.080
	Irregular	16	0	16	
Monthly Frequency of Coitus	>4 times	19	3	22	0.991
	≤4 times	42	6	48	
Infertility	Primary	25	7	32	0.039
	Secondary	36	2	38	

Previous intrauterine insemination (IUI) was associated with normal pregnancy outcome after 12 weeks of IVF treatment. Although previous endometriosis treatment (AOR = 1.400; 95% CI: 0.216, 9.054), normal BMI status (AOR=2.216; 95% CI: 0.663, 7.405) and regular menstrual cycle (AOR=1.406; 95% CI: 0.398, 4.973) increased the likelihood of a normal week 12 pregnancy outcome, these relationships were not statistically significant. There were no statistical associations reported among other reproductive disorders under review as shown on Table 4.6.

Table 4.6: Test of Association between clinical characteristics and Week 12 outcomes

		Abnormal n=9	Normal n=52	
Length of Marriage	≤4 years	2(22.2%)	19(36.5 %)	0.622
	>4 years	7(77.8%)	33(63.5%)	
Duration Trying to get Pregnant	≤4 years	4(44.4%)	18(34.6%)	0.844
	>4 years	5(55.6%)	34(65.4%)	
Menstrual Cycle	Regular	3(33.3%)	13(255)	0.600
	Irregular	6(66.7%)	39(75%)	
Monthly Frequency of Coitus	>4 times	1(11.1 %)	18(34.6%)	0.160
	≤4 times	8(88.9%)	34(65.4%)	
Infertility	Primary	4(44.4%)	32(62%)	0.336
	Secondary	5(55.6%)	20(38%)	
Previous IUI treatment	Yes	3(33.3%)	8(15.4%)	0.032
	No	6(66.7%)	44(84.6%)	
Endometriosis	Yes	1(11.1%)	4(7.7%)	0.730
	No	8(88.9%)	48(92.3%)	
Pelvic infection	Yes	0(0%)	9(17.3%)	0.176
	No	9(100%)	43(82.7%)	
Pelvic surgery	Yes	1(11.1%)	17(32.7%)	0.190
	No	8(88.9%)	35(67.3%)	
PCOS	Yes	1(11.1%)	10(19%)	0.559
	No	8(88.9%)	42(81%)	
BMI	Normal	5(55.6%)	17(32.7%)	0.187
	Abnormal	4(44.4%)	35(67.3%)	

Table 4.7: Multivariate analysis: Factors associate with positive outcome at 2 weeks

Variable	**AOR**	**95%CI**	**p-value**
Outcome of previous pregnancy			
Abnormal	1		
Term/Preterm	0.40	0.14, 1.10	0.081
Never been pregnant	0.51	0.19, 1.25	0.150
Pelvic Infection			
No	1		
Yes	2.45	0.76, 9.40	0.200

Table 4.8 Multivariate analysis: Factors associate with positive outcome at 12 weeks

Variable	AOR	95% CI	p-value
Education level			
Secondary and below	1		
Tertiary	2.63	0.78, 12.1	0.200
Outcome of previous pregnancy			
Abnormal	1		
Never been pregnant	0.91	0.36, 2.39	0.800
Term/preterm pregnancy	0.49	0.15, 1.50	0.200
Pelvic infection			
No	1		
Yes	2.94	0.89, 10.5	0.080
Previous IUI			
No	1		
Yes	3.19	0.91, 12.9	0.079

CHAPTER FIVE

5.0 DISCUSSION

This study enrolled 153 women with a mean age of 36.2 (±5.7) years. This finding was higher than two Chinese studies which reported median ages of 31 (±4.0) years (W. Liu et al. 2017b) and 32.75 (±3.52) years (Long et al. 2019). However, it matched the median age in a Korean study where the median age was 36 years (Yeung et al. 2014).

When age was categorized as either below or above 35 years, there were nearly equal proportions of both age categories at 49% and 51% respectively. This matched the findings in Turkey (Aba et al. 2017) where there were nearly equal proportions of women aged 35 years or less and those above 35 years at 52.6% and 47.4%. Similar findings were also reported in South Africa (Dyer and Kruger 2012) where there were equal proportions (50%) of both age categories.

The length of marriage was stratified as either 4 years or more versus those married for less than 4 years. This study reports that the majority (68.6%) of the women seeking IVF services had been married for 4 years or more. It has been previously reported (Lewis et al. 2013) that infertile couples have strains in their relationship, with research on marital discord associated with increased risk of depression and seeking of IVF treatment as a solution (Whisman 2006; Peterson and Lee 2003). Having children has been a widely shared value and a major determinant of the couple's perception of their position in life across multiple cultures. Other than creating a perception of inability to achieve personal goals, infertility affects the couple's quality of life by presenting a failure to achieve cultural values further leading to social stigma (Lewis et al. 2013).

Nearly three-quarters (71.2%) of the women seeking IVF treatment had medical insurance as a form of financing. Previous studies have reported high costs of IVF treatment which is often beyond the reach of many women in countries with developed and developing (Ombelet and Onofre 2019). In the United Kingdom, the proportions of IVF treatment that is paid for by the National Health Service (NHS) has been declining over the years, forcing many women to pay out of pocket (HFEA 2020). Insurance access in countries with high per capita has been demonstrated to improve access to IVF treatment and other assisted reproductive technologies (Adamson 2009). In St. Louis -Washington, United States America; it was reported that insurance coverage increases the chances of live birth (Jungheim et al. 2017).

The major clinical characteristics of interest in this study were body mass index (BMI), duration of trying to get pregnant, type of infertility and menstrual cycle, frequency of coitus, and the type of reproductive disorders. There was no statistically significant association between clinical characteristics and having a positive pregnancy test result 2 weeks after in vitro fertilization. Women with a normal BMI (AOR= 1.338; 95% CI: 0.960, 1.865), regular menstrual cycle (AOR= 1.089; 95% CI: 0.741, 1.599) and primary infertility (AOR= 1.051; 95% CI: 0.748, 1.477) were more likely to increase the likelihood of a positive pregnancy test.

The median BMI reported in this study was 26.2 (IQR: 23.5, 29.1) which was similar to the mean BMI reported in a Chinese study of women undergoing IVF treatment at 23.68 (±3.40) that was shown to have a favorable outcome to the rate of pregnancy (W. Liu et al. 2017b). A normal BMI was shown by a study by Kirkegard (2015) to increase the likelihood of pregnancy (AOR = 1.43; 95% CI 1.05-1.39).

Previous studies have found a challenge to stimulate follicular development in patients with an elevated BMI due to an increase in the number of days or ampoules

of the gonadotropins required. However, a study by Hill et al (2020) demonstrated that fewer ampoules of medication and days of stimulation were needed with an increasing BMI. They suggested that as the BMI increases, the amount of gonadotropins and days of stimulation decrease while the number of follicles produced increased. There has been no notable finding in previous studies regarding an increase in pregnancy rates post IVF. Hill et al. (2020) established through a sub-analysis of obese patients (BMI $\geq$ 25kg/m^2) that clinically obese patients may experience a decrease in the pregnancy rates post in-vitro fertilization. Salha et al (2019) also did a prospective evaluation of BMI and patient outcome in IVF cycles and determined that a BMI $\geq$ 26kg/m^2 was associated with a higher dose of gonadotropins, a fewer number of oocytes, and lower rates of fertilization and pregnancy.

Nearly two-thirds (62.1%) of this study's participants had been trying to get pregnant for at least five years. This is in contrast with findings from Turkey (Aba et al. 2017), China (W. Liu et al. 2017b), and Canada (Swift and Liu 2014). In Turkey, 84.3% of the women had been trying to conceive for less than 5 years and so were the 95% in Canada (Aba et al. 2017; Swift and Liu 2014). In China, the mean duration of attempting conception was 4.1 (±2.6) years. In this study women who had been trying to get pregnant for four years or less were 40% more likely to have a normal obstetric ultrasound at the twelfth-week follow-up compared to those who had tried for more than four years (AOR=1.406; 95% CI: 0.398, 4.973). However, none of these two relationships was statistically significant. This is in agreement with the study done by Mclernon et al. (2016) whereby an increase in the duration of infertility (3 versus 6 years) reduced the odds of a viable embryo at 12 weeks (OR o1.09 for 3years and 1.08 to 1.10 for 6 years)

The participants' infertility was classified as either primary or secondary with nearly equal proportions of participants at 53.2% and 45.8% respectively. This was lower than one Chinese study where the proportions of primary infertility were reported at 66.7% (W. Liu et al. 2017b) but higher than a later study (Y. Liu et al. 2018) in the same country with a proportion of primary infertility of 52.8%. In our multivariate analysis, there was an associated impact of the outcome of the previous pregnancy on the outcome of clinical pregnancy following the IVF procedure. Participants who had previous preterm or term delivery didn't have a significant association with the rate of positive pregnancy outcome with an AOR of 0.40{95% CI; 0.14-1.10, p = 0.081} at 2 weeks and an AOR of 0.49 {95% CI; 0.36-2.39, p= 0.800} at 12 weeks. Those who had primary infertility (AOR=1.051; 0.748, 1.477) were more likely to have positive pregnancy tests. Van Loendersloot et al. 2014 established that a previous live birth or prior ongoing pregnancy had a significant increase in the chances of success with IVF.

A majority (78.4%) of the women enrolled had regular menstrual cycles. This was different from the findings in China (Y. Liu et al. 2018) where having a regular menstrual cycle was the eligibility criteria to participate in the IVF treatment study. This could be explained by the different protocols of ovulation induction done on the patients in this study, therefore, enabling optimum induction for all the participants.

Nearly half (46.4%) of this study's participants had sex more than four times a month. Normal obstetric ultrasound showing intrauterine pregnancy during the twelfth week of follow-up was significantly associated (p=0.037) with a high frequency of coitus. This is also summed up by Tremellen et al (2010) whereby the proportion of viable embryos in groups classified as intercourse and abstain groups was 11.01 versus 7.69 viable embryos per 100 transferred.(P =0.036, OR 1.48, 95%CI 1.01-2.19). The study

showed that women exposed to semen via sexual intercourse post-IVF had significant improvement in the proportion of embryos that remained viable at 8 to 12 weeks gestation.

Previous studies (Peterson and Lee 2003; Whisman 2006; Lewis et al. 2013) have indicated high depression levels among women suffering from infertility further reducing their urge for sexual intercourse (Bokaie, Simbar, and Ardekani 2015) and likelihood of conception. Research has shown that seminal fluid acts to promote the reproductive and immune systems of a woman who has undergone ART (Tremellen et al., 2010). Mendoza et al (2000) determined that intercourse during the per transfer period of an IVF cycle was not harmful to early pregnancy outcomes. It was also established that women who were exposed to semen via sexual intercourse had a significant improvement in the proportion of transferred embryos that remained viable by 6 to 8 weeks gestation. Couples undergoing assisted reproduction treatment usually have a higher rate of early pregnancy loss compared to fertile couples, with approximately 70% of embryos being lost within the first 16 days of embryo transfer. However, there was no significant difference in the rate of clinical miscarriage between the intercourse and abstain groups. Since abstinence is quite common during IVF treatment cycles, a lack of exposure to semen could play a significant role in the high rate of early embryo attrition that is seen during IVF treatment (Mendoza et al (2008)

When pregnancy tests were conducted in the 145 women, 75(49%) of them were positive with the rest (45.6%; n=70) being negative. This resulted in a success rate of 49% at 2 weeks. Embryo transfer likelihood has been reported to be as high as more than 70% (Diedrich and Bauer 1992). This improves with a higher number of embryo transfers (HFEA 2020).

On the sixth week visit, 5 women of the 75 who had been positive to the pregnancy test did not return to the clinic, leaving only 70 to be subjected to pelvic ultrasound to monitor the progress of the pregnancy. 61 (39.9%) of the women who had an ultrasound done at the sixth week had a normal pregnancy with the rest having abnormal pregnancies. These abnormal pregnancies were either ectopic pregnancies (4.3%, n=3), miscarriages (2.9%, n=2) and an absent gestational sacs (5.7%, n=4). This resulted in a success rate of 39.9% at 6 weeks based on the initial number of participants. Previous studies have also reported low IVF success rates at the sixth-week visit (Lensen et al. 2019; W. Liu et al. 2017a). At the Cape Facility in South Africa, the pregnancy rate following IVF treatment was 45% at the sixth-week visit with higher pregnancy rates of 79% following three IVF cycles (CareFertility n.d.). Women aged 25 years or less had higher success rates of up to 60% following IVF treatment compared to the 10% rate reported among women aged 40 years or more (Balasch 2010; Care Fertility n.d.). Facilities with better laboratories, specialized personnel, and adequate infrastructure have also been attributed to have higher pregnancy rates following IVF treatment (Ombelet and Onofre 2019).

Adverse outcomes of IVF such as ectopic pregnancy result from infertility due to tubal factors (sterility), endometriosis, transfer at the blastocyst stage, the higher number of embryos transferred, decreased endometrial thickness, variation in culture media, and transfer of fresh embryos (Yoder, Tal, and Martin 2016). Ectopic pregnancy has been further reported to happen within the first eight weeks of pregnancy with a 3% increased risk (Sher 2016) among women who have undergone IVF conception; while women with a previous history of ectopic pregnancy have a four-fold risk for a subsequent one. In Kenya, the rate of ectopic pregnancy at the Nairobi in vitro fertilization center was reported at 3% which matches the findings of

the current study. A report on fertility treatment in the United Kingdom (HFEA 2020) recommended that single embryo transfer is the safest option against ectopic pregnancy for women of all ages.

According to Cheng et al. (2015), improvements within the IVF technology have resulted in a decrease in the rates of ectopic pregnancies following IVF through a restriction of the numbers of embryos transferred, transferring frozen-thawed embryos, and injecting a smaller volume of fluid during embryo transfer. The research conducted by Cheng et al. (2015) over 15 years determined a verified ectopic pregnancy rate of 1.5 % of the clinical pregnancies that was similar to a 2% rate observes following natural conception. The study, therefore, determined that ectopic pregnancy was no longer a complication that was specifically associated with in-vitro fertilization and embryo transfer. Different studies have shed light on the lower rate of ectopic pregnancies rate following a frozen-thawed embryo transfer. The rate of clinical pregnancy has been found to be higher following frozen-thawed embryo transfer than fresh embryo transfer. The lower rate of ectopic pregnancy after frozen-thawed embryo transfer could be due to the negative effect of ovarian stimulation of the fresh embryo transfer. However, several studies have reported no reduction in an ectopic pregnancy with thawed embryo transfer.

On the 12th week visit, all the 61 participants who had a normal pregnancy at the sixth week had a second ultrasound ordered to monitor their pregnancy. Of these, 52 (34%) still had a normal pregnancy while the remaining abnormal pregnancies were identified as either missed abortions (3.3%, n=2), abortions (6.6%, n=4), vanishing twins (3.3%, n=2), and blighted ovum (1.6%, n=1). This resulted in a success rate of 34% at 12 weeks. In a study by Tummers et al. (2013) conducted over 7 years, of 1200 singleton pregnancies post-IVF, 78.2% were ongoing, with a spontaneous

abortion rate of 21.8%. after detection of heart activity via ultrasound, the risk of abortion decreased to 12.2%. at 7 weeks, the risk decreased to 11.9% and 8.2% at 9 weeks. At 9 weeks, the risk of abortion was 4.2% and dropped to 2.25% at 13 weeks.

In the study, out of 397 twin pregnancies, 82.8% were ongoing, 12.15 ended with vanishing twins while 5.1% ended with a complete miscarriage. There was a significantly higher risk of abortion expressed per gestational sac in singleton pregnancies as compared with twin pregnancies. The difference remained significant until 11 weeks of gestational age. Following assisted reproductive treatment, the risk of miscarriage may seem quite higher than in spontaneous pregnancies, but this is thought to be due to earlier pregnancy detection on one hand, as well as older maternal age on the other hand. Within IVF treatment, inappropriate culture conditions could have a considerable impairment to the human embryonic development in-vitro and the implantation potential.

This study reports a statistically significant association between previous intrauterine insemination and early IVF outcome. Based on the multivariate analysis, a previous episode of intrauterine insemination was associated with pregnancy outcomes post IVF at 12 weeks gestation with an AOR 3.19, (CI; 0.91, 12.9 p= 0.079) This finding is consistent with the European IVF monitoring program report (Andersen et al. 2009) where a combination of IUI and IVF treatment increased the pregnancy rate of the study participants.

Reproductive disorders such as endometriosis have been associated with low rates of pregnancy among the affected women who seek IVF treatment. In a Finnish study (Kuivasaari et al. 2005), women with moderate to severe forms of endometriosis had statistically significant (p=0.009) lower pregnancy rates.

Normal obstetric ultrasound showing intrauterine pregnancy during the sixth week of follow-up was significantly associated (p=0.039) with women presenting with primary infertility. None of the clinical (BMI, menstrual cycle, frequency of coitus, and primary infertility) sociodemographic characteristics (length of marriage) of interest were associated with intrauterine pregnancy at the 6^{th} week. A normal BMI increased the likelihood of a normal obstetric ultrasound showing intrauterine pregnancy at the twelfth week of follow-up more than two-fold (AOR=2.216; 95% CI: 0.663, 7.405). This result is supported by the study done by Wang et al. (2021) where both low and high BMI was associated with a reduced rate of pregnancy post IVF (AOR0.81 for low BMI, and AOR 0.5 -0.81 for high BMI)

Based on the multivariate analysis the occurrence of previous pelvic infection had a significant effect on the outcome of IVF treatment both at 2 weeks (AOR 2.45 95% cI; 0.76.9.40) and 12 weeks (AOR 2.94 CI 95%; 0.89, 10.5). This aligns with the study conducted by Yang and Zhang (2007) whereby there was an adverse effect on IVF outcomes depending on the grades of pelvic inflammatory disease. The total dose of gonadotropins used and the low response rate increased with the aggravation of the grades of pelvic inflammatory disease ($p<0.05$) the number of oocytes, number of good embryos, and rate of pregnancy also had significant differences based on the grades of pelvic inflammatory disease. The study determined that in mild and severe groups of pelvic inflammatory disease, salpingectomy had no contribution to the outcome of IVF-ET treatment. Within the group with moderate pelvic inflammatory diseases, patients who received salpingectomy had more oocytes and good embryos, as well as higher rates of pregnancy in comparison to those who retained oviducts.

Ravel et al. (2020) established that bacterial vaginosis has been implicated in difficulty conceiving in the setting of IVF. Women with a lower prevalence of vaginal lactobacilli were less likely to have successful embryo implantation than those with higher lactobacilli prevalence. Women with lower microbial diversity and those with a higher proportion of abnormal vaginal microbiota had a higher likelihood of having poor reproductive outcomes following IVF. However, it was also shown that bacterial vaginosis did not have a significant impact on the live birth rate. Therefore, although there is a clear correlation between bacterial vaginosis and infertility, the causality is yet to be determined.

Our correlation of pelvic infection to the adverse outcomes of IVF success is similar to Ravel et al. (2020) whereby women undergoing IVF and having endometrial microbiota dominated by non-lactobacilli were significantly less likely to have successful implantation, pregnancy, or ongoing pregnancy than those with microbiota dominated by lactobacilli (90%) ($p<.05$).

Based on the multivariate analysis, tertiary education had an impact on the positive outcomes post IVF at 12 weeks though not statistically significant (AOR 2.63(CI 95%; 0.78-12.1, $p= 0.200$). This is in accordance with the findings by Mahangaiah et al. (2011) whereby there was no statistically significant difference across education groups for any IVF outcome. However, the study observed greater odds of cycle cancellation among women with lower educational attainment irrespective of age. This suggests that education might have a role in successful progression to egg retrieval. A woman's education was associated with her peak estradiol level, suggesting a relation between the educational level and understanding of the cycle instructions.

5.4 Study Limitation

This study was conducted in a private hospital where a majority of the women were employed, had medical insurance and a tertiary level of education. This finding could be biased as it is not the case in many healthcare settings where a majority of the women seek treatment in public hospitals.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

- Majority of the women who seek IVF treatment are married for four or more years, have a tertiary level of education, formally employed with health insurance and have reproductive disorders.
- The overall pregnancy success rate 12 weeks after IVF treatment at Mediheal Fertility Center is 34%.
- Previous IUI treatment is significantly associated with favorable early clinical outcomes 12 weeks after IVF treatment, while having a normal BMI and regular menstrual cycle increases the likelihood of normal pregnancy.

6.2 Recommendations

- Women who have had previous ART treatment other than IVF should be encouraged to try IVF treatment as it has been shown to have favorable outcomes.
- Future studies should assess reasons for loss to follow-up after IVF treatment and validate this study's findings in a public healthcare facility.

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APPENDICES

Appendix A: Informed Consent

You are invited to participate in a prospective study titled" Early pregnancy outcomes among infertile women undergoing in-vitro fertilization" because you have a infertility related-problem and you have received IVF as treatment of infertility. You will be followed up at intervals of second week, three week and third month after receive IVF at Mediheal hospitals. This form explains the purpose, benefits, and risks of the study. Please read this form and ask any questions you may have before agreeing to be in this study. You will be given a copy of this document to keep with you. There will be no consequences if you decline to consent to participate in this study.

The IVF procedures will be conducted by doctors from Mediheal Hospital and Fertility Centre, and the information derived from such procedures will be documented for this study.

Purpose: The purpose of this study is to help us understand in vitro fertilization as definitive treatment of infertility and to determine its clinical outcomes within three months of follow up among women undergoing IVF.

Participants: If you agree to participate, you will be one of women in pregnancy who have received IVF and are currently on follow up. Your interviews will be done individually to maintain your privacy.

Procedures: If you agree to participate, you will be privately asked questions about your medical condition and your medical care during your pregnancy and follow up by our research team till the third month of pregnancy outcome or terminal clinical outcome eg failure to sustain pregnancy, etc, whichever comes earlier. Our research

members will write down your responses during the interview and all of your answers will be kept private. The interview will take between 20 to 30 minutes in each phase.

Benefits & risks: There is no direct benefit to you to participate in the study. Your choice to participate will not affect your medical care and your pregnancy. However, your participation, along with other pregnant women who received ART will be used to improve future medical services for pregnant women with similar conditions. Furthermore, a closed follow up after the treatment of your condition, especially the success and early outcomes of pregnancy will be a useful part of this study. There will be very few risks involved with this study, especially if your identity and/or answers will not stay private. However, the researcher and trained research assistant will conduct the interview and will be the only persons to know your name. Your answers will be anonymous.

Confidentiality: All of your information will be kept secret and all discussions with you will be in private. Only the study team will know that you are in the study and your name will not be shared with anyone. All of your information will be collected under a number assigned to you so that no one other than the Study team knows your personal information.

Cost& payments: There will be no costs to you for any parts of the study and you will not receive payment for taking part in this study.

Contact: For questions about this study feel free to contact Moi University Institutional Research and Ethics Committee to the following address: Moi Teaching& Referral Hospital building, 2nd floor, Door no 219, P.O Box 3-30100 Eldoret, Kenya. Office line: 0787723677, Email: irec@mtrh.or.ke, Website: irec.or.ke

You can also contact Mediheal through +254(0)723578895or Dr. Chepkorir Jane through 0713547470. By signing this form below, you indicate that you have agreed to participate in this research.

Names and signature of participant: _____ Mobile:……. Date signed: _____Signature of witness_____

Appendix B: Work Plan

Month& year **Activities**	**March 2087 to May 2018**	**March 2018**	**May 2018**	**June 2018 to June 2019**	**August 2019 to March 2020**
Proposal Development and Approval					
IREC Submission and IREC approval					
Training of research assistants					
Data collection and Follow up					
Data analysis& Thesis writing					
Dissemination and feedback					

Appendix C: Study Estimated Budget

Items	**Quantity**	**Unit Price (Kshs)**	**Total (Kshs)**
Stationery & Equipment			
Printing Papers	5 reams	**Error! No bookmark name given.**500.00	2,500.00
Black Cartridges	2	2,000.00	4,000.00
Writing Pens	1 packet	500.00	500.00
Flash Discs	1	2,000.00	2,000.00
Box Files	2	200.00	400.00
Document Wallets	2	50.00	100.00
Research Proposal Development			
Printing drafts & final proposal	10 copies	500.00	5,000.00
Photocopies of final proposal	6 copies	100.00	600.00
Binding of copies of Proposal	5 copies	100.00	500.00
Personnel			
Biostatistician	1	10,000.00	10,000.00
Thesis Development			
Printing of drafts and final thesis	10 copies	800.00	8,000.00
Photocopy of final thesis	6 copies	200.00	1,200.00
Binding of thesis	6 copies	300.00	1,800.00
Sub total			**11,000.00**
Miscellaneous Expenditure (10% of Total)	**3,660.00**		
Grand Total			**40,260.00**

Appendix D: Questionnaire Document

QUESTIONNAIRE AND DATA COLLECTION TOOL ON EARLY CLINICAL OUTCOMES OF IVF AMONG INFERTILE WOMEN AT MEDIHEAL HOSPITAL CENTERS IN NAIROBI AND ELDORET- KENYA

<table>
<tr><th colspan="2">• DEMOGRAPHIC INFORMATION</th></tr>
<tr><td>

• **Identification**

Study ID number……../……..

IP/OP number [ ][ ][ ][ ][ ][ ][ ][ ][ ]

Date of birth: [ ][ ][ ][ ][ ][ ][ ][ ][ ]

Age at time of enrollment: [ ] years old

• **Family and social information**

Marital status: Tick ONE

Married [ ] Single [ ] Divorce [ ]

Widowed [ ]

Health insurance: Yes [ ] No [ ]

Profession: Tick ONE

Student [ ] Health provider [ ] Teacher [ ]

Business women [ ] other [ ], please specify…….

Residence (please fill accordingly):

County……Estate……..

</td><td>

• **Highest Level of education attained**

Please tick ONE

Primary school [ ]

Secondary [ ]

Tertiary(college/University) [ ]

Other [ ]

None [ ]

• **Life style**

Please tick ONE or more

Alcohol intake [ ]

Smoking [ ]

Drug abuse [ ]

Other [ ]

Please, specify……

• **Contacts**

Mobile number…….

Partner'smobile number……

Other (State the relationship with the user)

</td></tr>
</table>

- **PATIENT INFORMATION**

Please, fill all

Age [ ] years old

Weight [ ] Kg

Height [ ] cm

BMI [ ]

- Length of marriage, please tick ONE

1-2 years [ ]

3-4 years[ ]

≥5 years [ ]

- How long have you been trying to get pregnant, please tick ONE**:**

1-2 years [ ]

3-4 years [ ]

≥5 years [ ]

- Have you previously been pregnant? if yes go to question 5

Yes [ ] No [ ]

- Have you previously tried to get pregnant?

Yes [ ] No [ ]

- What was the outcome? Please, tick ONE

Term pregnancy [ ] Preterm birth [ ]

Miscarriage [ ] Induced abortion [ ]

MENSTRUAL HISTORY

- When was the first day of your period? ……./……/……..
- Do you have a period every month?

Yes [ ] No [ ]

- How many days do your periods last?

[ ] days

- Do you have painful periods?

Yes [ ] No [ ]

- Do you have bleeding between your periods?

Yes [ ] No [ ]

SEXUAL HISTORY

- Does your partner or you have any problems during sexual intercourse?

Yes [ ] No [ ]

- Do you have significant pain during intercourse?

Yes [ ] No [ ]

- Do you experience bleeding after intercourse?

Yes [ ] No [ ]

- Approximately how many times each month do you have intercourse? Please, tick all

- times [ ] 3-4 times [ ] ≥5 times [ ]

PATIENT INFORMATION

GYNECOLOGICAL HISTORY

- Have you been diagnosed or treated for endometriosis?
  Yes [ ] No [ ]
- Have you ever had a pelvic infection (PID, gonorrhea, chlamydia, trichomoniasis, genital herpes, syphilis)?

  Yes [ ] No [ ]
- Have you ever had pelvic surgery?

  Yes [ ] No [ ]
- Have you ever had an abnormal pap smear or cervical cancer screening?

  Yes [ ] No [ ]
- Have you ever had a surgery on your cervix such as LEEP, cone biopsy, cryotherapy?

  Yes [ ] No [ ]
- Have you ever been diagnosed with polycystic ovaries (PCOS)?

  Yes [ ] No [ ]

CONTRACEPTIVE USE

Have you been using contraceptive/family planning methods?

Yes [ ] No [ ]

MEDICATION/DIETARY HISTORY

- Do you take any prescription drugs, vitamins, dietary/herbal supplements?

  Yes [ ] No [ ]

- When is the last time you took birth control pills, Mirena IUD, Depo Provera?

  Yes [ ] No [ ]

- Do you have any allergies?

  Ye [ ] No [ ]

MALE HISTORY

- Has your partner ever fathered any children?

  Yes [ ] No [ ]
- Has your partner had a semen analysis?
  Yes [ ] No [ ], If yes what was the result? Normal [ ] Abnormal [ ]

- Does your partner take any medications/herbal supplements or alcohol?
  Yes [ ] No [ ]
- Has he ever had a genital injury?
  Yes [ ] No [ ]
- What is your partner's occupation?
  ……

BASELINE OF LABORATORY TESTS AND IMAGING EVALUATION	
• **Basal body temperature, please tick ONE** Normal [ ] Abnormal [ ] • **Urine LH surge (ovulation predictor kit)** Normal [ ] Abnormal [ ] • **Endometrial biopsy** Normal [ ] Abnormal [ ] • **HORMONES** -LH: Normal [ ] Abnormal [ ] -FSH: Normal [ ] Abnormal [ ] -Estradiol: Normal [ ] Abnormal [ ] -Prolactin: Normal [ ] Abnormal [ ] -Cortisol: Normal [ ] Abnormal [ ] -Thyroid tests (TSH, T4): Normal [ ] Abnormal [ ] - Testosterone: Normal [ ] Abnormal [ ] - Progesterone: Normal [ ] Abnormal [ ] • **Other test** -HIV: Normal [ ] Abnormal [ ] -HBV: Normal [ ] Abnormal [ ] -HCV: Normal [ ] Abnormal [ ] -Mycoplasma culture: Normal [ ] Abnormal [ ]	-Chlamydia culture: Normal [ ] Abnormal [ ] -Antichlamydia antibodies: Normal [ ] Abnormal [ ] -Anticardiolipin antibodies: Normal [ ] Abnormal [ ] -Lupus anticoagulant: Normal [ ] Abnormal [ ] -Antinuclear antibodies: Normal [ ] Abnormal [ ] -Karyotype genetic testing: Normal [ ] Abnormal [ ] **IMAGING** -Ultrasound: Normal [ ] Abnormal [ ] -Hysterosalpingogram (HSG): Normal [ ] Abnormal [ ] -Fluid/Saline sonohystogram: Normal [ ] Abnormal [ ] -Hysteroscopy : Normal [ ] Abnormal [ ] -Laparoscopy : Normal [ ] Abnormal [ ]

FERTILITY TREATMENT AND OUTCOMES	
• **Previous fertility treatment** **Please, tick all treatment applied** Clomiphene (Clomid,Serophene) [ ] Gonadotropins (Puregon, Gonal F) [ ] HCG (Ovidrel, Pregnyl) [ ] Progesterone [ ] Dexamethasone (Cortisol) [ ] GnRH agonist (Synarel, Lucrin) [ ] GnRH antagonist (Orgalutran, Cetrotide)[ ] Intrauterine insemination (IUI) [ ] Insemination with donor sperm [ ] In vitro fertilization (IVF) [ ] GIFT [ ] ZIFT [ ] IVM [ ] ICSI [ ]	• **CURRENT TREATMENT** Date of IVF……/……../…… **Pregnancy test done after 2 weeks, please tick ONE:** Positive [ ] Negative [ ] **Ultrasound done within 6 weeks, Please tick all positive findings** Intrauterine pregnancy [ ] Ectopic pregnancy [ ] Single intrauterine pregnancy [ ] Multiple gestation [ ] Complete molar pregnancy [ ] Partial molar pregnancy [ ] Gestational sac absent [ ] **Pregnancy outcomes within 12 weeks, please tick ONE:** Miscarriage [ ] Threatened abortion [ ] Missed abortion [ ] Blighted ovum [ ] Vanish [ ] If obstetric event occurs within 12 weeks of gestation age, please specify the gestation age at the time of event……

CO-MORBID CONDITIONS	
Check all that apply Adrenal problems [ ] Autoimmune problems [ ] Breast discharge [ ] Chronic headache [ ] Diabetes mellitus [ ] Maternal ≥35 [ ] Excessive stress [ ] Head injury [ ] Heart disease [ ] STIs [ ] UTIs [ ] TORCH [ ] Hypertension [ ] HIV/AIDS [ ] Neurological problems [ ] Thyroid disorders [ ] Epilepsy [ ]	Renal diseases [ ] Abdominal trauma [ ] Over weight [ ] Obesity [ ] Weight loss [ ] Tuberculosis [ ] Herbal medicine [ ] Cancer [ ] Anemia [ ] Malaria [ ] Alcohol [ ] Cigarette smoking [ ] Hyperemesis gravidarum [ ] Other conditions [ ], please specify …… …… …… ……...

Appendix E: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2017/175
Approval Number: 0002086

15th March, 2018

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
15 MAR 2018
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dr. Chepkorir Cheruiyot Jane,
Moi University,
School of Medicine,
P.O Box 4606-30100,
ELDORET-KENYA.

Dear Dr.Chepkorir,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Early Clinical Outcomes and Associated Clinico-Pathologic Characteristics of Infertile Women on Invitro Fertilization Treatment at Mediheal Hospitals, Kenya".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 2086*** on 15th March, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 14th March 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix F:Hospital Approval

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone:(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

20th March, 2018

Dr. Chepkorir Cheruiyot Jane,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Early Clinical Outcomes and Associated Clinico-Pathologic Characteristics of Infertile Women on Invitro Fertilization Treatment at Mediheal Hospitals, Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - DCEO, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM