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FACTORS INFLUENCING OUTCOME OF ASSISTED REPRODUCTIVE TECHNOLOGY IN SUB SAHARAN AFRICA: SYSTEMATIC REVIEW AND META-ANALYSIS

BY

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DECLARATION

With the exception of duly acknowledged references, I, **OSMAN FORZIA** hereby declare that this study was carried out by me at the School of Public Health, University of Ghana, under the supervision of **Dr. ANTHONY DANSO-APPIAH** and has not been presented for any other degree.

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ABSTRACT

Background: Infertility affects a significant number of people worldwide and has serious psycho-social effects, but too often neglected, particularly in Sub-Saharan Africa (SSA). Childlessness in most SSA countries is considered a failure and affected persons face severe social discrimination. Assisted Reproductive Technology (ART) is a cure for infertility which has revolutionized the management of infertility and its use has increased since its introduction in the 1980s. Unfortunately, the practice of ART in SSA has not been normalised. Most countries in Sub-Saharan Africa do not have ART included in their health insurance system which limits accessibility to only a few people who need it. There is a lack of adequate data and virtually no ART registries to support policy development in SSA. It is therefore extremely important that ART availability, utilization and outcome be assessed to provide evidence driven change to improve its practice in SSA.

Objective: To determine the common causes of infertility for which ART is implored, assess the availability of ART and the factors that inform the decision to seek ART as well as the factors that influence the outcome of ART in SSA.

Methods: The research was a systematic review of studies meeting pre-specified eligibility criteria. Six databases were searched including Cochrane central, African journals online, LILAC, CINAHL, PUBMED and google scholar for studies from **January 2000 to October 2020**. A total of 1,629 studies were retrieved, de-duplicated and screened for inclusion. Ten (10) studies met the inclusion criteria. Narrative descriptions of key outcomes were carried out and meta-analysis was conducted for the studies that assessed quantitative outcomes, presenting the results as forest plots. The quality of each of the included studies was assessed and the overall evidence level reported.

The standard reporting of systematic review and meta-analysis was followed to guide the reporting of this review.

Results: The majority of the studies was conducted in Nigeria (7 out of 10**). Results from the pooled estimates** Male factor infertility was more prevalent than female factor infertility (prevalence of 48.1% and 41.6% respectively) The positive outcomes with their corresponding pooled prevalence that were realised included pre-clinical pregnancy (37.5%), clinical pregnancy (27.5%), live births (12.6%). Multiple birth had a prevalence of 6.5%. The adverse outcomes that were measured was pregnancy loss (7.4%) and still birth. The ART complications identified from the studies analysed were multiple pregnancy, pre mature birth, intrauterine foetal death and ectopic gestation. **The factors that were identified to be associated with ART outcomes** included maternal age, the type of infertility, endometrial thickness, number of embryos transferred, number of oocytes retrieved as well as the ovulation protocol used.

Conclusions: From the present review, male-factor infertility was more common than female-factor infertility. Assisted Reproductive Technology use resulted in more positive outcomes than negative ones. The review of exiting studies showed that there is a dearth in information on ART use, outcomes and its correlates, and the costs involved in SSA. We recommend the expansion of research efforts in this area, to provide the necessary baseline data for public health practice and formulation of policies.

DEDICATION

I dedicate this dissertation to my family and all women who are battling with infertility.

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LIST OF ABBREVIATIONS

ART	Assisted Reproductive Technology
ICSI	Intracytoplasmic Sperm Injection
ZIFT	Zygote Intrafallopian Transfer
GIFT	Gamete Intrafallopian Transfer
IVF	In Vitro Fertilization
STD	Sexually Transmitted Disease
SSA	Sub Saharan Africa
PCOS	Polycystic Ovarian Syndrome
PID	Pelvic Inflammatory Disease
FSH	Follicle Stimulating Hormone
HMG	Human Menopausal Gonadotropin
HCG	Human Chorionic Gonadotropin
UNICEF	United Nations Children's Fund
IMAR	Inter-country medically assisted reproductive

CHAPTER ONE

1.0 Introduction

Infertility is the inability of a couple to achieve conception after 1 year of regular unprotected sexual intercourse (Harzif et al., 2019). It is a major problem and affects about 80 million persons globally (Elhussein et al., 2019). Approximately, 5-30% of couples or persons in the reproductive age suffer infertility (Parsanezhad, 2013). Assisted Reproductive Technology (ART) which was introduced in the 1970s when the first test tube baby was born has been a source of hope to couples and individuals who have challenges with childbirth (Gerrits, 2016). Assisted reproductive techniques may be employed in a number of circumstances including the following; inability to achieve pregnancy through adequate natural sexual intercourse, the desire of some women to become pregnant without sexual intercourse, distant resident partners for any reason who want biological children but cannot have adequate sexual intercourse, men with testicular cancers at early stage can store sperms for future use, men with amputated or malformed penis that cannot deposit sperms at the right place in the vagina who desire biological children, women who want to defer having children can harvest their ova for future fertilization before menopause, and same sex partners who desire children.

Assisted Reproductive Technology includes fertility treatments in which eggs or embryos are handled in a laboratory, and by far, in vitro fertilization is the most common type (Sunderam et al., 2019). The main types of Assisted Reproductive Technology include in vitro fertilization, intra cytoplasmic sperm injection, zygote intrafallopian tube transfer (tubal embryo transfer) and gamete intrafallopian transfer. For some of these procedures donor eggs or sperm are utilized and a surrogate may be used (Zsuza, 2019). Other forms of treatment for infertility (non-tubal) include

ovulation induction and artificial insemination. Assisted Reproductive Technology has rapidly spread throughout the world although sub-Saharan Africa (SSA) is seen to be the least developed in the application of this technique so far (Ombelet, 2013). Coincidentally, SSA has the highest burden of infertility (Dyer, 2009), likely as a result of poor access to reproductive health in the region.

Infertility may be a complication of lack of or inadequate treatment of sexually transmitted diseases (STDs) which affects both men and women and pregnancy-related infections resulting from unsafe abortions and home deliveries in unhygienic circumstances mostly in developing countries (Ombelet, 2013). Advanced maternal age is an important factor that contributes to infertility in women all over the world as a result of significant increase in aneuploidy and spontaneous abortion rates (Farhi et al., 2019). The burden of infertility is not only medical but also psychosocial. Even with the advent of ART there have been some cultural and religious backlashes and opposition, and couples who go through this treatment would usually want to **conceal** it as much as possible. Despite the progress made in this technology, the success rates are still quite low with associated complications for mother and baby (Dyer et al., 2019a; Lei et al., 2019; Zhao et al., 2020). This notwithstanding ART has gained popularity over time and more people are opting for it.

Infertility has been a major issue right from biblical times. Childlessness, according to Harzif et al (2019) is often a source of stigma in society and the blame is often placed on the woman. Therefore, it is not surprising when it was revealed in a study among couples that infertility was attributed to females more than males (Elhussein et al., 2019). In sub-Saharan Africa, women

who are faced with infertility tend to use less reliable methods of healthcare seeking such as visiting religious leaders or using not-proven traditional and herbal medications. On many occasions they end up worsening their condition, which could have been treated effectively and early if they presented earlier or sought reliable methods and treatment.

ART is very expensive and not readily available across the African continent especially in sub-Saharan Africa (Naab et al., 2019). Paradoxically, despite the relatively high infertility rate in West Africa, there is high population growth rate which creates a counter-effort in sensitization. As a result, funds meant to support infertility activities are channelled towards family planning programmes instead (Naab et al., 2019). Meanwhile, the stigma and resultant psychosocial suffering from infertility is profound.

1.1 The situation in Sub Saharan Africa

Sub Saharan Africa is made up of 48 countries according to the World Bank records (https://data.worldbank.org/country/ZG). Infertility statistics are not adequately reported or documented across SSA which makes it difficult to find reliable information about the true magnitude of the problem. Notwithstanding, it is suggested that a third of all couples within SSA experience infertility even amidst the high population growth rate (Naidu et al., 2014).

In the African culture within the first year of marriage, the couple is expected to have a child or to be expecting a child. In sub-Saharan Africa, there is a relative silence on the attribution of men as cause of infertility (Odunvbun et al., 2018; Zarrabi & Kruger, 2018). Culturally, women are blamed for the inability of a marriage couple to produce children because it is widely believed that only women experience infertility (Naab et al., 2019). In contrast to Western countries, couples

experiencing infertility in SSA feel a deeper sense of guilt, shame, worthlessness and depression (Gerrits, 2016). In SSA, the main aetiology of infertility from previous studies is preventable-direct consequences of poorly managed pelvic and sexually transmitted infections leading to tubal pathology (Naidu et al., 2014).

According to Naidu et al (2014), conventional ART is extremely expensive and only a small fraction of couples with infertility are able to afford it. This is compounded by the fact that infertility is not considered as a healthcare priority and barely a handful of states in SSA have considered subsidizing this form of treatment. Expenses for one private ART cycle were described by the authors to be as high as 4000–5000 USD in Nigeria and Mali, and 3500USD in Uganda (Botha et al., 2018). In Ghana, the average cost of a cycle of ART was reported as equivalent to over 18 months earnings of a nurse (Gerrits, 2016). Kenya has been found as the only country in sub-Saharan Africa where regulations exist on reimbursements when ART cycle was unsuccessful (Botha et al., 2018). This means that for most couples who have to undergo more than one cycle of treatment this is a serious drain on their resources. In certain circumstances, despite several cycles, the couple still remains unsuccessful and childless.

Unintentional childlessness is a lucrative field for private health care (Gerrits, 2018), and the lack of laws and regulations concerning the use of ART leaves many private fertility centres practicing unchecked, making the patients even more vulnerable. This venture has become a thriving business in many SSA countries. In Ghana there is an active gamete donation market within the country which usually consists of university students (Gerrits, 2018). Also available are agencies that recruit surrogates who are mostly semi-literates and single mothers. The opportunity to exploit

desperate couples with infertility is endless. Public hospitals generally provide only infertility investigations but cannot offer ART.

Low- and middle-income countries (LMICs) are faced with complex and numerous barriers to provide basic and advanced ART. Prominent problems of ART in SSA aside the cost, is the lack of information and regulation of the industry, as well as the associated complications and the uncertainty of the outcome. When factors that affect ART outcomes can be predicted with a significant level of confidence then efforts can be made to justify the inclusion of ART in national health insurance. However, this is not yet the case in most countries in SSA.

1.2 Problem Statement

Infertility among couples remains a major concern throughout the world. About 15% of couples around the world in the reproductive age group are affected by infertility (Luna & Wolf, 2014a). The high prevalence of genital infections in developing countries is compounded by a less well-developed diagnostic services together with lack of effective and affordable interventions serves as a nidus for subfertility and infertility (Ombelet, 2013).

Since 1978 when the first test tube baby was made, assisted reproductive technology has been used to help couples achieve child birth and over 8million children have been born so far via ART (Qiu et al., 2019). For some couples, they have had to try several times before achieving a childbirth, whiles others have been unsuccessful despite several attempts. The women involved in this treatment are faced with greater health risks and financial burden (Qiu et al., 2019). In Africa, the extent to which childless women are mocked and stigmatized is quite disheartening (Aiyenigba et al., 2019). It causes these women a lot of psychological issues including depression. They

become desperate and seek all manner of solutions with appropriate medical care usually being the last resort when all have failed. Infertility affects their self-esteem and psychosocial wellbeing. The cost involved in ART is exorbitant as it was originally created for upper and middle class professional women who had put their careers before childbirth and were now too old to conceive naturally (Luna & Wolf, 2014a). For most couples who go in for Assisted Reproductive Technology, they may have to spend about half or more of their annual income (Qiu et al., 2019) which makes it accessible to only those in moderate to high socio-economic status. The factors affecting the success rates of these techniques are varied. Maternal complications from ART are generally higher compared to natural conception. Therefore, if there is a way to minimise this risk to the mother while also saving the couple the psychological trauma from unsuccessful ART cycles it would go a long way to improve the lives of people who are affected by infertility. This could be a step towards developing an evidence-based tool to help predict outcome with a significant level of confidence for couples who want to try ART.

1.3 Justification

Infertility is a public health problem and an important aspect of reproductive health worldwide but so often neglected (Mascarenhas et al., 2012). ART serves as a curative treatment for many infertile couples but this undoubtedly comes at a high cost. Also, in most instances' health insurance does not cover this cost. This venture is capital intensive, emotionally and psychologically stressful.

Though the start of ART in Africa can be traced to the early 1980s, there has been a lag in the development of data registries to monitor and repot the utilization and outcome of the practice (Botha et al., 2018). This has made it almost impossible to ascertain the scope, practice and

outcome of ART in SSA. This lack of knowledge makes it difficult to have evidence-driven change in ART policy and practice.

Currently, infertility is still seen as a divine punishment and people affected are marginalized and ostracized (Akarsu & Beji, 2019; Bornstein et al., 2020) and there is a need to let the society understand that there is a cure for this condition. There is still huge sociocultural misunderstanding about infertility in SSA. By creating awareness about the availability of effective treatment for infertility, the society will come to the realization that it is not a punishment from God and will be more supportive of couples affected by infertility (Naab et al., 2019). Regulations for ART services in SSA have been lacking creating a high potential for abuse, especially in the area of stem cell research, to the lack of awareness and research availability to inform government policy which makes it impossible to have a standardized practice. This also makes it difficult for policy makers to actually consider ART favourably since the industry appears chaotic to some extent. By systematically reviewing the various studies on ART conducted in the sub region, the more successful approaches will be made evident.

This review sought to provide evidence-based predictive outcomes of ART based on the factors identified through our systematic synthesis of primary research findings. With this evidence, policymakers can be engaged to consider including ART on state insurance as long as certain conditions of predictability are met. The study will also throw more light on which particular ARTs work best for the sub- Saharan African population so that efforts will be made to optimise those technologies within SSA and improve outcome. This study seeks to analyse the factors that may influence the outcome of ART and by extension provide a better understanding of the outcomes obtained in our settings. This study will also look at the most common causes of infertility for

which women seek treatment and based on this knowledge steps to address the avoidable causes can be taken.

1.4 Conceptual Framework

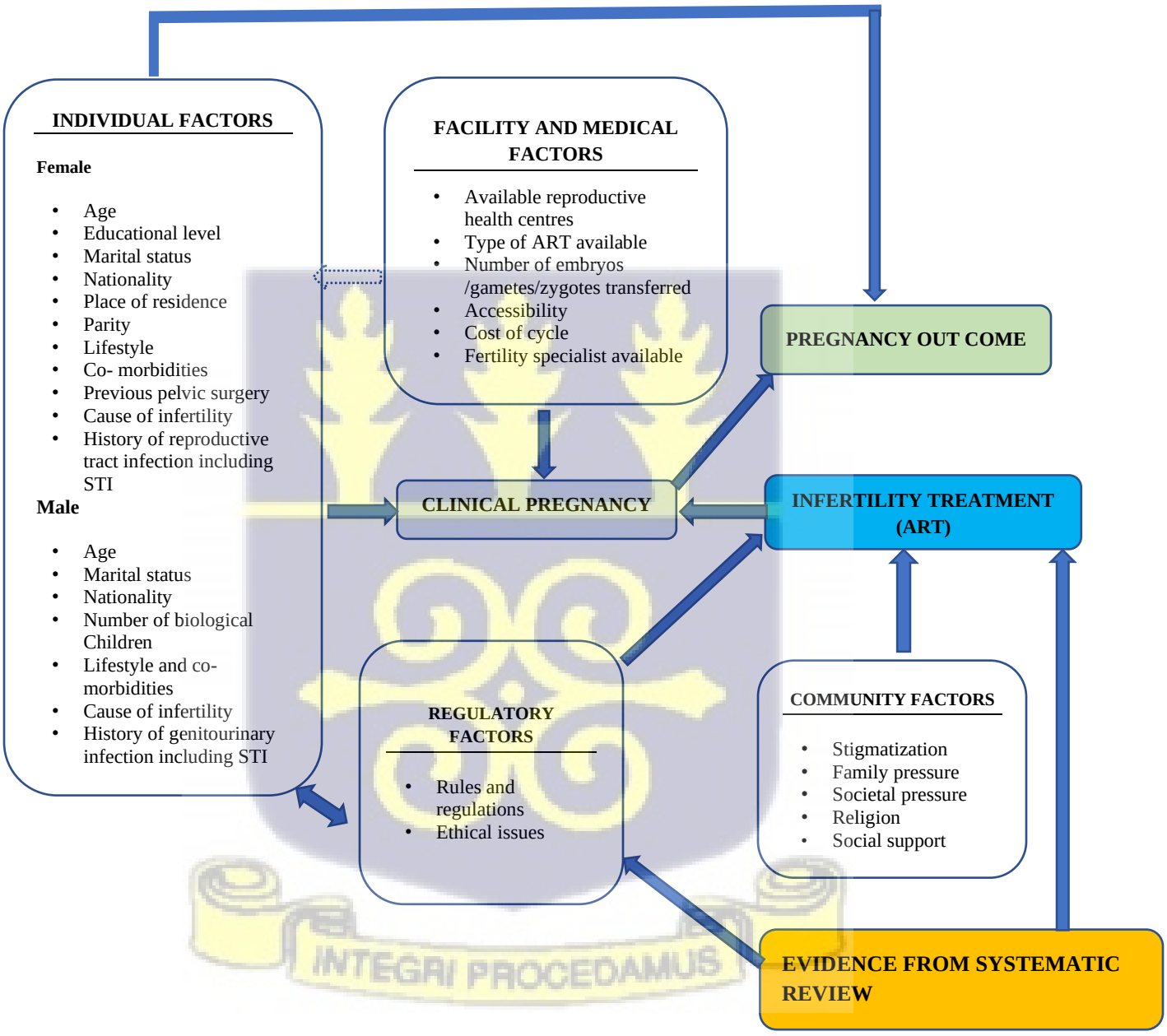

Figure 1: Conceptual framework of the factors influencing the outcome of ART

1.4.1 Narrative of Conceptual Framework

The framework above looks at the common factors that generally affect fertility in women and also likely to affect the outcome of ART. According to Ombelet (2013), the high prevalence of genital infections in LMICs, compounded by a complete lack of diagnosis, and together with incomplete, inappropriate or no intervention at all, serves as a nidus for subfertility and infertility. Therefore, pelvic infections are a major cause of infertility and as such have a bearing on the outcome of pregnancy. According to Luna & Wolf (2014a) after the first episode of pelvic inflammatory disease, there is a 15 percent probability of infertility. After the second episode, the probability increases to 38 percent, and after a third occurrence, it rises to almost 75 percent. In the same light persons with a higher socioeconomic status have better access to health care and are able to report early when they have any pregnancy-related complications. This enables timely interventions and improves the success of treatment outcome. Advanced maternal age alone is an important factor that contributes to infertility in women all over the world due to significant increase in aneuploidy and spontaneous abortion rates (Farhi et al., 2019).

Studies have shown increased risk of conditions like pre-eclampsia among women who conceive via IVF (Watanabe et al., 2014). Pre-eclampsia has a significant effect on the outcome of every pregnancy and it increases maternal and foetal morbidity and mortality. A meta-analysis demonstrated that female obesity negatively and significantly impacts live birth rates following IVF (Qiu et al., 2019). Additionally, obesity is a risk factor for developing complications like gestational diabetes and pre-eclampsia which implies that these co-morbidities are interrelated and t may compound the effects of each other.

Other conditions like diabetes and gestational diabetes cannot be ignored. Therefore, a woman who has chronic hypertension, diabetes or other co morbidities may stand a higher chance of developing complications during pregnancy and this may impact significantly on the outcome of the pregnancy (Tromp et al., 2011). A past surgical history (especially pelvic), a history of ectopic gestation, previous pregnancies and previous deliveries may also serve as a predictor of the outcome of pregnancy. It is therefore relevant to look at these factors and explore their impact on the outcome of ART. Lifestyle habits such as smoking, alcohol intake, lack of exercise have also been associated with subfertility (Wiltshire et al., 2019).

Facility and medical factors are crucial to a successful outcome of ART. The competence of the facility in terms of the specialist who would undertake the procedure, the available treatment options, the cost of a cycle of ART as well as how accessible the facility is to the patient (Dierickx et al., 2019). Each patient is unique and the ART should be tailored to the specific needs of the patient for maximum outcome.

Regulatory factors dwell on the availability of guidelines and regulations for the proper implementation of fertility treatment so that a standard protocol is used in ART. Infertility care in most developing countries has been fragmented between public and private spheres with a paucity of rules and regulations concerning ART, commercial interests may lead to unethical practices (Ombelet, 2013).

Community factors stem from the cultural importance of bearing children. The community is the main driver about the perception of infertile persons and aa well as stigma towards infertile persons. The unrelenting pressure that comes from family members and society lead to couples

seeking infertility treatment. Some cultures do not believe in ART and this influences the health seeking behaviour among the infertile couples in such a community. The role of religion on the choices of people cannot be ignored. Religion is a great source of influence when it comes to fertility issues. In infertility as well as its treatment requires an ongoing emotional and instrumental support which is essential to the wellbeing and quality of life of the affected persons and the community they find themselves can either facilitate this or not (Ried & Alfred, 2013).

1.5 Review Questions

- What are the common causes of infertility for which ART is used?
- What types of ARTs are available in sub-Saharan Africa?
- What factors influence the decision to seek Assisted Reproductive Technology in sub-Saharan Africa?
- What factors influence the outcome of ART treatment in sub-Saharan?

1.5 General Objective

To determine the types of ART available as well as the factors that influence the choice and outcome of Assisted Reproductive Technology in sub-Saharan Africa.

1.5.1 Specific Objectives

- To examine the common causes of infertility for which women seek ART in SSA.
- To explore and assess available ART in SSA.
- To assess factors that influence the decision to seek ART in SSA.
- To evaluate the factors and choices that influence the outcome of ART treatment in SSA.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Infertility

Infertility is a very serious condition that affects many lives. It is an ancient condition that dates back to biblical times. This problem significantly affects more people in sub-Saharan Africa than those in other parts of the world. Infertility is said to be the inability of a couple to achieve conception after 1 year of regular unprotected sexual intercourse (Harzif et al., 2019). The definition of infertility may vary across different socio-cultural backgrounds and the above definition may not be absolute. More recent definitions of infertility incorporate the maternal age and existing co-morbidities.

Infertility is primarily caused by lack of, or inadequate, treatment of reproductive system infection though there are other important causes of infertility. Advanced maternal age alone is an important factor that contributes to infertility in women all over the world due to significant increase in aneuploidy and spontaneous abortion rates (Farhi et al., 2019). The extremes of age have been associated with adverse outcome of pregnancy. There are still some uncertainties about the origin of this association; whether it is a result of biological immaturity, behavioural factors or socio economic disadvantages (Londero et al., 2019). The burden of infertility is not only medical but also psychosocial.

Childlessness according to Harzif et al (2019) is often a source of stigma in society and the blame is often borne by the woman regardless of the cause of the infertility. Infertility leads to isolation and causes women to question their sense of identity as well as their life expectations and their

perceived value in society (Ried & Alfred, 2013). It is therefore curious that in their study, **Elhussein et al (2019)** discovered that female infertility was higher compared to male infertility among couples. Women faced with the diagnosis of infertility in parts of the world such as Australia have engaged in activities such as yoga, meditation, self-hypnosis, internet forums as a way to overcome isolation and find emotional support (Ried & Alfred, 2013). In the Ghanaian setting, women who are faced with infertility almost always turn to religious leaders and other traditional methods including herbal medications (Hiadzi & Woodward, 2019). On more occasions than not they end up with worsened conditions that may have been treated earlier with less invasive methods than IVF or ICSI (Armah et al., 2021).

Infertility is classified into two broad groups; primary and secondary. Primary infertility is when conception has never been achieved while secondary infertility is being unable to achieve pregnancy after a previous conception. Primary infertility is due to genetic, anatomical abnormalities, endocrinological derangements as well as immunological problems. These factors may exist by themselves or may co-exist. For people affected with primary infertility, they are unable to conceive at all. It accounts 5% of childlessness among couples worldwide (Mumtaz et al., 2013).

Secondary infertility is the major cause of infertility among couples especially in lower income countries. It is usually due to environmental factors such as poor health care practices, lack of adequate health care, exposure to toxic substances , sexually transmitted diseases and socio-cultural practices such as endogamous marriages (marriage between relatives) and female genital mutilation (Mumtaz et al., 2013). Most of these factors are preventable. The causes of infertility may overlap between these two broad classifications. Furthermore infertility causes can be

grouped into male factor infertility and female factor infertility and in about 28% of cases infertility is unexplained (Ried & Alfred, 2013).

Even with the advent of ART there has been some cultural and religious backlash and opposition and couples who go through this treatment would usually want to keep it to themselves as much as possible. Despite the progress made in this ART the success rates are not optimum, approximately 39% success and also the associated complications for mother and baby are undeniable (Sunderam et al., 2019).

2.1.1 Effects of Infertility

The burden of infertility on the couple cannot be over emphasized. The infertile couple is faced with emotional and psychological as well as financial issues. The emotional issues arise from the realisation that they are incapable of achieving something as natural as pregnancy and may require help. They are reminded about this problem every single time they run into a pregnant woman or receive pregnancy announcements from their peers. This is especially more difficult for the women within the African setting where infertility is mainly seen as a female problem (Hasanpoor-Azghdy et al., 2014). Family and friends alike are constant reminders of their "failure" as they always remember to ask "When is the baby coming?"; "You are not getting any younger**" (Bornstein et al., 2020)**. This only causes the couple to worry more and may start to affect their relationship and even put pressure on their sex life. Infertility and its treatment can have profound effect on the sexual life of couples- sex becomes mechanical and less spontaneous because it becomes focussed on procreation rather than recreation and relaxation. Many couples indulge in sexual intercourse as a form of emotional connection and when sex becomes associated with failure and frustration this emotional connection is lost. (Ezzell, 2016). Their whole existence begins to revolve around

finding a solution to their predicament and this makes them vulnerable to all manner of people who claim to have a cure for them.

Naturally, most people will try alternative medicine and traditional and religious leaders first because it is believed that infertility is a curse or a punishment for some wrongdoing in the past. Eventually if they decide to seek medical help, they are faced with a financial hurdle which they have to overcome if they really want to produce children. They may have to undergo more than one cycle and even with that a successful outcome may not be realised. For some couples who may need donor gametes it makes the process more stressful and more expensive. Couples are therefore likely to keep these events to themselves until they have a successful outcome because of the stigma attached to infertility and also their unwillingness to validate the claims of the people around them concerning their childlessness. This means that they have no proper support system even as they go through the treatment and all their fears and hopes are kept to themselves. Especially for the woman who undergoes the major part of the treatment it results in anxiety and sometimes depression which may further compound the problem they are facing (Naab et al., 2019).

Hasanpoor-Azghdy et al (2014) in their qualitative study among infertile women in Iran concluded that the participants had experienced some psychological issues such as psychological turmoil, fear, anxiety, worry, grief and depression following uptake of infertility and medical interventions but consequences like mental engagement, loneliness, guilt, and regret were only reported as infertility consequences. Consequently, they developed difficulty in self-control, reduced self-esteem, feelings of failure and helplessness, and hopelessness following treatment process (Hasanpoor-Azghdy et al., 2014). Therefore, the devastating psychosocial effects of being

childless cannot be ignored and a strong support system is needed to serve as a source of constant encouragement to see affected couples through treatment.

2.1.2 Causes of infertility

Infertility causes may change depending on local demographics (Korgaonkar et al., 2018). Studies worldwide show that 50% of infertility cases to be associated with male issues. However emphasis has always been on female infertility primarily because in Africa and many other parts of the world women are automatically blamed for childlessness (Moyo & Muhwati, 2013). Male infertility is feared in many cultures worldwide mainly because men see themselves as invulnerable and any question about their fertility or virility tarnishes their image immensely among their peers and in the society as a whole (Moyo & Muhwati, 2013).

The age of marriage and of the couple is related to the inability to conceive– this may be correlated to the increasing age with a consequent reduction in quality and quantity of male and female gametes. For couples who have been married for less than 5 years, tubal factors attributable to pelvic infections usually due to sexually transmitted and hormonal abnormalities have been identified as the main cause of infertility. On the other hand, in those who have been married for more than 5years, there is increased prevalence of male factor infertility and unexplained infertility (Korgaonkar et al., 2018). Sometimes both male and female factors are present and contribute to inability to conceive (Elhussein et al., 2019).

2.1.3 Male factors associated with infertility

According to the European Association of Urologists, the causes of infertility in men may be classified based on aetiology as congenital or acquired urogenital abnormalities, malignancies, urogenital tract infections, increased scrotal temperature, endocrine disturbances, genetic abnormalities, malnutrition and immunological factors. Malignancies such as testicular cancer, lymphoma, leukaemia, scrotal cancers as well as the chemotherapeutic agents that are used to manage these conditions are known causes of infertility in men.

Other studies have also classified male infertility according to the ability of the causal factor to be treated. For example, according Jameson et al (2016), there is untreatable sterility such as primary seminiferous tubule failure and treatable conditions including sperm autoimmunity, obstructive azoospermia, gonadotrophin deficiency, disorders of sexual function and reversible toxin effects. There is also subfertility which generally describes any form of reduced fertility with prolonged unwanted non-conception (Gnoth et al., 2005). Sterility on the other hand refers to the inability to procreate (Gnoth et al., 2005). Abnormalities in sperm production and function alone accounts for 35-50% of male infertility (Balasch, 2012). Genetic causes arise form chromosomal abnormalities and microdeletions of the azoospermia factor on the Y chromosome, sex chromosome aneuploidies such as Klinefelter's syndrome, mutations in the cystic fibrosis transmembrane conductance regulator gene causing cystic fibrosis and absence of the vas deferens, mutations in the androgen receptor gene that leads to androgen insensitivity (Stouffs et al., 2014).

Systemic or neurological diseases, iatrogenic injury and trauma are also significant causes of male infertility (Katz et al., 2017). Conditions such as diabetes mellitus and hypertension have been associated with damage to the nerves and consequently impotence.

Prognostic factors for male infertility are: duration of infertility, primary or secondary infertility, results of semen analysis, age and fertility status of female partner according to Jungwirth et al (2015).

2.1.4 Female factors associated with infertility

Females are usually the focus when it comes to infertility because they are automatically assumed to be the cause of infertility. Korgaonkar et al (2018) in their study about chromosomal aberrations in couples with pregnancy identified and categorised female factor infertility into five main groups: endocrine abnormalities including anovulation, tubal factors, congenital malformations, pelvic infections and uterine factors. Some of these aetiological factors may co-exist in one individual while others such as pelvic infections may come with complications that will result in a different factor like tubal damage (Luna & Wolf, 2014b).

The hypothalamus and the pituitary gland are responsible for the regulation and production of hormones that ensure normal ovarian function. Anovulation occurs when a woman does not ovulate during a menstrual cycle and it is caused by a number of conditions including polycystic ovarian syndrome (PCOS), diminished ovarian reserve and premature ovarian failure (Kim et al., 2017).

Polycystic ovarian syndrome was the commonest cause of anovulation and infertility among women as a whole (Korgaonkar et al., 2018). Pelvic inflammatory disease is a known cause of tubal damage from the effects of chronic inflammation leading to adhesions that narrow the lumen of the tubes or even block them completely. Women are born with a fixed number of germ cells which progressively reduce in number throughout life. Diminished ovarian reserve implies that

there is a reduction in quantity and quality of oocytes in a women in the reproductive age group(Jirge, 2016). Apart from the natural progressive decline in oocyte numbers other factors such as endometrioma, pelvic infections, ovarian surgery and chemotherapy/radiation may further deplete the ovarian reserve by interfering negatively with intrafollicular endocrine and other regulatory mechanisms as well as blood flow (Jirge, 2016). One emerging trend is the recognition of genital tuberculosis as a cause of diminished ovarian reserve(Malhotra et al., 2012).

Premature ovarian failure is described in women under 40 years of age who develop amenorrhoea, infertility and hypogonadism ; thus the ovaries cease functioning (both geminal and hormonal function) according to (Jankowska, 2017). It is a devastating condition for women and comes with other complication aside the inability to have children including osteoporosis, autoimmune disorders, ischemic heart disease and psychological distress (Jankowska, 2017).

Other forms of endocrine abnormalities have also been associated with infertility. Hypothyroidism was the most common endocrine disorder associated with infertility followed by diabetes mellitus according to Korgaonkar et al (2018).

Tubal factors result from poorly treated pelvic infections, pelvic surgery, endometriosis and congenital abnormalities. Pelvic inflammatory disease which is an ascending infection of the female genital tract is the commonest cause of tubal damage. Sexually transmitted infections such as chlamydia and gonorrhoea are implicated in PID. Sub-Saharan African women are particularly vulnerable to the development of tubal blockade from poorly treated infections because of the paucity of reproductive health care services especially in the rural areas as health providers typically prefer to stay in the urban areas (Ogundele et al., 2018).

Endometriosis is another major cause of infertility in women and affects 5.5million reproductive aged females in the USA (Greene et al., 2016). It is basically the presence of endometrial tissue outside the uterine cavity and is associated with chronic pelvic pain since the predominant sites of attachments are within the peritoneum (Greene et al., 2016).

Congenital uterine abnormalities/malformations ranging from aplastic uterus to incomplete septate uterus are relatively common in the society- up to 10% (Jacquinet et al., 2016) and affected are at a higher risk of spontaneous abortions and adverse pregnancy outcomes (Mørk et al., 2018).

Acquired uterine abnormalities may result from benign conditions such as uterine fibroids as well as malignant conditions such as uterine sarcomas, cervical cancers. These acquired conditions may directly or indirectly affect fertility. Indirect in the sense that treatment modalities that include surgery may damage vital reproductive structures or even result in the removal of the entire uterus. Genetic aberrations lead to conditions such as Kallmann syndrome, fragile X syndrome that are characterised by ovulatory problems, karyotype abnormalities and primary cilia dyskinesia.

Maternal age has been shown in various studies across the world to be associated with diminishing fertility. The female is born with a fixed number of oocytes which are arrested. The reproductive aging process is associated with an obvious reduction in number and quality of oocytes begin to decline after age 32 and after age 35 this decline accelerates rapidly. Older maternal age has been associated with lower rates of spontaneous pregnancy as well as ART according to Aflatoonian et al (2011).

Other factors such as physical activity (moderate) have been shown in various studies to improve female fertility as well as improve the outcome of pregnancy and the opposite of sedentary lifestyle

and excess weight gain has been associated with PCOS (Rao et al., 2018). The treatment for infertility in Africa can either be traditional or biomedical. Traditional treatment of infertility is an alternative source that doubles as a coping mechanism for the affected couple (Tabong & Adongo, 2013). It combines spiritualism as well as the use of herbs to treat infertility with a skewed focus on the female partner. It is usually the default choice of treatment among many ethnicities within the continent. Medical treatment is multidisciplinary involving the gynaecologist, obstetrician, embryologist, psychologist as well as religious leaders. It takes a significant toll on the couple's emotions, finances and their relationship/marriage. Medical treatment is tailored to the cause of infertility and ranges from having ovulation induction, intrauterine insemination, Assisted Reproductive Technology including surrogacy to adoption.

Intrauterine insemination is often done after stimulation of the ovaries. The sperms are placed within the uterus at the time of ovulation which is usually within 24 to 36 hours after the luteinizing hormone surge is detected (Tsuji et al., 2012). Other forms of treatment for acquired structural uterine abnormalities such as uterine fibroids may require surgery to improve fertility (Moungala et al., 2019).

2.2 Management of Infertility

The treatment for infertility in Africa can either be traditional or biomedical. Traditional treatment of infertility is an alternative source that doubles as a coping mechanism for the affected couple (Tabong & Adongo, 2013). It combines spiritualism as well as the use of herbs to treat infertility with a skewed focus on the female partner. It is usually the default choice of treatment among many ethnicities within the continent. Medical treatment is multidisciplinary involving the gynaecologist, obstetrician, embryologist, psychologist as well as religious leaders. It takes a

significant toll on the couple's emotions, finances and their relationship/marriage. Medical treatment is tailored to the cause of infertility and ranges from having ovulation induction, intrauterine insemination, Assisted Reproductive Technology including surrogacy to adoption.

According to Amoatwo (2019) the usual agents used are 5 day of clomid 50-100mg from day 2 to day 6 of the cycle followed by injection FSH / HMG 75-150iu on day 7 ,8 and 9 followed by injection HCG to trigger ovulation. This together with timed intercourse alone can achieve pregnancy in women with no tubal or uterine problems (Szmelskyj & Aquilina, 2014).

Intrauterine insemination is often done after stimulation of the ovaries. The sperms are placed within the uterus at the time of ovulation which is usually within 24 to 36 hours after the luteinizing hormone surge is detected (Tsuji et al., 2012).

2.2.1 Assisted Reproductive Technology

Reproductive and childbirth remain one of the essential themes of life globally according to (Johansson et al., 2011). Assisted Reproductive Technology is a treatment for infertility that involves the handling of eggs or embryos outside the human body in the laboratory setting. By this definition procedures such as the intra uterine insemination do not qualify as ART. ART is now accepted as an alternative to natural conception in many parts of the world (Nouri et al., 2013) ART typically is made up of 4 types including in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT) and Intra Cytoplasmic Sperm Transfer. The majority of ART procedures performed are IVF; Approximately 99% according to (Sunderam et al., 2019) of ART procedures performed are IVF. ART is made up of a number of critical steps

that averagely span a period of 2 weeks and this is referred to as a cycle of treatment (Qiu et al., 2019).

2.2.1.1 In Vitro Fertilization

An IVF cycle usually begins with drug-induced ovarian stimulation. There are 2 main drugs that are used for this purpose, clomiphene tablets and gonadotrophin injections. They are administered at the beginning of menstruation with the aim to stimulate the ovaries to produce more eggs that can be harvested. If the egg stimulation process is successful then the second stage, the egg-retrieval stage, which involves surgically removing the eggs from the ovaries commences. After egg retrieval, the eggs are combined with sperm in the laboratory during the IVF procedure (Sunderam et al., 2019). The successful outcomes (the embryos that appear most viable) are selected and implanted into the patient's uterus. An obstetric ultrasound is carried out on the patient after 2 weeks of the transfer and if there is a detectable gestational sac implying that an embryo has successfully implanted then a clinical pregnancy has been achieved. Within the first trimester (first 13 weeks of pregnancy) most pregnancy losses are experienced. During this period the pregnant women are advised to have bed rest and are given hormonal therapy to help maintain the viability of the pregnancy. According to (Sunderam et al., 2019) Survival of pregnancy ranges from 95.0% at 16 weeks to 98.0% at 20 weeks. IVF may result in normal healthy babies but there is a higher risk of complications- both maternal and neonatal (Nouri et al., 2013).

2.2.1.2 Intracytoplasmic Sperm Transfer

Intracytoplasmic sperm injection (ICSI) was developed for the treatment of couples with severe male-factor infertility to enable fertilization and pregnancy rates regardless of semen characteristics (Farhi et al., 2019). It has revolutionized management of male factor infertility.

ICSI involves the injection of a single sperm into the cytoplasm of an oocyte and can be carried out with fresh and frozen-thawed epididymal sperm following a sperm retrieval procedure (Merchant et al., 2011). Oocyte retrieval for ICSI is similar to that of IVF with a programmed superovulation induction followed by retrieval of oocytes. However the retrieved oocytes undergo a denudation step which is an absolute essential pre requisite for ICSI and this is carried out under conditions of constant pH of 7.3 and a stable temperature of 37 degrees Celsius (Balasch, 2012). The rates of fertilization and consequently pregnancy after ICSI have been associated with the morphology of the eggs used Balasch (2012).

2.2.1.3 Gamete Intrafallopian Transfer

GIFT is a type of ART that involves the removal of the eggs from the ovary, mixing the eggs with the sperm and placing it in the fallopian tube for fertilization to occur in the natural environment (Szmelskyj & Aquilina, 2014). It is therefore only feasible in a female with at least one normal tube. This procedure is carried out laparoscopically in one sitting under general anaesthesia (Szmelskyj & Aquilina, 2014).

The woman is given medication such as progesterone to prepare the endometrial lining for implantation. This method of infertility treatment has been used for couples with unexplainable infertility, couples who have not had success with IVF, couples who have a religious or moral reluctance to use IVF, women who have at least one healthy fallopian tube and among couples in with male factor infertility such as a low sperm count.

2.2.1.4 Zygote Intrafallopian Transfer

This is a form of ART that involves transferring a zygote into the fallopian tube after IVF has been done (I. Szmelskyj & Aquilina, 2015). A zygote is a fertilised egg that has not divided yet. This

procedure combines both IVF and GIFT. The eggs are retrieved using the same procedure as in IVF. The transfer of the zygote is laparoscopically done. This means that two surgical procedures are carried out in ZIFT (I. Szmelskyj & Aquilina, 2015).

2.2.2 Surrogacy

The history of surrogacy can be traced to biblical times where Hagar, the servant of Abraham was used as a surrogate for Abraham and Sarah in the book of Genesis. The problems associated with human procreation embodies interpersonal relationships at the religious, social, political, moral and scientific level (Bakova et al., 2018). Advances in biomedical technology has led to sophisticated procedures that have bridged the gap between modern biomedicine and value of human life (Dar et al., 2015). They have provided an alternative to conception and therefore facilitating human existence. With the changing trends in childbearing among women – being more career focused and delaying childbirth until they are well past the optimum reproductive age (Tromp et al., 2011), sometimes a little too late making them poor candidates for ART. Others due to adverse complications of pregnancy, congenital or acquired structural abnormalities may prevent some women from carrying to term. Being unable to conceive the natural way leaves the option of ART to couples who can afford it. The issue of ART and surrogacy has gained popularity over the years and the surrogate industry has increased.

Surrogacy is the process where a woman carries and gives birth to a baby for a couple or a person who are called the intended parents. Issues that may arise with surrogacy often have ethical and legal implications. In recent years it has been marketed as a profitable venture with young girls being lured into surrogacy due to the seemingly high financial rewards especially in less developed countries (Dar et al., 2015). Surrogacy is practised in two forms; Genetic/traditional surrogacy

where the embryo is created from fertilization between sperm of the intended father and the egg of the surrogate such that the offspring has half of its genetic material from the surrogate mother (Bakova et al., 2018).

Gestational surrogacy where the gestating mother receives the embryo after the gametes from the intended parents have been fertilized in vitro. Thus the offspring does not share any genetic material with the birth mother (Bakova et al., 2018).

The first formal legal surrogacy agreement was in 1976 in the United States of America. Since the 1980s there have been an intense custody battles which has resulted in law makers coming up with guidelines and regulations regarding surrogacy. Legislature such as the Surrogacy Arrangement Act of 1985 in the United Kingdom of the Great Britain and Northern Ireland allows for non-commercial surrogacy. Canada also has the Assisted Human Reproductive Act and in some parts of Europe surrogate motherhood is conditionally allowed while in other parts it is prohibited. Surrogacy in Ghana is yet to encounter any legal (Faccio et al., 2019).

2.2.3 Adoption

Adoption is the legal process by which a child becomes the child of persons other than his/her biological parents (Norman, 1943). In a typical African society couples are expected to start their families with their biological offspring and though they may take in children of relatives legal adoption is not readily seen as a solution to infertility (Nachinab et al., 2019). Ghana has a comprehensive law on adoption and the procedure though cumbersome, is well defined. There are over 160000 orphans in Ghana and the total child adoptions for the year 2015 was about 85 with an estimated average cost of adoption of eighteen thousand dollars(Team, 2019). Therefore, there are more than enough orphans that need homes and families and this is an excellent option for

couples who have been unsuccessful with ART treatment. The preference for biological children is a major barrier to child adoption in Ghana and the culture of the Ghanaian people shrouded in misconceptions, stigmatizations and financial burden does not make it any easier (Nachinab et al., 2019) The requirements and total cost of adopting a child in Ghana however serve as a deterrent for the few people who want to adopt children (Nachinab et al., 2019).

2.3 Factors influencing Assisted Reproductive Technology outcomes

Assisted Reproductive Technology are influenced by a myriad of conditions. The success or failure is determined by both intrinsic factors related to both male and female as well as other extrinsic factors that include the expertise of the specialist as well as the available techniques (Balasch, 2012).

The infertility specialist must fully comprehend the various laboratory tests including their limitations and strengths and also have adequate knowledge about their indications, cost and success rates of all treatment options (Merchant et al., 2011). This will ensure careful patient selection to allow for each patient to have the best chance of achieving a successful outcome. Several studies have shown decreased quality of gametes of both males and females to increasing age among others (Park et al., 2018).

2.3.1 Individual factors

The success of IVF outcomes may be influenced by factors such as age of the oocyte donor, quality, and number of embryos transferred, age and endometrial receptivity of the recipient among others (Amoatwo, 2019). Age, quality of the embryo and endometrial receptivity are the most important factors for the success of IVF (Farhi et al., 2019). The paternal age does not

independently affect the outcome of ART according to Park et al (2018). The positive correlation between increasing maternal age occurs because of the ovarian aging and associated diminishing ovarian follicle count but studies have demonstrated that the uterine endometrium does not loose function with age; thus it is able to maintain pregnancy throughout the reproductive life of a woman (Amoatwo, 2019). The high success rates obtained when oocytes from women in their twenties are used depict that the egg quality affects the outcome of ART procedures.

It has been estimated that uterine receptivity accounts for about 31–64% of implantation (Gahlot, 2014). Studies reported a threshold of <7 mm with a significant reduction in the implantation rate and pregnancy rate when endometrial thickness is less than 7mm. A systematic review and meta-analysis investigated both the independent predictive capacity and the prognostic value of endometrial thickness on pregnancy outcomes after IVF. This study found that the probability of clinical pregnancy for an endometrial thickness ≤7 mm was significantly lower compared with cases with endometrial thickness >7 mm (23.3% versus 48.1%) with odds ratio of 0.42 (95% CI 0.27–0.67) (Kasius et al., 2014).

2.3.2 Facility and medical factors

There are limited fertility clinics in Africa though Africa has the highest prevalence of infertility globally. The limited access to fertility clinics in Africa restricts patients to private settings (Moungala et al., 2019) with associated issues of affordability and accessibility. The situation is no different in Ghana. The competence of the health facility influences the quality of service that will be rendered. Proper diagnosis of the cause of infertility and excellent assessment based on available diagnostic imaging and laboratory tests. The availability of the fertility experts as well as embryologist will enhance the ART services that will be rendered (Balasch, 2012). The facility

should be well positioned to deal anticipate and resolve any complications that may arise at any stage of the treatment. Patients decision to seek ART treatment is influenced by the reputation of the facility which is mainly from recommendations from other patients who have gone through the treatment already (Gerrits, 2018). The right facility with the right infrastructure and expertise is therefore a very crucial decision that will affect the outcome of ART.

2.3.3 Health System Factors

Health system factors that affect ART brings up serious questions about how money, markets, choice and care relationships are related. With recent expansion in the scale and scope of medical tourism and transnational reproductive travel, it has become very important to regulate the activities of the fertility clinics as regards to the provision of ART (Wiltshire et al., 2019). In the more developed countries, there are guidelines and legislature on ART which are constantly being updated to protect the patient and ensure that things are done right. In developing countries such as ours these standards are lacking which makes it more convenient for transnationals to come for infertility treatment in our facilities (Ombelet, 2013).

There is no real framework in Ghana which looks at the treatment of infertility in the public setting. Reproductive tract infections are a preventable cause of infertility which can be reduced by early treatment of the infections thereby having the effect of decreasing the incidence of infertility and the subsequent need for ART (Ogundele et al., 2018). The lack of guidelines implies that during the implementation of the treatment the fertility specialist and their facilities use their own discretion to make decisions. Sometimes these decisions may not produce the best outcome for the patient but since there is no standard to ensure that the clinicians follow protocol not much can be done about the situation. These factor directly or indirectly affect the outcome of ART.

2.4 Knowledge, Attitude and Practices of Persons Seeking ART

Despite the growing ART industry, awareness about fertility, risk factors for infertility as well as the treatment available for infertility is lacking (Moghadam & Ganji, 2019). There are gaps in knowledge about infertility and ART even among educated persons (Sabarre et al., 2013) . Studies conducted in Pakistan assessing knowledge and perception regarding infertility among selected adult population in Pakistan revealed that there was limited knowledge of infertility as only 25% of the study participants correctly identified infertility as a pathology, while the alternative treatment for infertility remained a popular option for 28% of the participants as a primary preference and 75% as a secondary preference (Moghadam & Ganji, 2019). The role of ART in the management of infertility is well acclaimed but the knowledge and attitude of the general public in some parts of the world about the procedure and babies born through IVF has been split between acceptance, reservation, and in some instances rejection, particularly in some aspects such as third-party IVF (Moghadam & Ganji, 2019). Social factors such as religion, culture, personal belief, and cost are some factors that affect the acceptance of ART by the public.

To ensure the effective utilization of ART treatment the knowledge and perception of the prospective patients is very critical (Silva, 2016).

2.5 Guidelines and Ethical Considerations

Since its inception ART has attracted a lot of criticism from various religious bodies, moralists and even among the society as a whole with various legal concerns (Londra et al., 2014). ART is a controversial subject with varying political, religious, legal, scientific, professional and ethical views. There has been strong opposition from certain interest groups like the spiritual leaders as some regard it as a direct contradiction to their religious faith (Silva, 2016). The treatment is

expensive and the process can be very emotionally draining. Ghana currently has no regulations or guidelines to chaperon the practice of ART and as a consequence the fertility specialist here usually use their own discretion coupled with their experience from their place of training to guide their work.

There is no special system set in place to evaluate and monitor the work of fertility specialist in Ghana and the situation is no different in other developing countries. This means that there are no rules to determine any criteria for selection of patients, sale of gametes or the use of surrogates as well as what to do with unused embryos and gametes. With the donation/sale of gametes to infertile couples there is a chance that the children who are born may share genetic material without knowing and can even end up getting into relationships with each other clueless that they are indeed siblings (Faccio et al., 2019).

Controversies also arise with same sex couples who desire to have children- whether or not they should have that privilege and the potential of abuse of ART among this community of people. This is a very serious moral and religious concern. It also means that there is a possibility that certain human rights may be violated during the treatment especially for women who are surrogates – they may undergo needless invasive procedures to please the couple they are working for (Deonandan et al., 2012).

With the global burden of infertility there has been a steady growth of inter-country medically assisted reproductive (IMAR) which involves couples travelling to other countries to undergo infertility treatment and may involve the use of a 'third party' as a surrogate (Deonandan et al., 2012). ART is dynamic and the guidelines need constant reviewing to be able to deal with issues that arise with time. For more developed countries there are institutional bodies that provide these

principles in alliance with existing national legislature such as the National Health and Medical Research Council of the Australian government.

In Australia there is an existing law (the Victorian legislation) that guides the practice of ART which covers the welfare and interests of children born as a result of the treatment , the reproductive capabilities of both men and women, the right to information of the children born about their birth genetics, discrimination against people seeking ART treatment as well as the health and well-being of the persons undergoing the treatment (Johnson, 2014).

Legal and ethical consequences of ART bring up challenges that need to be addressed both on the local (both national and community levels) and international fronts involving both the individuals involved in ART with the assistance of bioethicists, legal counsellors and members of the society in general (Londra et al., 2014). Improving access to ART services while ensuring that the procedures are reported with their resultant outcomes are needed for setting a baseline and developing guideline updates to regulate ART practice nationally and worldwide.

The Indian Council of Medical Research provides guidelines that cautions the use of embryos from ART procedures for commercial purposes and recommend that sale or transfer of human embryos or gametes to any party outside the country must be prohibited (Murthy & Subramanian, 2007).

There is a real possibility of misuse and abuse of ART and clear guidelines that will address issues related to social justice and gender inequality, go beyond technicalities and build effective safeguards so that the unequal power relationship between the providers and participants in ART treatment is minimised are needed to help regulate this industry. The treatment for infertility will

only get more sophisticated in future and defining the ethical framework for biomedical research is critical (Murthy & Subramanian, 2007).

CHAPTER THREE

METHODOLOGY

The methods of this thesis used systematic review approach and collated all empirical evidence meeting a pre-specified eligibility criterion of ART in SSA. The data obtained from ART studies in SSA was synthesized to obtain evidence-based estimates and conclusions of clinical relevance and outcomes of ART. It used 'PICOS' (P-Patients, I-intervention, C-control, O-Outcomes, S-Study) to describe the population, intervention, comparators, outcome of intervention and study types included in primary studies used for the systematic review. The protocol of this systematic review was successfully registered in the PROSPERO – an International Prospective Register of Systematic Reviews. A copy of the published protocol can be found at the appendix.

3.0.1 Criteria for considering studies for this review

Studies

All studies including randomised controlled trials (RCTs), cohort studies, case-control and cross-sectional studies that report the availability and outcome of ART as well as on the causes of infertility for which women/couples living in SSA seek ART treatment were eligible for inclusion in this review. The studies should have been conducted in SSA from 1st January 2000 to 31st October 2020. The studies were to be reported in English or French.

Population/patients

Women in the reproductive age who live in sub-Saharan Africa (any of the countries as defined by the World Bank) and have undergone at least one cycle of ART in a health facility in SSA were eligible for inclusion. Women who went through assisted reproductive technology as surrogates were excluded from the review. Women who had artificial insemination or ovulation induction alone without any form of assisted reproductive technology were also excluded.

Intervention

Studies that reported on the use of Assisted Reproductive Technology including in-vitro fertilization, gamete intrafallopian transfer, zygote intra fallopian transfer, intracytoplasmic sperm transfer and outcome of treatment. Studies that reported on the use of artificial insemination or ovulation induction alone without any form of assisted reproductive technology were excluded.

Comparison/control

Women who live in SSA of comparable ages who had spontaneous pregnancy without any form of assisted reproductive technology.

Outcomes

Primary outcomes

Clinical pregnancy (singleton/multiple gestation), progression of pregnancy to term, live birth)

ART – clinical pregnancy

Secondary outcome

Pregnancy loss, still birth, maternal complications, foetal complications, low birth weight, foetal anomalies, early neonatal death.

Adverse events

Ectopic gestation, ovarian hyperstimulation syndrome and all ART-related complications.

3.1 Search methods for identification of studies

3.2.1 Electronic database searches

Relevant abstracts of studies reported in English or French on ART and its outcomes in sub-Saharan Africa were identified by conducting an advanced search on the following databases- PubMed, African Journals Online and Google Scholar, Cochrane Central, LILAC and CINAHL (carried out by FO under TDA's supervision) The electronic search focused on studies conducted from the year 1st January, 2000 to 31st October, 2020 that met the eligibility criteria. Though the onset of ART in Africa is dated as far back as the 1980s, 2000 was chosen so as to allow the inclusion of relatively recent findings in the review. The key search concepts were "Assisted reproductive technology (ART, assisted reproductive technique(s), reproductive in vitro fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, intra cytoplasmic sperm transfer)", "outcome (Clinical pregnancy, pregnancy loss, abortion, miscarriage, stillbirth, live birth, ART complications)"and "sub- Saharan Africa (including all the countries in the region according to the World Bank records). Through the aforementioned means, the bibliographies pertaining to the relevant studies were accessed and where full text articles remained inaccessible despite searches then the authors were contacted directly to obtain the information required.

3.2.2 Other sources

The references of all relevant articles were searched for additional studies, and the full texts of resources identified and accessed were obtained through the aforementioned means. The reference lists of existing systematic reviews conducted within the last ten years was used to identify

potentially relevant primary studies and the studies were evaluated based on the specified criteria for inclusion of studies.

3.2.3 Selection of studies

Eligible studies were assessed independently by two members of the research team (FO and ADA). This was achieved using an assessment tool that incorporated the inclusion and exclusion criteria. The pre-defined selection criteria were applied to all the studies that were retrieved from the electronic database search to ensure that the process was unbiased and reliable. Studies that satisfied these conditions unanimously were retained and included in the review. Disagreements were resolved through consensus meeting between the reviewers.

3.3 Data extraction and management

Information about the included studies was collected onto a data extraction form that encompassed certain key characteristics of the various studies including; the author (s) and year of publication, country and language of publication, the study design, sample size, type of ART used, number of ART cycles, ART outcome statistics (clinical pregnancy, miscarriage, live birth and stillbirth), ART complications, infertility diagnosis, population characteristics- relevant socio demographic data (parity, comorbidities , age and BMI). Where there were challenges in acquiring information on any of the key characteristics or variables, the authors of the corresponding research were contacted directly to help provide the information needed. For studies that involved a number of countries (multinational studies), all attempts were made to segregate the findings based on country. FO extracted data which were independently verified by ADA. Any discrepancies were resolved through discussion.

3.4 Assessment of risk of bias in the included studies

Two reviewers independently assessed the risk of bias in all included studies. This was evaluated using the checklist developed by Hoy et al (2012). The checklist incorporates assessments of risk of bias across core domains including sampling technique and sample size, outcome measurement, response rate, and statistical reporting. All disagreements the during critical appraisal were resolved through discussion.

3.5 Data synthesis

The data that was retrieved from the studies **were** analysed using the statistical software STATA version 15.0. A meta-analysis was done for the various types of observational studies included in the review. Thus, cross sectional studies were pooled together and analysed as such. The same approach was used for cohort studies. Standard errors for the study-specific estimates were calculated using the point estimate and the appropriate denominators, assuming a binominal distribution. Through a random-effects meta-analysis model, the ART outcome specific estimates from the various studies were pooled to obtain an overall summary estimate of the prevalence/incidence, after stabilising the variance of individual studies using the Freeman-Tukey double arc-sine transformation. A meta-analysis was performed to assess the association between factors that affect ART and ART outcome. The results obtained were presented by geographic region (central, eastern, northern, southern and western Africa). A 95% confidence level was applied as the level of significance.

Heterogeneity was evaluated by the Chi square test on Cochrane's Q statistic, which is quantified by I squared values, that assume that I squared values ≤25%, 50% and >75%, as representing low, medium and high heterogeneity, respectively. Publication bias was assessed using funnel plots analysis and Egger's test.

3.5.1 Addressing missing data

The data extraction template was used to collect information from all the selected studies. The team contacted authors of the included studies directly for any missing information or data not accessible in the published study. In situations where attempts to reach the authors were unsuccessful, the affected studies were exempted from the data extraction process and listed as pending. The studies with missing data were included in the review and their contribution to the pooled evidence assessed through sensitivity analysis where possible.

3.5.2 Subgroup analysis

Where substantial heterogeneity was detected, a subgroup analysis was performed to detect its possible sources using the following grouping variables: age group, sex and geographical area (central, eastern, northern, southern and western Africa).

3.5.3 Sensitivity analysis

Studies that include for example, large sample sizes, high prevalence or incidences, very narrow confidence intervals were considered as outliers and subjected to sensitivity analysis. Meta-analysis was carried out on the studies that satisfied the eligibility criteria with and without the studies that did not fully meet the eligibility criteria. The effects of risk of bias, missing data and unpublished studies was also assessed thoroughly using sensitivity analysis.

3.6 Grading level of evidence

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach was used in assessing the quality of evidence presented by the studies that were included in the review. The overall quality of evidence of the reported outcome of ART from the included

studies was evaluated applying the 5-GRADE considerations: imprecision, inconsistency, risk of bias, publication bias and inconsistency. The result of the evaluation was ranked as high, moderate or low quality accordingly.

3.7 Reporting the systematic review

A flow diagram was used to depict the study selection process highlighting the various databases from which the studies were obtained. This followed the MOOSE guidelines for Meta-Analysis and Systematic Review for Observational Studies standards of reporting. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines guided the conduction and reporting of this systematic review. Tables were used to capture quantitative data for the individual studies as well as the summaries of the various studies. Where appropriate, funnel plots were used. The factors that affect ART outcome was examined by region and specific time periods based on the data available. The risk of bias of each included study was described and summarised using tables.

3.8 Ethical issues and dissemination

This study is a systematic review and meta-analysis and used data obtained from electronic databases. Therefore, no ethical approval was required as there was no direct contact with individuals. The aim of this systematic review and meta-analysis was to provide evidence to guide the designing of early preventive and control strategies as well as provide a road map for future research based on gaps identified. The final report will be published in a peer-reviewed journal. The findings will be further presented at appropriate conferences and submitted to relevant health authorities. This will hopefully influence health service as regards ART and policy solutions.

3.9 Declaration of conflict of interest

The researcher and collaborators hereby declare no conflict of interest pertaining this research.

3.10 Funding the study

This study is in partial fulfilment of requirements towards the award of a Master of Public Health (MPH) degree at the School of Public Health, College of Health Sciences, University of Ghana, Legon, hence, there is no funding from any source and all estimated cost of the study was borne solely by the principal investigator. The University of Ghana Centre for Evidence Synthesis and Policy (UGCESP) and Africa Communities of Evidence Synthesis and Translation (ACEST) / jointly supported the training on how to conduct systematic reviews.

CHAPTER FOUR

RESULTS

4.1 Characteristics of studies included in the review

A flow diagram was used to depict the study selection process highlighting the various databases from which the studies were obtained, the number of studies that satisfied the pre-defined inclusion criteria as well as the number of studies that were excluded (Figure 2). The reasons for the exclusion were documented. A total of 10 studies including one registry report were incorporated in this systematic review after completion of the screening process. The majority (6) were retrospective studies. There were 2 prospective studies and 2 cross sectional studies. 7 out of the 10 studies were conducted in Nigeria between June 1999 and June 2011. One study was conducted using data across 18 African countries three of which fell outside the sub-Saharan African sub region while the remaining two studies were from Kenya and South Africa conducted in 2005 to 2008 and 2009 respectively. Two studies reported on female- and male-factor infertility while two others reported on the female-factor infertility alone. The remaining studies did not report on infertility or reported on different categorizations of infertility which could not be pooled together. The outcomes of interest for most of the studies were type of ART, number of embryos transferred, pre-clinical pregnancy rate, clinical pregnancy rates, pregnancy loss or miscarriage rates as well as complications. For two studies the endometrial thickness was also an outcome of interest. Five studies commented on the type of ART used while three out of the 5 studies gave distinct number of cycles for the ART type used.

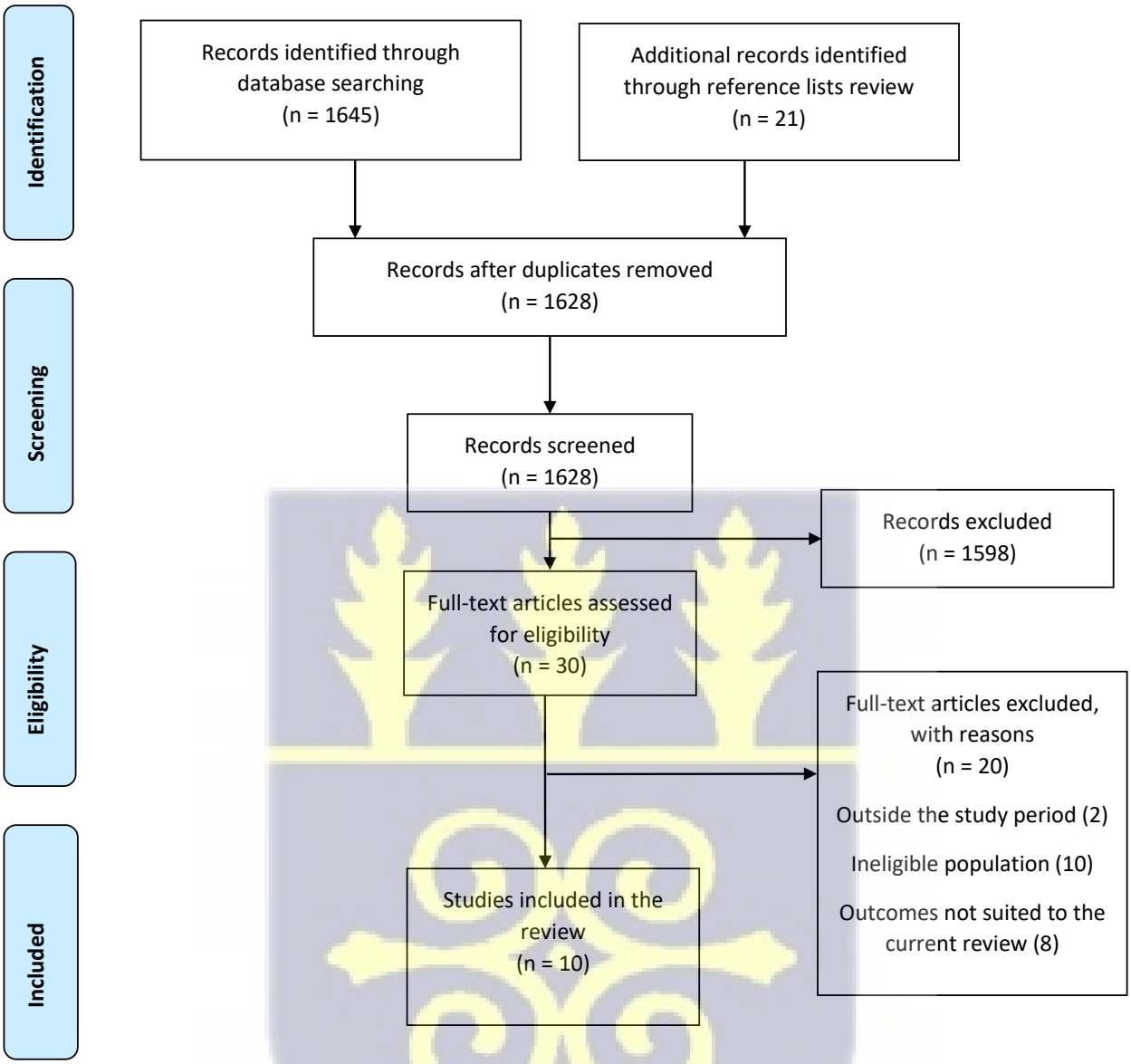

Figure 2: Flow diagram showing the study selection process

Table 1: Characteristics of the included studies

							Denominators and outcomes reported							
Reference	**Country**	**Type of Study**	**Study period**	**Prognostic factors**	**Treatment**	**Total cycles**	**patients**	**PC**	**CP**	**LB**	**GE**	**SB**	**PL**	**CO**
Noreh et al., 2009	Kenya	retrospective cohort	August 2005 to July 2008	female & male	IVF&ICSI	362	318	Y	Y	Y	Y	Y	Y	Y
okohue et al., 2009	Nigeria	prospective cohort	May 2005 to April 2006	female & male	IVF&ICSI	900	276	Y	Y	-	-	-	Y	Y
Okohue et al., 2013	Nigeria	retrospective cohort	December 2004 to April 2008	female	IVF&ICSI	76	72	Y	Y	-	-	-	Y	Y
Ogunmokun & Richardson., 2002*	Nigeria	retrospective cohort	June 1999 to December 2002	-	IVF&ICSI	1147	-	Y	Y	Y	-	-	Y	Y
Okohue et al., 2010	Nigeria	retrospective cohort	July 2005 to June 2008	-	IVF	-	64	-	Y	-	-	-	-	Y
Dyer et al., 2020	18 countries	retrospective cohort	2013 to 2017	-	-	-	-	-	-	-	-	-	-	-
Olukoya et al., 2012	Nigeria	Cross-sectional	2009 to 2011	-	-	-	-	-	-	-	-	-	-	-
Akande et al., 2019	Nigeria	Cross-sectional		female	-	-	202	-	-	-	-	-	-	-
Orhue et al., 2012	Nigeria	prospective cohort	June 2007 to June 2011	-	-	-	600	-	Y	-	Y	-	Y	Y
Dyer and Kruger, 2012	South Africa	retrospective cohort	2009	-	IVF/ICSI	-	2813	-	Y	-	-	-	-	-

***Only data from 2000-2002 was included in the meta-analysis PC = Preclinical pregnancy CP = Clinical pregnancy LB = Live birth**

GE = Gestation SB = Stillbirth PL = Pregnancy loss CO= Complications

4.2 Risk of Bias in included studies

The risk of bias in the included observational studies was assessed using the Hoy et al (2012). The summary risk of bias score and interpretation were; 0-3 (low risk), 4-6 (moderate risk) and 7-9 (high risk). Most studies (6 out of 10) were scored as having low risk of bias as they reported detailed methods regarding the target population, sampling frame, sampling, validity of outcome measurements, response rate and data analysis. One study was found to have moderate risk of bias. Three studies were rated as unclear risk due to the unavailability of full-text which made the assessment incomplete. A sample of the risk of bias tool by Hoy et al (2012) is in the appendix of this document.

Table 2: Risk of Bias Assessment of included studies

Study ID	Risk of Bias Score	Interpretation
Noreh et al., 2009	3	low risk
Okohue et al., 2009	2	low risk
Orhue et al., 2012	4	unclear risk
Ogunmokun & Richardson, 2005	1	low risk
Okohue et al., 2010	4	unclear risk
Olukoya et al., 2012	4	unclear risk
Okohue et al., 2013	5	moderate risk
Dyer et al., 2020	3	low risk
Akande et al., 2019	0	low risk
Dyer and Kruger, 2012	1	low risk

4.3 CAUSES OF INFERTILITY

4.3.1 Female factors

In all, four studies reported on infertility with two of them differentiating on the female and male factors. Among the remaining two studies one reported on infertility as being primary or secondary and the last study focused on tubal factors and polycystic ovarian syndrome as causes of infertility associated with ART. Two studies (Noreh et al., 2009; Okohue et al., 2009) from Kenya and Nigeria provided data on female factors as cause of infertility among women seeking ART. The pooled prevalence estimates from the two studies showed a 41.6% (95% CI: 17.1% to 66.2%) female factor as a cause of infertility. With Higgins I^2 value of 97.6% and a significance test from the Cochrane's Q statistic (p=0.00), there was significant heterogeneity from the two studies which suggests that the two studies should not be pooled (Figure 3).

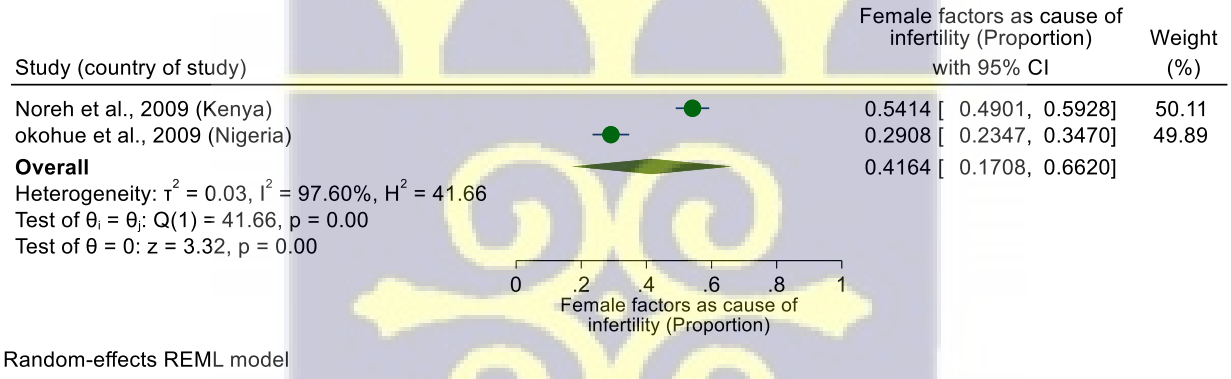

Figure 3: Forest plot of the proportion female factors as a cause of infertility

4.3.2 Male factors

There was no study that reported on male factors alone as a cause of infertility. The same two studies (Noreh et al., 2009; Okohue et al., 2009) from Kenya and Nigeria mentioned earlier provided data on male factors as cause of infertility among women seeking ART. The pooled estimate of the prevalence estimates from the two studies showed a 48.1% (95% CI: 11.2% to 84.9%) male factors as a cause of infertility among women seeking ART. With Higgins I^2 value of 98.9% and a significance test from the Cochrane's Q statistic (p=0.01), there was significant heterogeneity from the two studies (Figure 4)

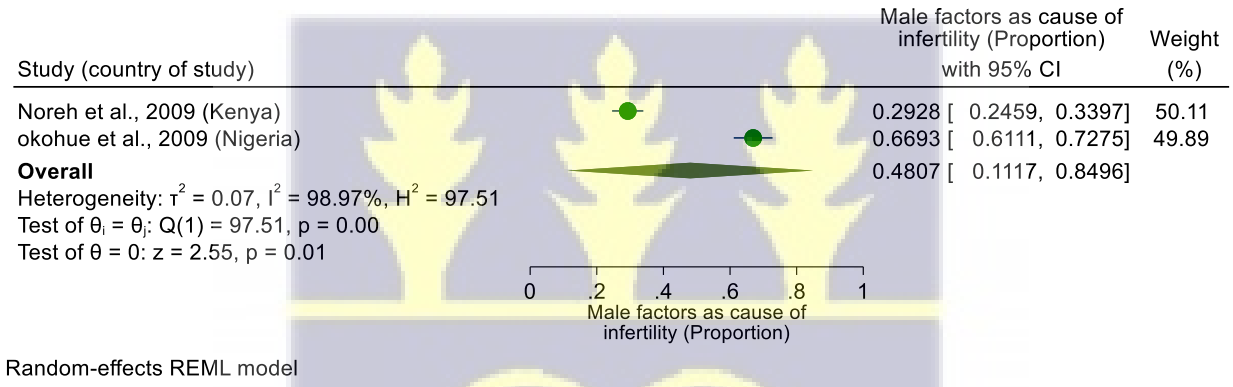

Figure 4: Forest plot of the proportion male factors as a cause of infertility

4.4 POSITIVE OUTCOMES

4.4.1 Preclinical pregnancy

Four studies (Noreh et al., 2009; Ogunmokun & Ajayi, 2006; Okohue et al., 2009, 2013), one from Kenya and three from Nigeria provided data on preclinical pregnancy outcome among women seeking ART. The pooled prevalence estimates from the four studies showed a 37.5% (95% CI: 23.7% to 51.4%) preclinical pregnancy among the women seeking ART. With Higgins I^2 value of 96.7% and a significance test from the Cochrane's Q statistic ($p < 0.0001$), there was heterogeneity in the estimates obtained from the four studies (Figure 5).

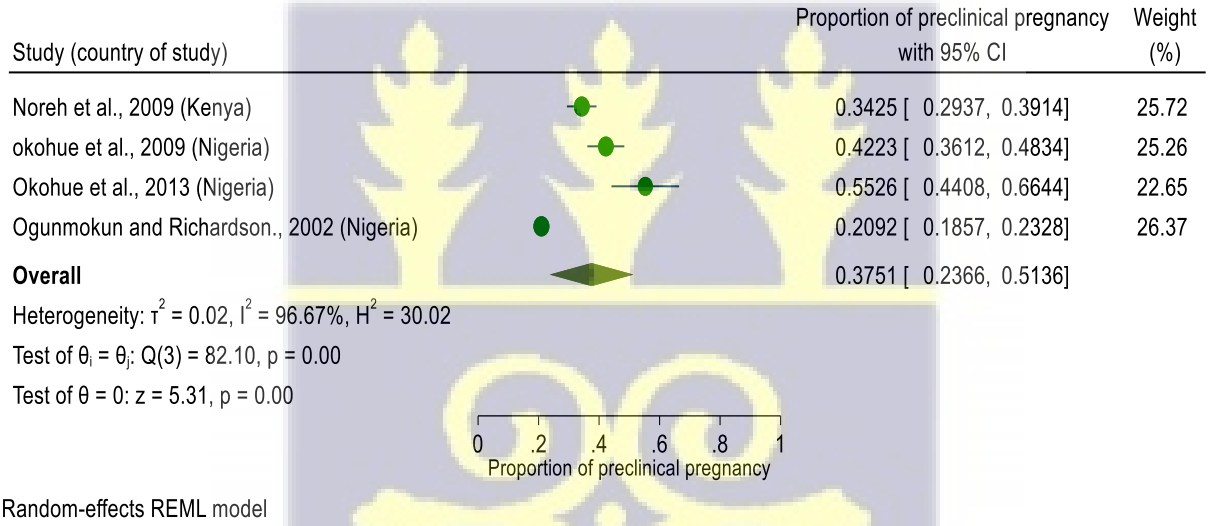

Figure 5: Forest plot of the preclinical pregnancy

4.4.2 Clinical pregnancy

Nine studies reported on clinical pregnancy rates or numbers. Four out of the nine studies did not contain figures that could be analysed due to very diverse categorizations. Five studies (Dyer & Kruger, 2012; Noreh et al., 2009; Ogunmokun & Ajayi, 2006; Okohue et al., 2013; Orhue et al., 2012), one from Kenya, one from South Africa and three from Nigeria provided data on clinical

pregnancy outcome among women seeking ART. The pooled prevalence estimates from the five studies showed a 27.5% (95% CI: 19.5% to 35.4%) clinical pregnancy among the women seeking ART. With Higgins I^2 value of 97.0% and a significance test from the Cochrane's Q statistic ($p < 0.0001$), there was heterogeneity in the estimates obtained from the five studies (Figure 6)

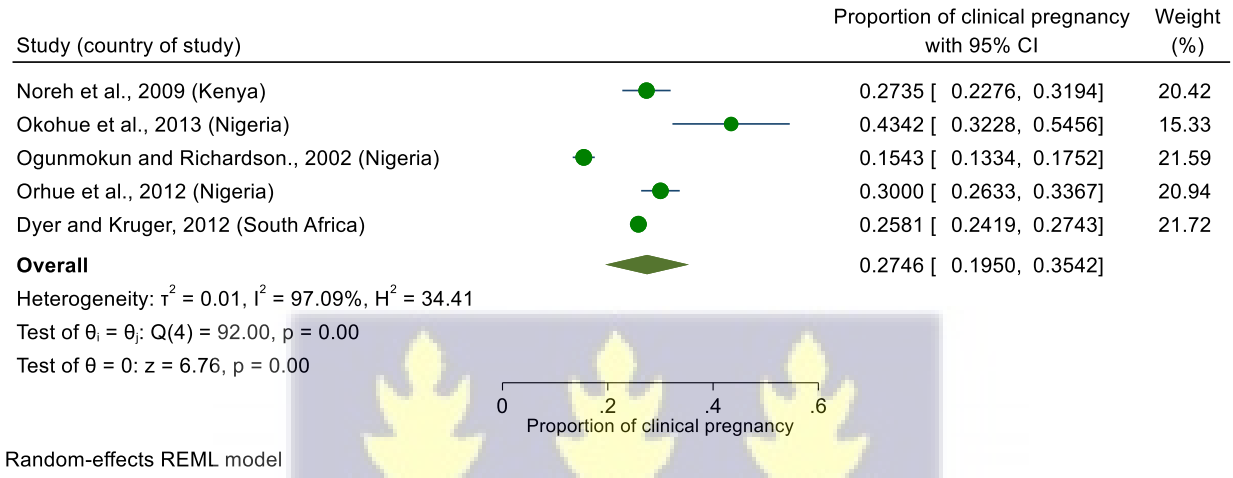

Figure 6: Forest plot of the proportion of clinical pregnancy

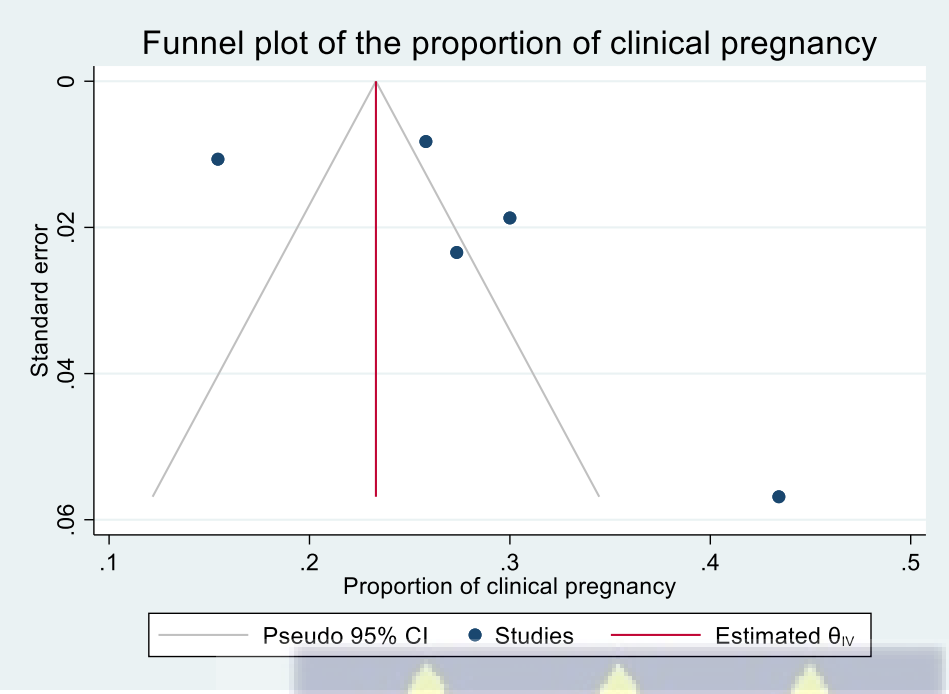

Figure 7: Funnel plot of the proportion of clinical pregnancy

4.4.3 Live births

Nine out of the ten studies identified the clinical pregnancy rate even though the majority of them did not have absolute figures to support a meta-analysis. Two studies (Noreh et al., 2009; Ogunmokun & Ajayi, 2006) from Kenya, and Nigeria provided data on livebirths outcome among women seeking ART. The pooled prevalence estimates from the two studies showed a 12.6% (95% CI: 10.3% to 14.9%) prevalence of livebirths outcome among the women seeking ART. With Higgins I^2 value of 31.5% and a non-significance test from the Cochrane's Q statistic (p=0.23), there was homogeneity from the two estimates (Figure 8).

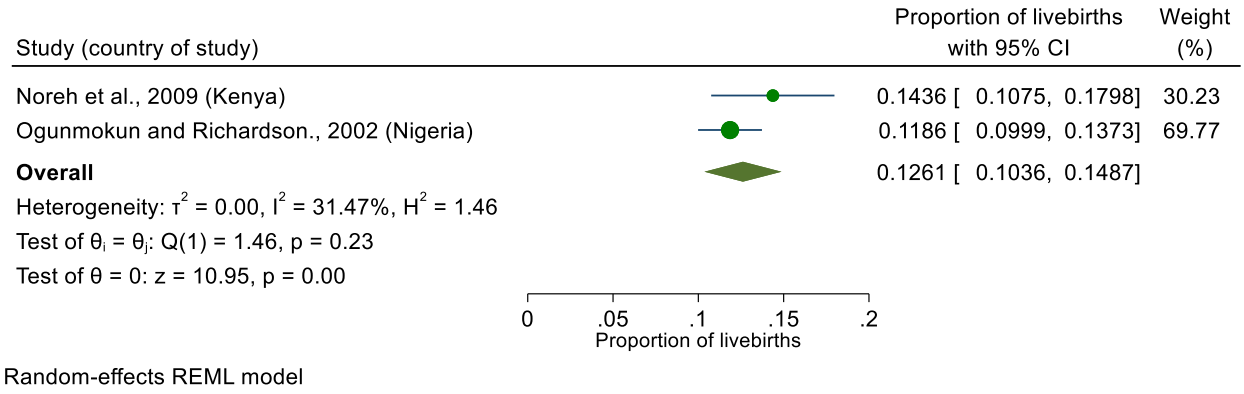

Figure 8: Forest plot of the proportion of livebirths

4.4.4 Multiple births

One other study mentioned multiple gestation but the finding was not incorporated in the analysis. Two studies from Kenya (Noreh et al., 2009; Orhue et al., 2012), and Nigeria provided data on multiple birth outcome among women seeking ART. The pooled prevalence estimates from the two studies showed a 6.5% (95% CI: 4.9% to 8.0%) prevalence of multiple birth outcome among the women seeking ART. With Higgins I^2 value of 0.07% and a non-significance test from the Cochrane's Q statistic (p=0.39), there was homogeneity from the two estimates (Figure 9)

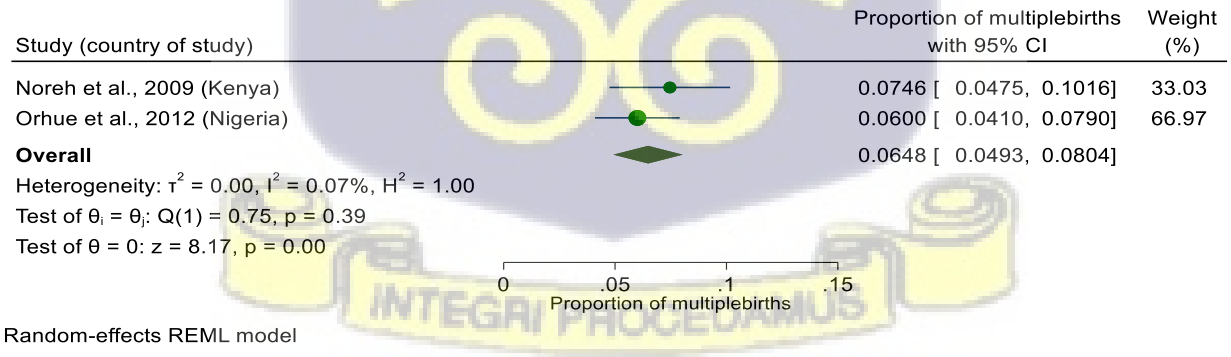

Figure 9: Forest plot of the proportion of multiple birth outcomes

4.5 ADVERSE OUTCOMES

4.5.1 Pregnancy loss

Five studies reported on pregnancy loss but one study (Noreh et al., 2009) did not provide absolute figures and could not be added to the analysis. Four studies (Ogunmokun & Ajayi, 2006; Okohue et al., 2009, 2013; Orhue et al., 2012), all from Nigeria provided data on pregnancy loss among women seeking ART. The pooled prevalence estimates from the five studies showed a 7.4% (95% CI: 6.3% to 8.5%) prevalence of pregnancy loss among the women seeking ART. With Higgins I^2 value of 0.03% and a non-significance test from the Cochrane's Q statistic (p=0.27), there was no heterogeneity from the four estimates (Figure 10).

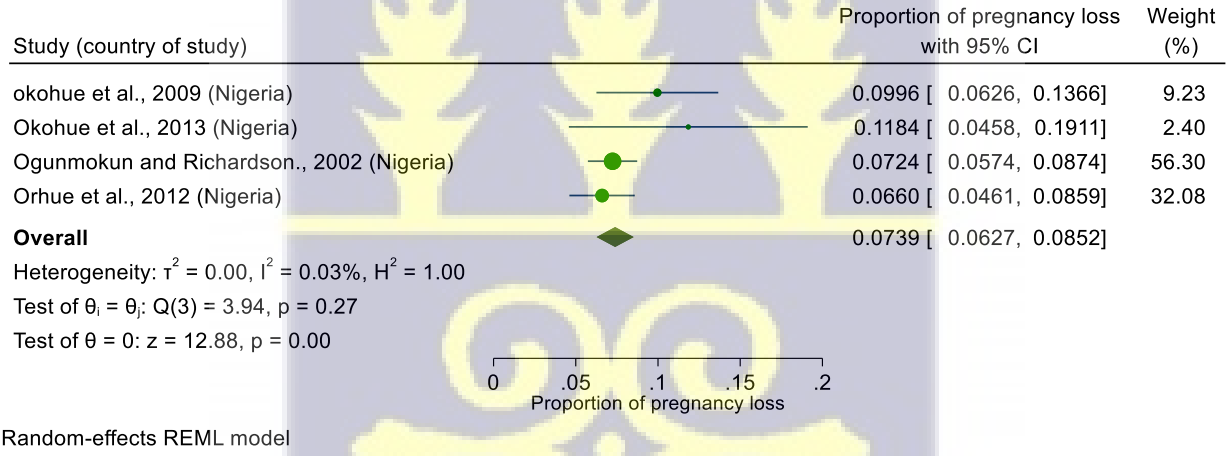

Figure 10: Forest plot of the proportion of pregnancy loss

4.5.2 ART complications

ART complications were recorded in 8 studies 4 of whom reported specific complications as percentages or across strata that were not comparable. Four studies (Noreh et al., 2009; Ogunmokun & Ajayi, 2006; Okohue et al., 2010, 2013), all from Nigeria provided data on complication of ART among women seeking ART. The pooled prevalence estimates from the four

studies showed a 7.4% (95% CI: 0.7% to 10.2%) prevalence of ART complications among the women seeking ART. With Higgins I^2 value of 92.7% and a significance test from the Cochrane's Q statistic ($p < 0.0001$), there was heterogeneity from the four estimates (Figure 11).

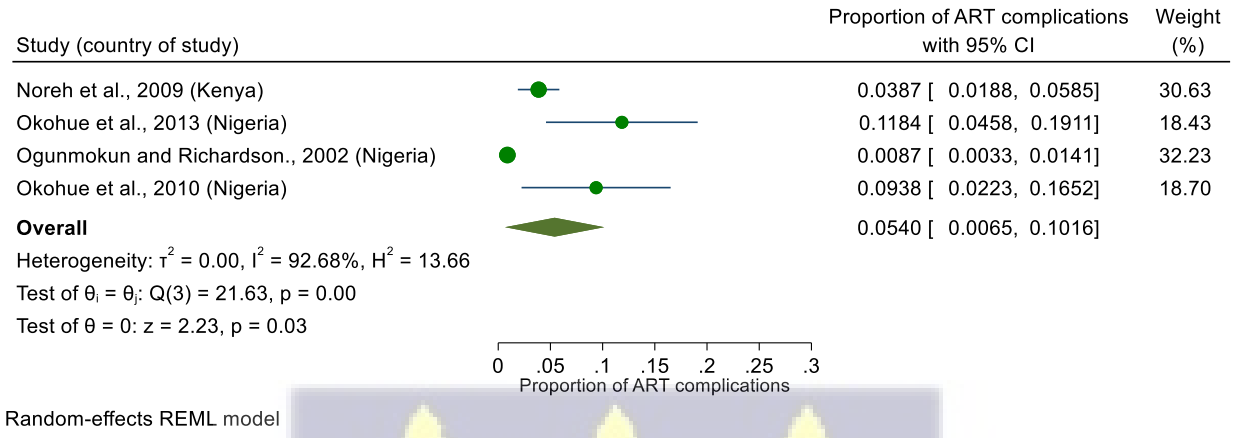

Figure 11: Forest plot of the proportion of ART complications

4.5.3 Stillbirth

A single study (Noreh et al., 2009) out of the 10 studies included in the current review reported on stillbirth as an outcome of ART. Out of 52 deliveries, three were reported to be stillbirths.

4.6 Fertilization rate

Three studies (Noreh et al., 2009; Okohue et al., 2013; Orhue et al., 2012) looked at the fertilization rates in each cycle of ART. This was in one study reported as an average rate, in another study as a total rate per each type of ART described and in the third study as the number /rate per cause of infertility. This made it challenging to compare fertilization across each group.

4.7 Other factors identified

Factors identified from the various studies under review were varied and could not be grouped for a proper comparison. One study cited the improvement in the ART process as a factor for better outcome. The number of embryos transferred was also reported in 6 studies and is pointed out as a factor affecting ART success. Four studies mentioned either the mean or total number of oocytes retrieved from each cycle. Another study looked at people's attitudes towards ART and their willingness to actually go through ART thus the factors that influence the decision to seek ART.

4.8 Quality of Evidence presented by studies included in this review

All studies included in this systematic review were observational studies. Though four of these studies reported rigorous and stringent methods and thus had low to moderate risk of bias, their general quality grade was low. Primarily, observational studies are less likely to incorporate measures that meet certain quality standards. Thus, despite the considerably low risk of bias detected in the included studies, their quality is only one level higher than the base quality (very low). This is because, the other three criteria for upgrading or downgrading the quality of evidence presented by observational studies (plausible confounding, dose-response effect and large effect) were lacking. This means that, the findings and conclusions of these studies may be different from what actually exists. For the lack of access to the full-text articles of three studies (Okohue et al., 2010; Olukoya et al., 2012 and Orhue et al., 2012), it was impossible to assess their overall quality using the GRADE approach.

CHAPTER FIVE

DISCUSSION

A systematic review is considered a critical form of amalgamating primary studies to come up with evidence-based conclusions that are meant to inform clinical practice. The current review showed that there is a deficit in the research into ART in SSA which must be improved upon. Ten studies were reviewed in the review.

Across four studies, both male and female causes of infertility were identified. In one study, female factors accounted for 58% of infertility with blocked tubes in the majority. Male factors accounted for 31.4% most of which was attributed to oligospermia. 9.8% of infertility remained unexplained. In another study, female causes of infertility accounted for 29.1% whiles male factors accounted for 66.9% with unexplained infertility accounting for 15.9%. The pooled prevalence estimates from these two studies showed a 41.6% (95% CI: 17.1% to 66.2%) female factor as a cause of infertility compared to 48.1% (95% CI: 11.2% to 84.9%) male factors which falls within the range of distribution of male infertility as reported by Agarwal et al (2015). The same study also showed that male infertility rates were highest in Africa and Central/eastern Europe. Significant heterogeneity was found among these two studies but subgroup analysis was not possible because there was no common variable with which the data could be stratified and this challenge was encountered across the other analyses.

The remaining two studies reported infertility as primary or secondary and PCOS or tubal factor respectively. Primary infertility was most prevalent which was an unusual finding as other studies (Mascarenhas et al., 2013) have reported secondary infertility as the most common cause of

infertility citing reasons of poorly treated reproductive tract infections as the main aetiological factors. This finding in the review could however be an indication of an improvement in health care as regards reproductive tract infections. However, with a finding of tubal factors as the most common factor of female infertility as earlier mentioned, it is curious that secondary infertility was not the most prevalent in the studies reviewed.

Nine out of the ten studies assessed ART availability in one way or the other. Overall, seven studies were conducted in Nigeria, one in Kenya, one in south Africa and the last one conducted using data across eighteen countries in Africa. IVF and ICSI were the most common types of ART used among these studies. Only one study out of the lot reviewed mentioned GIFT in addition to IVF. The studies ranged from years 2000 to 2020 and there has been a gradual increase in the number of ART cycles that have been carried out over the period. Admittedly, most of these studies were carried out in Nigeria and may not fully reflect the situation in SSA. One study gave a registry report on ART involving eighteen countries. Registry participation started with thirteen countries in 2013 and ended up with a total of eighteen countries in 2017 which further reiterates the point that ART practice in SSA has grown. Three out of the eighteen countries were Northern African countries and not all the centres gave yearly updates of all their activities. A total number of 153917 ART Cycles was reported cumulatively over the five-year period. The age of the patients was stratified and that was the basis for comparisons for the pregnancy outcomes over the years. Correcting for the three Northern African countries the total number of cycles per million population in 2013 ranged between 4.5 to 144.6. In 2017 the total number of cycles per million population ranged from 0.6 in Kenya to 193 in South Africa. The number of ART centres in the fifteen SSA countries range from 78 in 2013 to 126 in 2017.The participating centres in 2013 were 32 and by 2017 there were 40 participating centres in SSA. The figures also showed that the

number of ART cycles per year increased exponentially within the 5-year period. This is a clear indication of the increase in ART centres across the sub-region and by extension the availability of the service.

The factors reported in the included studies included; willingness of infertile couples to seek ART maternal age, type and cause of infertility, type of ART used, number of oocytes retrieved, average number of ART cycle as well as number of embryos transferred per cycle. The cost of ART was mentioned in most of the studies reviewed although specific values were not provided. The cost of ART has always been a challenge for a lot of couples and it even influences the number of embryos clinicians decide to transfer because they want to achieve pregnancy without laying undue financial burden on the couple. The cost associated with ART has been described as direct and indirect by Chambers, Adamson, & Eijkemans, (2013). Direct cost is explained as the cost associated with the ART process only while indirect cost involves any cost that is incurred from complications or other issues arising because of the ART process.

Two studies from Nigeria and Kenya evaluated endometrial thickness and the results showed that it was an important factor in achieving clinical pregnancy among those undergoing ART. For the study in Nigeria, among women undergoing IVF of similar ages there were higher pregnancy rates associated with endometrial thickness of 7 to 14mm. Among the same age group, no pregnancy was achieved whilst significantly lower clinical pregnancy rates were associated with endometrial thickness of more than 14mm. The Kenyan study reported an average endometrial thickness falling within 7 to 14mm associated with clinical pregnancy among women with PCOS and tubal factor infertility. Similar results were obtained when endometrial thickness was correlated in another study by Kasius et al., (2014). Endometrial thickness is associated with hormonal changes that

occur during the ovulation process. Therefore, the type of ovulation induction protocol used is of some importance. Among the 4 studies that reported on the method of ovulation induction used the standard long protocol of pituitary desensitization was used. The number of oocytes retrieved with this protocol was between 5.49 to 12.7. The clinical pregnancy rate has been showed to be improved when the ultra-long protocol was used for ovulation according to Li et al., (2008) in their meta-analysis.

Over the years there has been a constant debate concerning the number of embryos transferred per cycle among fertility specialist (Ezugwu & der Burg, 2015). More often than not multiple embryos are transferred with resultant higher order gestations. Globally efforts have been made to try and decrease the number of embryos transferred per cycle. Elective single embryo transfer has been employed in some parts of Europe for couples who have a good prognosis (Ezugwu & der Burg, 2015) and this is worth considering especially when the projected cost of catering for an extra child outweighs the cost of a repeat ART cycle. The studies reviewed had a mean of 2 to 5 embryos transferred per cycle. The average clinical pregnancy rates when the 2 studies were compared was 36.7%when 3 to 4 embryos were transferred. Studies have shown that double embryo transfers are associated with a higher live birth rate as compared to single embryo transfers. However, there is no significant difference between triple embryo transfers and double embryo transfer. This fact coupled with the high multiple pregnancy rates associated with increasing number of embryo transfer presupposes that a safe upper limit will be 2 embryos being transferred per cycle. According to Kissin et al., (2014) the highest chance of obtaining a good perinatal outcome among patients younger than 35 years is associated with a single embryo transfer.

One study evaluated the attitudes and willingness of infertile persons as regards the usage of ART and found that 52% of the study participants have negative attitudes towards ART. These participants were stratified by religion, ethnicity, marital status, level of education and occupation. Persons with primary infertility were more willing to try ART (45%) as compared to persons with secondary infertility (31%). For people to embrace an intervention like ART they have to be well informed about it so they can make sound decisions. the negative attitude towards ART that was reported in one study makes it clear that more education about ART has to be instituted. Across the various stratifications that were included in that study people with 55.5% had tertiary education, 50% were Muslims, 49% were Christians which indicates a diverse background of respondents. It also shows that despite the population having a greater portion being formally educated, there was still some misconception and deficiency in the depth of their knowledge about ART.

The outcome of every ART is to achieve clinical pregnancy and have a live birth. Between these two outcomes there are a number of events that can occur including early pregnancy loss/miscarriage, pre-mature birth with an increase in neonatal demise, stillbirth as well as early neonatal death post term delivery. There was not enough information to deduce the direct effect of the number of embryos transferred across the studies on pre-clinical pregnancy rate.

Four studies from two countries, provided data on preclinical pregnancy outcome among women seeking ART. The pooled prevalence estimates from the four study showed a 37.5% preclinical pregnancy rate among the women seeking ART. However, there was significant heterogeneity among the studies. From the data retrieved pre-clinical pregnancy rates were fairly higher when

fresh embryos were transferred compared to thawed frozen embryos which was contrary to the findings of Roque et al (2018).

The pooled prevalence of clinical pregnancy from five studies was 27.5% (95% CI: 19.5% to 35.4%) among the women seeking ART but there was significant heterogeneity.

Live birth is the ultimate measure of the success of an ART cycle. It is the desire of every pregnant woman to have a safe delivery to a live baby. 9 studies out of the 10 gave reports of the live birth. Two studies from Kenya, and Nigeria provided data on livebirths outcome among women seeking ART. 12.6% of clinical pregnancies from ART resulted in live births from the pooled prevalence estimates and there was low heterogeneity in the two studies. The average age of females who were involved in the studies ranged from 20 to 50yrs. Other studies outside the sub region recorded much higher live birth rates of 51% (Malizia et al., 2009) after IVF/ICSI among patient's 35 years or below. The disparity in the age ranges may have been the underlying cause of the vast difference in the live births identified.

Complications of ART are important outcomes that must be considered. Multiple pregnancy with the resultant increase in maternal and foetal complications are the most common complications encountered in ART. Studies in SSA have reported high numbers of preterm labour (41.6%), severe preeclampsia (33.3%), antepartum haemorrhage (8.3%), preterm prolonged rupture of membranes (8.3%) and active hepatitis (8.3%) among higher order gestations (Ezenwa et al., 2017). One study (Olukoya et al., 2012) did a case review series on multiple gestation as an outcome of IVF and twin gestation was the most common form followed by triplets. Quadruplets and quintuplets were not as common. In that same study the average number of embryos transferred per cycle was 5 which further highlights the need for specialists to be circumspect in

the number of embryos transferred and tailor their ART process towards the needs of specific patients instead of using a general approach. Two studies from Kenya, and Nigeria provided data on multiple birth outcome among women seeking ART (Noreh et al., 2009; Orhue et al., 2012). The pooled prevalence estimates from the two studies showed a 6.5% prevalence of multiple birth outcome among the women who were in the study with a confidence interval of 4.9 to 8.0%. Other studies outside SSA have reported multiple pregnancy rates as high as 34% in the United States, 24% in the United Kingdom and 10% in Australia and Europe (Chambers et al., 2013). Admittedly, there was not much information about number of embryos transferred which could be an important contributor the number of multiple gestations realised.

Another important complication that has been identified is extrauterine gestation. Ectopic pregnancy rate was reported in 4 studies and ranged from 0.6% to 7.8% with one case of heterotopic pregnancy. These values compare well with other studies (Perkins et al., 2015).

Adverse outcomes such as pregnancy loss/ miscarriages, intrauterine foetal death, still birth. There was a single study that mentioned stillbirth, intra uterine foetal death with corresponding values of 3 and 5% respectively. These proportions though look small have devastating effects on the couples that they affect. The pooled prevalence rate of pregnancy loss among ART candidates was 7.4% with a 95% confidence level. The average rate of pregnancy loss among women who undergo ART has been documented to be 26.3 % from other studies outside SSA (Bates & Ginsburg, 2002). Another study by compared clinical pregnancy loss in IVF to spontaneous pregnancies and reported the prevalence 14.3% and 25.8% and this was independent of the cause of infertility (Tamhankar et al., 2015). This depicts that there are higher rates of miscarriages in spontaneous pregnancies. However, this low pregnancy loss rates may be attributed to the scrutiny

that is attached to conceptions via ART by clinicians and even participants because of the "precious baby". There was limited data on these adverse outcomes as not all studies commented on them.

Strengths and Limitations of this review

The strengths of this study include the extensive attempts made to identify all relevant studies for screening against the eligibility criteria for inclusion. The search concepts and strategies used were both sensitive and specific in order to draw in peer reviewed articles, conference abstracts and grey literature. For a large part of the review and analysis process, two reviewers independently completed their assessments in order to reduce bias and subjectivity.

The review however had several limitations. One key limitation was the inability to perform some subgroup analyses and meta-regression which would have better depicted the association between the factors and the outcomes of ART. This was mainly as a result of the wide disparities in the methodologies as well as outcomes reported by the included studies. Three out of the total ten studies included in the review and analysis did not have full-texts available despite efforts to retrieve them. Data from these three studies were therefore disjunct, with several key details missing. This made it unfeasible in assessing the risk of bias and also grade the quality of the evidence presented.

CHAPTER SIX

CONCLUSION

This study has revealed that the outcome of ART is multifaceted and cuts across the infertile couple, maternal characteristics, the ART process itself, as well as the cost involved. In the current review, the common causes of infertility included chiefly, blocked tubes, anovulation and premature ovarian failure in females, and oligozoospermia, asthenozoospermia and tetratozoospermia among males. Also, significant proportions of infertility in the included studies were reported to have had unexplained causes. From studies that reported the type of assisted reproductive technique used, only IVF and ICSI were mentioned. Other known techniques such as ZIFT and GIFT were not used in any of the included studies. The studies that were included in this review did not report on the driving factors for participants' decision to seek ART or the choice of technique. However, some of the factors that were reported to be associated with ART outcomes included the number of embryos transferred, number of ART cycles, type of embryo transferred, endometrial thickness and pre-evaluation work-up.

RECOMMENDATIONS

Public health practice

Health professionals especially those with reproductive health units should actively provide education to patients and the general public on infertility at every opportunity. Health education should also be targeted at making the public aware of the fact that male-factor infertility is prominent and that there are also people with unexplained infertility. When this is adequately done, the primary and secondary causes of infertility will be reduced considerably thereby decreasing the number of people that will need interventions like ART.

Policy

Institutionalising assisted reproductive care will provide the required backing for reproductive health practitioners to extend their services to affected people and possibly lead to introduction of other advanced techniques with higher success rates. Also, policy-backed public education will lead to a decrease in the prevalence of preventable causes of infertility such as infection leading to tubal blockage among others.

Research

There is an obvious paucity of information on ART in SSA, as such, there is the need for extensive research targeting help-seeking behaviours for infertility, extent of ART use, outcomes and predictive factors. The evidence generated from such research would serve as the baseline for drafting and implementing policies and interventions targeted at solving the problems associated with ART.

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APPENDICES

APPENDIX I

Report of study protocol registration on the International Prospective Register of Systematic Reviews (PROSPERO)

Systematic review

To edit the record click *Start an update* below. This will create a new version of the record - the existing version will remain unchanged.

1. * Review title.

Give the title of the review in English

Factors influencing outcome of assisted reproductive technology in sub-Saharan Africa: systematic review and meta analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/10/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

04/10/2021

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed.
Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO.
If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Anthony Danso-Appiah

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Dr. Danso-Appiah

7. * Named contact email.

Give the electronic email address of the named contact.

tdappiah@yahoo.co.uk

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information, i.e. personal home address

Give the full institutional/organisational postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+447958721346

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Ghana

Organisation web address:
www.ug.edu.gh

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.
NOTE: email and country now MUST be entered for each person, unless you are amending a published record.

Dr Forzia Osman. University of Ghana
Dr Anthony Danso-Appiah. University of Ghana
Mr David Owiredu. University of Ghana

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)
State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

1. What types of assisted reproductive technologies are available in sub-Saharan Africa?
2. What are the factors that influence the decision to seek ART in SSA?
3. What factors influence the outcome of assisted reproductive technology in sub-Saharan Africa?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Relevant studies published in English or French on assisted reproductive technologies (ART) in sub-Saharan Africa will be identified through searching PubMed, EMBASE and LILAC published between 1st January, 2000 to 31st October 2020, without language restrictions. Other sources such as Google Scholar and African Journals Online, HINARI, ScienceDirect or relevant journals will be searched. All the 48 sub-Saharan African countries (World Bank records) will be included individually in the search strategy in addition to the key concepts. Reference list of retrieved studies will be manually searched and experts in the field will be contacted for additional studies.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible.

Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/208304_STRATEGY_20200910.pdf

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Infertility, an important aspect of reproductive health that is overlooked worldwide, is an increasing public health problem. Assisted reproductive technology is a treatment for infertility that involves the handling of eggs or embryos outside the human body in the laboratory setting. Though ART started in the early 1980s in Africa, there has been a lag in the development of data registries to monitor and report the utilization and outcome of the practice making in impossible to ascertain the scope, practice and outcome of ART. There is paucity of information which makes it difficult to have evidence-driven ART in SSA.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Women who live in sub-Saharan Africa (any of the 48 countries as defined by the World Bank) and have undergone at least one cycle of ART in a facility in SSA. Women who went through assisted reproductive technology but were surrogates will be excluded from the review. Women who had artificial insemination or ovulation induction alone without any form of assisted reproductive technology will be excluded.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

ART including in vitro fertilization, gamete intra fallopian transfer, zygote intra fallopian transfer, intracytoplasmic sperm transfer and the outcome of the treatment. Studies that reported on artificial insemination or ovulation induction alone without any form of assisted reproduction technology will be excluded.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

None.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

All studies including RCTs, cohort studies, case control and cross sectional studies that report on the outcome or availability of ART as well as on the causes of infertility for which women/couples seek ART treatment from 1 January 2000 to 31 October 2020. Completed studies as well as unpublished studies accessible electronically that fall within the stipulated period will also be included.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies conducted between1st January 2000 to 31st October 2020 in sub-Saharan Africa.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Clinical pregnancy (singleton/multiple gestation), progression of pregnancy to term, live birth

* Measures of effect

Dichotomous outcomes will be presented as relative risk or odds ratio and for continuous outcomes, mean difference will be used, all presented with their 95% confidence intervals (CIs).

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Pregnancy loss, still birth, maternal complications, foetal complications, low birth weight, foetal anomalies, early neonatal death.

* Measures of effect

Dichotomous outcomes will be presented as relative risk or odds ratio and for continuous outcomes, mean difference will be used, all presented with their 95% confidence intervals (CIs).

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Eligible papers will be assessed independently by two members of the research team. This will be achieved using a pre-tested assessment tool that incorporates the inclusion and exclusion criteria. The pre-defined selection criteria will be applied to all the studies that will be retrieved from the electronic database search to ensure that the process is unbiased and reliable. Studies that satisfy these conditions unanimously will be retained and included in the study. Any studies that generate conflict or disagreement will be solved by consensus or by a third assessor if the need arises. Information about the included studies will be collected onto a pre-tested data extraction form that will encompass certain key characteristics of the various studies including; the author(s) and publication details, the study design, sample size, type of ART used, number of ART cycles, ART outcome statistics (clinical pregnancy, miscarriage, live birth and stillbirth), maternal complications, infertility diagnosis, population characteristics- relevant sociodemographic data (parity, comorbidities , age and BMI).

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The standardized Cochrane guidelines available in Review Manager V5.4 (www.tech.cochrane.org/revman) will be used to assess risk of bias in each of the included studies in six domains: sequence generation, allocation concealment, blinding (investigators, outcome assessors and participants), incomplete outcome data, selective outcome reporting and other sources of bias (Higgins et al. 2011). For each domain, we will make a judgment of 'low risk' of bias, 'high risk' of bias or 'unclear' risk of bias. The Cochrane guidelines will be used in addition to the Risk of Bias Tool for Prevalence Studies developed by Hoy et al (2012). The risk of bias will be assessed for four domains: selection bias, non-response bias, measurement bias and bias related to data analysis. This shall be done independently by each of the two members of the team. Any discrepancy will be resolved through discussion between the two team members.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data.
If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

The data retrieved from the studies will be analysed using the statistical software STATA version 15.0. A meta-analysis will be done for the various types of observational studies that may be included in the review. Thus, cross sectional studies will be pooled together and analysed as such. The same approach will be used for, RCTs, cohort and case control studies. Standard deviations for the study-specific estimates will be calculated using the point estimate and the appropriate denominators, assuming a binominal distribution. Through a random-effects meta-analysis model, the ART outcome specific estimates from the various studies will be pooled to obtain an overall summary estimate of the prevalence/incidence, after stabilising the variance of individual studies using the Freeman-Tukey double arc-sine transformation. A meta-analysis will be performed to assess the association between factors that affect ART and ART outcome.

Heterogeneity will be evaluated by the χ^2 test on Cochran's Q statistic, which is quantified by I^2 values, assuming that I^2 values of 25%, 50% and 75%, represent low, medium and high heterogeneity respectively. Publication bias will be detected using funnel plots analysis and Egger's test. The results obtained will be presented by geographic region (central, eastern, northern, southern and western Africa). A 95% confidence level will be applied as the level of significance.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Where substantial heterogeneity is detected, a subgroup analysis will be performed to detect its possible sources using the following grouping variables: age group, sex, geographical area (central, eastern, northern, southern and western Africa) and study quality.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness No

Diagnostic	No
Epidemiologic	No
Individual patient data (IPD) meta-analysis	No
Intervention	No
Meta-analysis	Yes
Methodology	No
Narrative synthesis	No
Network meta-analysis	No
Pre-clinical	No
Prevention	No
Prognostic	No
Prospective meta-analysis (PMA)	No
Review of reviews	No
Service delivery	No
Synthesis of qualitative studies	No
Systematic review	Yes
Other	No

Health area of the review

Alcohol/substance misuse/abuse	No
Blood and immune system	No
Cancer	No
Cardiovascular	No
Care of the elderly	No
Child health	No
Complementary therapies	No
COVID-19	No
Crime and justice	No

Dental	No
Digestive system	No
Ear, nose and throat	No
Education	No
Endocrine and metabolic disorders	No
Eye disorders	No
General interest	No
Genetics	No
Health inequalities/health equity	No
Infections and infestations	No
International development	No
Mental health and behavioural conditions	No
Musculoskeletal	No
Neurological	No
Nursing	No
Obstetrics and gynaecology	Yes
Oral health	No
Palliative care	No
Perioperative care	No
Physiotherapy	No
Pregnancy and childbirth	Yes
Public health (including social determinants of health)	Yes
Rehabilitation	No
Respiratory disorders	No
Service delivery	No
Skin disorders	No
Social care	No

Surgery	No
Tropical Medicine	No
Urological	No
Wounds, injuries and accidents	No
Violence and abuse	No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

England
Ghana

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them.
If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

No I do not make this file publicly available until the review is complete

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Assisted reproductive technology; in vitro fertilization; intracytoplasmic sperm injections, fertilization in vitro, gamete intrafallopian transfer, clinical pregnancy; pregnancy loss; miscarriage; live birth; still birth; Sub-Saharan Africa.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.
New registrations must be ongoing.

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint.
List authors, title and journal details preferably in Vancouver format.

APPENDIX II

Risk of Bias Tool (Hoy et al., 2012)

Name of author(s):
Year of publication:
Study title:

Risk of bias items	Risk of bias levels	Points scored
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes** (**LOW RISK**): The study's target population was a close representation of the national population.	0
	No (**HIGH RISK**): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes** (**LOW RISK**): The sampling frame was a true or close representation of the target population.	0
	No (**HIGH RISK**): The sampling frame was NOT a true or close representation of the target population.	1
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes** (**LOW RISK**): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (**HIGH RISK**): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes** (**LOW RISK**): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (**HIGH RISK**): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes** (**LOW RISK**): All data were collected directly from the subjects.	0
	No (**HIGH RISK**): In some instances, data were collected from a proxy.	1
6.Was an acceptable case definition used in the study?	**Yes** (**LOW RISK**): An acceptable case definition was used. **No** (**HIGH RISK**): An acceptable case definition was NOT used	0 1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes** (**LOW RISK**): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (**HIGH RISK**): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes** (**LOW RISK**): The same mode of data collection was used for all subjects.	0
	No (**HIGH RISK**): The same mode of data collection was NOT used for all subjects.	1
9.Were the numerator(s) and denominato r(s) for the parameter of interest appropriate	**Yes** (**LOW RISK**): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (**HIGH RISK**): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

APPENDIX III

List of countries included by Dyer & Kruger, (2012)

Benin, Burkina Faso, Cameroon, Egypt, Ethiopia, Ghana, Ivory Coast, Kenya, Mali, Mauritius, Morocco, Nigeria, Senegal, South Africa, Togo, Tunisia, Uganda, Zimbabwe

List of included studies

(Noreh et al., 2009; Okohue et al., 2009, 2010, 2013)(S. Dyer et al., 2019b; S. J. Dyer & Kruger, 2012)(Akande et al., 2019; Ogunmokun & Ajayi, 2006; Orhue et al., 2012)(Olukoya et al., 2012)