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Fertility Treatments of Women in Nigeria: Using Long Versus Short Protocols

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Abstract

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Dissertation Submitted in Partial Fulfillment

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Abstract

A global estimate indicates that over 70 million heterosexual married couples live with the burden of infertility, and Nigeria accounts for about 30%. Although protocols exist, it appears there are no standardized treatment guidelines for practicing fertility experts in Nigeria. This study, therefore, aimed to determine which protocol provides a better outcome across a given population of infertile women in Nigeria as a method to move towards developing standardized treatment guidelines. The study was grounded using the Patient-Centered Care Treatment Model, and the method of inquiry was a retrospective, cross-sectional, quantitative, and nonexperimental technique, and the influence of the patient's socioeconomic status, age, education, ethnicity, medical condition on treatment outcome were examined. A 3-year secondary dataset of assisted reproductive technology was collected from 10 fertility centers covering the 6 geographical zones of Nigeria. A sample size of 605 women, aged 20 to 50 years, was used in this study. Descriptive and nonparametric, Wilcoxon rank-sum, Kruskal-Wallis, and Pearson's correlation tests statistical analysis were performed. The Wilcoxon rank-sum test showed a statistically significant difference between long protocol (Median 8) and short protocol (Median 4). Also, there were statistically significant differences between the number of oocytes and patients' characteristics such as; age, education, socioeconomic status, medical condition, ethnicity, and religion, at $p < 0.05$. The result demonstrated that long protocol was superior to the short protocol in terms of number and quality of oocytes yielded across the study population. The study findings serve as a guide for practicing fertility experts in Nigeria with the view to improve fertility treatment outcomes in women.

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Dedication

This research work is dedicated to Dr. Ibrahim Wada for his unbeatable contributions to assisted reproductive technology in Nigeria. Sir, you shared this knowledge liberally without prejudice, and have built capacity across the length and breadth of the Nation. God bless you for putting a smile on those couples you had assisted in getting pregnant when all hope was lost! Thank you for being selfless and open-handed.

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Chapter 1: Introduction to the Study

A full-term pregnancy is desired for many married couples worldwide. The presence of children binds families and marriages together in a certain culture, religion, and beliefs (Becker, Castrillo, Jackson, & Nashtigalle, 2016). In many African cultures, in particular, such beliefs are so strong that marriages that bear no fruit of a child, especially a male child, often withers without remedy, and such marriages are associated with polygamy (Okoroike, 2009).

Although 75% of married couples achieve pregnancy naturally within the first 6 months of living together, 90% of others accomplish the same feat within 12 months, and another 10% and even more cannot become pregnant naturally despite numerous attempts of unprotected sex (Merviel et al., 2015). This 10% of married couples who cannot conceive naturally after 12 months are referred to as an infertile couple (National Institute for Health and Clinical Excellence, 2006). Infertility is of two types: *primary* and *secondary* infertility. It is referred to as primary infertility when the woman has not experienced conception before, and it is secondary infertility when the woman has experienced repeated pregnancies without success of carrying the pregnancy to term or live birth (Consineau, 2007; Mascarenhas, Flaxman, Boerma, & Vanderpoel, 2012). Consineau (2007) reported that the most diagnosed type of infertility worldwide is secondary infertility.

The number of reported cases of infertility is increasingly high in both developed and developing countries, with the latter suffering more due to lack of modern technologies, treatment options, government policies, and adequate knowledge. This is compounded by the difficulty of accessing or procuring treatment because of location (Carter et al., 2011).

Infertility, as a condition, is now referred to as a severe public health issue of importance, as the burden has continued to increase worldwide (Mascarenhas et al., 2012). The World Health Organization reported that infertility affects 15% of women of reproductive age globally. Approximately 60 to 169 million heterosexual couples worldwide experience infertility related issues, which implies that one out of every 10 heterosexual couples suffers impotence (Ali, Ebraheem, & Mohamed, 2012; American Society for Reproductive Medicine [ASRM], 2015).

The impact of infertility varies by country and region or continent in the range of 5 to 30% (Mascarenhas et al., 2012). In the United States, about 8.3 million married women are experiencing infertility (Boivin, Bunting, Collins, & Nygren, 2007). This figure translates to 15% of married heterosexual couples having difficulty with achieving pregnancy (Resolve, 2013). The burden is higher in low-middle income countries, with more than 30% of heterosexual couples experiencing infertility issues (Ebomoyi & Adetoro 1990; Adetoro & Ebomoyi, 1999; Larsen, 2000).

Recent studies have debunked the misconception that the infertility burden exclusively affects women, showing that both sexes are significantly involved in infertility across nations and socio-economic status (Inhorn & Fakih, 2006). The cause of infertility issues stems equally from men and women; men account for 35% of cases seen, and women also account for 35% of cases, 20% is attributable to both male and female factors. Some other unexplained or idiopathic attributes account for

10% of cases seen worldwide (Mascarenhas et al., 2012). Some factors ranging from hormonal, lifestyle, medical, and structural are implicated in the cause or pathogenesis of infertility in men and women.

The diagnosis of infertility can be devastating in women because such a diagnosis may change her orientation about life and may even result in fear of losing her marriage or living without a child should there not be any solution or difficulty accessing any form of existing intervention (Boivin et al., 2007).

Modern approaches exist to address infertility in the form of advanced technology, such as pre genetic diagnosis and screening, intrauterine insemination, *in vitro* fertilization (IVF), and intracytoplasmatic injection, which have restored marriages and brought relief and completeness to couples worldwide (Lundborg, Plug, & Rastmussen, 2017; Okwelogu, Azuike, Ikechebelu, & Nnebue, 2012).

IVF is the most prominent approach or intervention for infertility treatment. Two treatment protocols exist for IVF: (a) short antagonist protocol and (b) long agonist protocol, and the course of treatment using either of these protocols is 2 to 4 weeks (Carter et al., 2011; Okwelogu et al., 2012). The procedure requires using hormonal medications for down-regulation, stimulating the ovaries, collecting matured follicles (ova) from the ovaries, mixing the egg and washed sperm cells (viable sperms) to fertilize and to form embryos and transferring embryo(s) into the uterus (American Society for Reproductive Technique, 2015; Lundborg et al., 2017). The nidation or early implantation of the fetus is the measure of a successful transfer of the embryo, which often determines the outcome of clinical pregnancy in the IVF procedure. This modern technology has restored homes and mended marriages on the verge of collapse, though it is challenging to procure and expensive where it is available (Carter et al., 2011).

The study focused on Nigerian women and how factors such as religion, cultural beliefs, geographical location, ethnicity, and educational level interplay with her decision to seek early help in the form of IVF treatment using agonist-antagonist protocols. The knowledge of the dynamics of these factors can help to influence government policies that can promote awareness, attitude, and behavioral practices of infertile women to seek early treatment intervention when diagnosed with infertility. Besides, the knowledge can help fertility physicians as to which treatment protocol to apply at any given situation.

Background of the Study

There is limited literature on the prevalence of infertility in low-middle income countries. A 1-year prevalence study on infertility in low-middle income countries in sub-Saharan Africa reported showing the variation in prevalence of infertility by countries from the range of 6.9% to as high as 50%; Gambia 9%, Ghana 11.8%, and Ethiopia 21.8%, and in Nigeria, the prevalence is 30 to 50% (Boivin et al., 2007; Sherrod, 2004). The significant regional differences in the prevalence as reported were due to variations in cultures, beliefs, SES, environmental influence, and ethnic diversity (Adetoro & Ebomoyi, 1999; Ebomoyi & Adetoro, 1990; Larsen, 2000). A search of the literature, however, revealed a dearth of information on fertility treatment and the determinants of help-seeking behavior of infertile women in Nigeria. Several studies have compared existing different ovarian stimulation protocols for IVF (Carter et al., 2011; Okwelogu et al., 2012), but there is no research yet on the Nigerian situation.

The two existing IVF treatment protocols that were comparatively studied are long agonist and short antagonist protocols using gonadotropin-releasing hormones (GnRH). According to Toftager et al. (2016), GnRH agonist protocol and GnRH antagonist protocol are similar in cumulative live birth rates, although more oocytes were collected in the agonist protocol. Toftager et al. recommended the enhancement of embryo culture, thawing and freezing approaches, and elective single embryo transfer.

Sudewo and Halim (2016) recommended the use of the antagonist protocol, which seems to be less of an adverse effect than agonist protocol in terms of the outcome of severe ovarian hyperstimulation syndrome (OHSS). However, both ovarian stimulation protocols have comparable efficacy in IVF outcomes (Sudewo & Halim, 2016).

Long agonist protocol instead of short antagonist protocol is recommended because it yields a better outcome of quality oocytes (Sudewo & Halim, 2016). The disadvantages of long agonist protocol are higher gonadotropin consumption and longer length of stimulation. However, the outcomes are comparable between all protocols (Dakhly, Bayoumi, & Gad Allah, 2016).

According to Dakhly et al. (2016), short antagonist protocol should be the recommended protocol for females less than 40 years, whether she is a poor or good responder to IVF treatment. A fixed gonadotrophin dose should be considered to prevent the risk of OHSS and other unexpected complications.

Toftager et al. (2016) conducted research that showed the rates of nidation and pregnancy per IVF cycle using long agonist and short antagonist protocol, as comparable in poor responders to stimulations in IVF. They recommended that the treatment of poor responders be re-evaluated regarding the likely contribution of age and the influence of lifestyle changes and other determinants of outcomes (Toftager et al, 2016). The reevaluation should also include consideration for bespoke ovarian stimulation, screening of blastocyst before the transfer, and consecutive IVF cycles (Ali et al., 2012).

A short antagonist protocol produces more top-quality embryos than the long agonist protocol (Aslih, Ellenbogen, Michaelis, Samara, & Shalom-Paz, 2015). According to Aslih et al. (2015), endometrial receptivity of embryos is regulated by the modulatory effect of estrogen (E2) and progesterone (P), and the ratio of progesterone and estrogen can be used to estimate the likelihood of pregnancy outcome.

Spremović-Radjenović et al. (2015) carried out a randomized controlled trial on a large scale to assess available IVF treatment protocols. They discovered that the available protocols for stimulating the ovaries are inadequate and still a challenge mainly because fecundity decreases with age, especially in women (Spremović-Radjenović et al., 2015).

Gizzo et al. (2014) reported that larger doses of progesterone are better than lower doses when considering high pregnancy rates. Gizzo et al. indicated that E2 supplementation is better in the case of short antagonist protocol and recommended this in every protocol when E2 reaches max < 5 nmol/l and endometrial thickness

< 10 mm. However, they explained the need for further investigation of the actual benefit of E2 supplementation, which remains debatable (Gizzo et al., 2014).

Short antagonist protocol is more suited for patients who respond poorly to stimulation. The long protocol does not favor these categories of patients. However, the long microdose protocol is comparable to the short antagonist protocol (Kdous, Elabed, Zhioua, & Zhioua, 2014).

Xiao, Chang, and Chen (2013) recommended long agonist protocol over antagonist protocol because the antagonist protocol produces fewer matured and quality follicles to decrease estrogen level and thin endometrium when compared with long agonist protocol. However, cycle cancellation and pregnancy outcomes were similar.

Problem Statement

The problem is that there is no standard infertility treatment protocol guideline for infertile women seeking intervention in Nigeria. The lack of this standard has led fertility experts in Nigeria to apply any treatment protocol to treat infertile women desiring conception, and there is little or no information on how patient characteristics influence the outcome of fertility treatment.

Generally, fertility treatment requires using hormonal medications to stimulate the ovary and generating matured follicles, harvesting eggs, and mixing the eggs in a specialized test tube with viable sperm cells for fertilization into embryos. These embryos are subsequently transferred back into the woman's uterus using a special catheter under an ultrasound machine. This procedure is referred to as IVF. More than 70 million married women worldwide are unable to conceive and are living with infertility; the majority of them reside in low-middle income countries (Boivin et al., 2007; Mascarenhas et al., 2012). Sub-Saharan Africa, especially Nigeria, South Asia, Middle East, and North Africa were reported to have the highest prevalence of infertility (Mascarenhas et al., 2012013).

The global negative impact of infertility is on the rise worldwide, and Nigeria is no exception, with a high infertility prevalence rate of 30.3% (Adetoro & Ebomoyi, 1991; Dattijo, Andreadis, Aminu, Umar, & Black, 2016; Ikechebelu et al., 2016). Given the value placed on having children and culture in Nigeria, women or couples without children as a result of infertility are bound to face social and psychological consequences, such as emotional stress, stigmatization, ostracism, economic loss, and mental stress (Consineau, 2007; Okoroike, 2009). According to Cousineau, 2007; Ikechebelu et al., 2016) report, couples facing infertility are at risk of sexually transmitted diseases, divorce, and marital instability.

However, there is a solution for infertility using advanced assisted reproductive technologies (ART; e.g., IVF). This technology has been in existence since 1970 and has helped couples to complete families (Altmäe, Hovatta, Salumets, & Stavreus-Ever, 2011; Shrestha, La, & Feng, 2015). In a report completed for the Human Fertilisation and Embryology Authority, Cheshire (2013) noted that the new IVF technology required to address this challenge is scantly available and expensive in Nigeria and other developing countries. IVF uses the principle of controlled ovarian hyperstimulation (COH) of the ovaries with GnRH. The use of GnRH defined the protocol as either long agonist or short antagonist protocol (Altmäe et al., 2011). Several modifications to COH protocols have also evolved to date (Orvieto, 2015;

Toftager et al., 2016). These protocols are assessed based on the number of matured follicles generated, which directly correlates with successful conception rates and adverse events (e.g., OHSS) following COH stimulation in patients receiving IVF treatment (Hohmann, Macklon, & Fauser, 2003).

Specific reasons for using or adopting a COH protocol may range from patient's poor ovarian response (Okoroike, 2009; Venetis, 2014), age, disease conditions (e.g., polycystic ovary syndrome), SES, treatment duration, previous IVF treatment, cost of IVF, knowledge of protocols, treatment outcome, and safety consideration (Al-Inany & Aboulghar, 2002; Bosch et al., 2010; Murber, Fancsovits, Ledó, Gilán, & Urbancsek, 2009; Orvieto et al., 2009; Oudendijk, Yarde, Eijkemans, Broekmans, & Broer, 2012).

According to Lai et al. (2013), the exact impact of these protocols on treatment outcomes has not been established and has remained controversial. Merviel et al. (2015) argued that no clear guideline currently exists for the COH treatment protocol in IVF despite several studies comparing COH treatment protocols.

In Nigeria, the experience may differ, as no researcher has looked at which of these COH treatment protocols is better regarding treatment outcomes following the IVF procedure and the determinants of these outcomes. Besides, seeking treatment behavior is determined by patient characteristics, such as beliefs, gender, education, ethnicity, and SES, and no study has yet addressed the impact of these factors vis-à-vis treatment-seeking behavior and treatment outcome.

Hence, there is a need to study the relationships between these variables to determine which treatment protocol is most suitable and cost-effective to adopt for

Nigeria and other developing countries. Similarly, it is expected that such a protocol can positively influence the development of an interventional program that can reverse the negative experience of infertile women or couples in Nigeria.

Purpose of the Study

This study aimed at establishing the IVF treatment protocol that is most suitable for the majority of infertile women in Nigeria. Patient characteristics, age, medical conditions (e.g., PCOS), SES, education, ethnicity, and other factors such as duration of treatment and safety consideration were also examined. Secondary data from 10 existing fertility treatment centers in five states across Nigeria, where IVF services are being offered (i.e., Abuja, Port Harcourt, Enugu, Jos, and Lagos) were used. These five states cover Nigeria's capital city, South-South, South-East, North-Central, and South-West, respectively. This study examined the outcome between long agonist and short antagonist treatment protocols used in these centers.

Research Questions

The research questions for this study were as follows:

Research Question RQ1: What is the relationship between types of fertility treatment protocol and treatment outcome?

$H_0$1: There is no significant difference in the relationship between fertility treatment protocol and treatment outcome.

$H_1$1: There is a significant difference in the relationship between fertility treatment protocol and treatment outcome.

RQ2: Do patient characteristics (age, education, SES, medical condition, ethnicity, religion) influence the outcome of fertility treatment protocol?

$H_0$2: Patient characteristics have no significant influence on the outcome of the fertility treatment protocol.

$H_1$2: Patient characteristics have a significant influence on the outcome of the fertility treatment protocol.

Conceptual Framework

A theoretical or conceptual framework is composed of specific constructs, concepts, and propositions that guide and provide direction on the expectation of research (Fawcett & Garity, 2009; Glanz, 2002). The theoretical foundation for this research was grounded by the patient-centered care treatment model (PCCTM).

According to the Institute of Medicine (2001), PCCTM is an intervention that supports, respects, and responds to patients’ characteristics, needs, and values at all levels of treatment decisions given the expected outcome. This conceptual model was developed by healthcare professionals in the 1980s and has been widely applied to examine treatment protocols and algorithms of disease intervention (Danga, 2018). This model has gained popularity in understanding fertility treatment and outcomes (Duthie et al., 2017). In 2014, Duncan et al. used PCCTM for infertility treatment to explain the dimensions of fertility treatment, outcome (effectiveness and potential risk), financial cost, and patient characteristics.

The concept of effectiveness in this model is defined as the probability that any chosen treatment protocol will yield the expected positive outcome when applied across the population of infertile women seeking fertility treatment. The inherent risk in this model explains the possibility of adverse events that may result from treatment (e.g., OHSS). The financial cost of treatment in this model explains the effect of financial cost on treatment protocol and prices for different options, and patient characteristics stressed the impact on age, education, ethnicity, medical condition, SES.

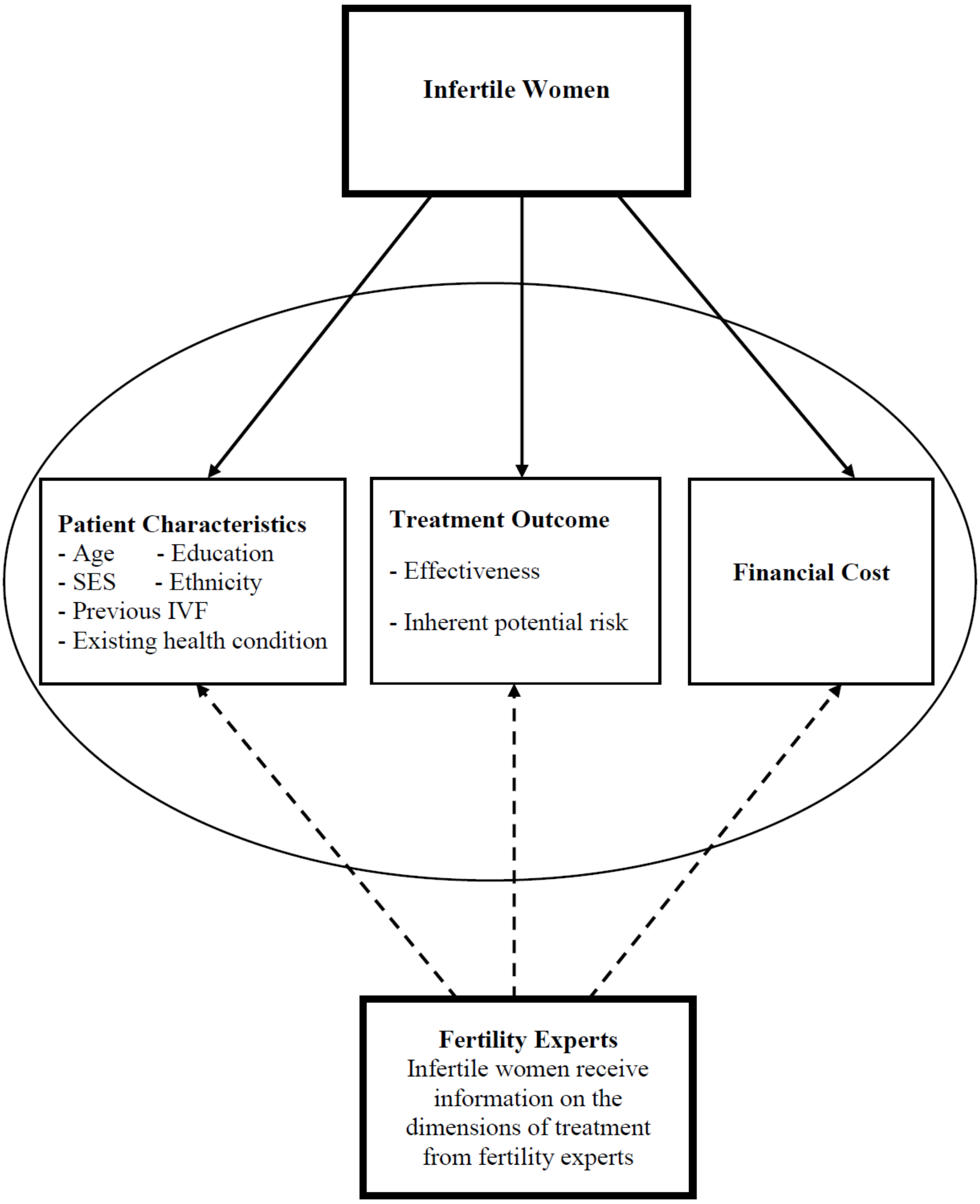

Figure 1. The conceptual framework for patient-centered fertility treatment

Definition of Key Terms

Antimullerian hormone: An inhibitory glycoprotein hormone that plays a significant role in folliculogenesis.

Assisted reproductive technique: The technique or procedure, such as in-vitro fertilization, intrauterine insemination, and surrogacy, used for fertility treatment to achieve pregnancy outcome.

Control ovarian hyperstimulation: A process used in ART to stimulate the ovarian follicles in a fashionable manner using hormonal medications to generate multiple follicles for the induction of ovulation.

Follicle-stimulating hormone: A natural hormone that is produced by the cells of the anterior lobe of the pituitary gland; it promotes the development of ova in women and sperm in men.

In vitro fertilization: The process of stimulating the ovary with hormonal medication to grow ovarian follicles to maturity, harvesting the eggs, and inseminating it with viable sperm cells in a cultured tissue dish to fertilize, and then transferring the generated embryo(s) into the uterus.

Luteinizing hormone: A gonadotrophic hormone of the anterior pituitary lobe that triggers ovulation at its peak level in females and facilitates the development of corpus luteum. In a male, it helps to promote testosterone by stimulating Leydig cells.

Ovarian hyperstimulation syndrome: A drug-induced condition that may result during ART following stimulation of the ovary with exogenous hormonal medication. Most of the time, the situation is mild but could be severe.

Polycystic ovarian syndrome: A combination of symptoms that result from elevated male androgen hormones in women.

Socioeconomic status: This is a measure of a person's, family's, income, education, occupational, work experience, and social position in a society using economic and sociological indices.

Assumptions

Several assumptions were made for this study. Given the nature of this study, it was assumed that all the fertility hospitals used for this study met standards of the hospital accreditation committee of the state or federal government of Nigeria and were licensed to render fertility treatment. It was also assumed that the facilities that offer such treatments were ISO-9001:2015 certified by the Standard Organization of Nigeria. The Association of Fertility and Reproductive Health of Nigeria is a registered professional organization recognized by law to regulate the practice of fertility professionals in Nigeria. Hence, all stakeholders in the fertility facilities used for this study were registered members of the Association of Fertility and Reproductive Health of Nigeria.

Likewise, it was assumed that the infertile women who were treated in these hospitals were appropriately diagnosed using all the diagnostic tools and fertility scores before embarking on treatment. Additionally, the language of communication between the women and doctors was English.

Scope and Delimitations

The data of all ART procedures conducted between 2015 and 2017 in the entire 10 fertility treatment centers across the five states in Nigeria were collected.

Only women aged 20 to 50 years were considered because the median reported age that is safe for most infertile women seeking help is 23 years (Frankfort-Nachmias & Nachmias, 2008). Such eligible women were diagnosed as infertile by a qualified medical doctor considering all the parameters from her history, complaints, physical examination, ultrasound scan, and laboratory results (FSH, LH, prolactin, AMH, progesterone, estrogen). Only women who had successful egg collection were considered. The educational level, SES, and sociodemographics of all qualified women who had IVF procedures up until the point of egg collection are discussed and examined. Two treatment protocols were considered in this study, long and short protocol, and the measure of successful treatment outcome was the number of eggs collected.

All women who had attended the named fertility clinics without full evaluation were excluded from this study. Similarly, women who had started treatment after evaluation but had canceled procedures along the line, as well as egg recipient cycles, were also exempted from this study.

Limitations

Limitations were anticipated. First and foremost was that the research work required moving around the six geographic zones of Nigeria and visiting a total of 15 fertility centers. Only 10 centers were successfully visited because of poor logistical systems and infrastructure in some states or geographic zone. Secondly, the study required the use of secondary data of infertile couples who had accessed treatment in those fertility centers. The implication is that some relevant information was not captured in an organized pattern. Thirdly, some of these fertility centers were handled by medical officers who lacked adequate skills in IVF procedure; the effect was on the quality of the decision as to which treatment protocol could best suit a case of infertility.

Significance of the Study

The educational and SES of residents of these five states were classified into high, middle, and lower, with the high class comprising of professionals (i.e., doctors, lawyers, engineers, and accountants), politicians, and nurses. The middle class included bankers, teachers, journalists, and entrepreneurs, while lower-class referred to the skilled (e.g., technicians, mechanics, carpenters), semiskilled, and unskilled workers, and petty traders. In Nigeria, like most other countries of the developing world, the class determines the income, but the city of residence also affects the SES (e.g., the cost of living is believed to be generally higher in Port-Harcourt, an oil-rich state, than Kebbi state, an agrarian state). These factors played a role in residents seeking fertility treatment and outcomes. The second part of this study was the stimulation protocols used in IVF treatment. Although several scholarly reports compared the results of various stimulation protocols in IVF treatment, none of these reports looked at Africa’s most populous nation, Nigeria, and a literature search of “early online’’ articles revealed no such pending reports. This study was the first in this area in Nigeria that has attempted to solve this puzzle.

Moreover, there was a need to conduct an audit of the treatment outcome(s) of stimulation protocols, whereby fertility specialists are informed of the effectiveness of protocols employed and infertility conditions treated. The result of this study revealed the required information, which is nonexistent in Nigeria.

The Implications for Social Change

The positive social change of this study is that the research findings can serve as a guide for practicing fertility specialists or intending specialists within or outside Nigeria. The evidence-based rationale has been provided to initiate treatment on an individual patient basis and the implications of deciding which treatment protocol befits each who presents at the fertility clinic. Likewise, findings have provided the foundation to apply a particular protocol across a defined population with an understanding of treatment outcomes of the two protocols.

Summary

Pregnancy is the desired expectation of many married couples, especially in Africa, where children are cherished and valued (Okoroike, 2009). In some cultures in Africa, an infertile woman is not given her due respect and entitlements in marriage if she has not given birth to a male child. In these situations, her marriage is threatened by her husband taking another wife, or she may face divorce. Infertility is when heterosexual couples living together and have regular unprotected sex for 1 year but fail to achieve a natural pregnancy.

Infertile women or couples who experience infertility require help after the diagnosis to become pregnant. The diagnosis could either be primary infertility or secondary infertility. The former is when the woman has not given birth before, and secondary infertility is when a woman had given birth previously and failed subsequently to become pregnant again. Secondary infertility is the most commonly diagnosed type of infertility experienced by most infertile women (National Institute for Health and Clinical Excellence, 2004).

Infertility issues are recognized as an essential public health issue, with over 70 million heterosexual married couples living with this condition worldwide (Dattijo et al., 2016; Ikechebelu et al., 2016). The majority of these couples live in African countries, of which Nigeria is one. The high number of infertile women on the African continent has been attributed to differences in lifestyle, culture, beliefs, and poverty, among others. Based on the available data, the prevalence of infertility varies by regions; sub-Saharan Africa ranges from 9% in the Gambia to 11.8% in Ghana and 21% in Ethiopia, and as high as 20% to 30% in Nigeria (Boivin et al., 2007; Ebomoyi & Adetoro, 1999).

The high number of infertile women in Nigeria is very alarming, despite the limited data. It is a general belief by most infertile couples in Nigeria that access to IVF is very prohibitive and is for the rich. This may not be entirely true, as several factors interplay to influence the help-seeking behavior of infertile women. Consequently, there was a need to assess these factors and available treatment protocols accurately.

Chapter 2: Literature Review

There is a dearth of information on infertility treatment and factors that influence fertility treatment outcomes in Nigeria. Therefore, this study was designed to answer questions regarding infertility treatment and the behavior of infertile women towards early treatment in Nigeria. The overall aim of this study was to assess the factors affecting treatment outcomes and the choice of IVF treatment protocol by the provider. The results of this study provide the basis for designing an intervention that influences the choice of protocol for fertility treatment in Nigeria.

The relevant literature on infertility in Nigeria are reviewed in this chapter. Also reviewed is the research on causative factors, treatment protocols, nondrug treatment of infertility, barriers to treatment-seeking behavior of women with infertility, as well as the current trend in infertility treatment. There are nine sections in this chapter, which ends with a summary.

Literature Search Strategy

There are few research articles on some aspects of the study, especially recent publications and those spanning the past 10 to 20 years. I found a few articles using Walden Library as my primary source of peer-reviewed articles, scholarly publications, dissertations, and electronic databases; ProQuest and PubMed were the major electronic databases used for the literature search. Fertility-related publications were identified with keywords such as *infertility, infertility treatment protocols, determinants of infertility treatment, help-seeking behavior,* and *Nigeria*.

Global Studies and Sub-Saharan Africa, Nigeria

Infertility, as a health challenge, initially receives little or no attention in some societies of the world because of cultural beliefs and religious practices (Van Belen & Inhorn, 2002). Research in this area was limited as a result of the lack of data and the failure of those affected to declare infertility status (Adegbola, 2013). Infertility is not seen as a contagious disease or illness that affects the population but only individuals (Van Balen & Inhorn, 2002). The issues of nondisclosure and religious and cultural beliefs leading to a high prevalence of infertility were reported to be strongly associated with the developing non-Western countries, especially in sub-Saharan Africa.

Infertility is an issue in all the countries of the world. One in every 10 couples suffers infertility-related issues caused by either the male or female factor globally (Adegbola, 2013). This reported statistic may be more because of under disclosure due to fear of stigmatization and failure to seek help (Van Balen, 2002).

Hammerli, Znoj, and Barth (2009) noted that the prevalence rate of infertility in the United States was 11 to 18%, while that of Africa was as high as 30%. This finding implies that the problem of infertility is high in sub-Saharan Africa. Carter et al. (2011) and Hammerli et al. (2009) reported that infertile women are prone to anxiety, depression, and stress that could result in other illnesses if not properly treated. Therefore, infertility is a public health problem that needs to be addressed in every society. The prevalence of infertility can be reduced through an all-inclusive educational program that increases awareness and strengthens attitudinal and behavioral changes towards infertility treatment (Ali et al., 2012)

Two types of infertility exist, namely, primary and secondary infertility. Primary infertility is the nonachievement of conception by the couple that has resulted in a live birth, while secondary infertility occurs when couples find it difficult to achieve conception after a previous live birth or any difficulty with achieving term pregnancy (Schmidts & Munster, 1995).

The length of infertility varies irrespective of the type. Conkling (2003) reported that the probability of heterosexual couples living under the same roof, having regular unprotected sex, and becoming pregnant within 1 month is between 20 to 30%. Sixty to 75% of these couples will become pregnant by the sixth month, and 75 to 90% will be pregnant by 12 to 18 months (Conkling, 2003). About 40 to 60% will become pregnant in the second year of trying (Dunson, Baird, & Columbo, 2004).

The duration of infertility is a critical prognostic factor providing information on the severity of the condition and the level of intervention that may be required (Smith, Pfeifer, & Collins, 2003). The longer the length of infertility experienced by a couple, the less likely it is to have a positive outcome following the intervention. Those with less than 3 years of infertility have a better chance to conceive than those living with this condition for 3 years and more (Smith et al., 2003). Sixty percent of couples with secondary infertility achieve pregnancy within 3 years of waiting compared to 40% with primary infertility who will wait likewise to achieve the same feat (White, McQuillan, & Greil, 2006).

Causative Factors in Infertility

There are known and unknown causes of infertility in men and women worldwide. About 35 to 40% is attributed to female-related causes, and a similar proportion is also due to male-related causes (Conkling, 2003). The remaining 20 to 30% are due to idiopathic, primary, or unknown causes (Conkling, 2003). The female known causative factors are old age; poor egg quality; hormonal imbalance; reduced ovarian reserve; blocked tubes; uterine fibroids; history of uterine surgeries like cesarean sections, myomectomy, and salpingectomy; repeated miscarriages; pelvic inflammatory disease; postpartum infection; abortion; sexually transmitted diseases; and other surgeries like appendectomies and cystectomy (Klein & Sauer, 2001). Male infertility is a function of sperm quality and quantity regarding count, motility, and morphology (American Society of Reproductive Medicine, 2015a; Debrovner & Debrovner, 2002; Klein & Sauer, 2001).

Unexplained infertility occurs when couples still experience difficulty in achieving pregnancy despite standard laboratory and clinical findings. These can include normal FSH, LH, AMH, and prolactin levels, patent fallopian tubes, healthy endometrium, regular ovulation, and good quality semen (Speroff, Glass, & Kase, 1999).

Age

The ability to get pregnant declines as age increases. This relationship between age and fertility is more pronounced in females. Age is the most influential and most common causative factor in female infertility. One in seven couples aged 35 years suffer infertility (Faitt-Weller, 2001). This rate rises to 1 in 5 among couples aged 40 and above (Faitt-Weller, 2001). Older females have more difficulty trying to conceive, and they are more likely to have recurrent miscarriages, stillbirths, underweight babies, preterm babies, babies with genetic disorders like Down syndrome, and placental complications (Adegbola, 2013; Kelly-Weeder & O'Connor, 2006). More than 50% of older women have miscarriages (Kelly-Weeder & O'Connor, 2006). Age is a known and consistent factor in female infertility worldwide (ASRM, 2006). Males are also affected by age-related infertility caused by hormonal imbalances, sperm conducting system blockages, varicocele, erectile dysfunction, loss of coital power, and poor sperm quality as they age above 40 years (ASRM, 2006; Clavey, 2003; Rochebrochard & Thonneau, 2003).

Lifestyle

Certain social, behavioral practices or lifestyles are the reason for infertility in both men and women. These practices or lifestyles include smoking and excessive intake of alcohol, which negatively impact the overall sperm quality, count, morphology, and motility in males (Macaluso et al., 2010). According to Akhter and Jebunnaher (2012) as well as Kelly-Weeder and O'Connors (2006), obesity is associated with higher levels of estrogen, which has a contraceptive effect, resulting in miscarriages, menstrual disorders, anovulation, and poor pregnancy outcome. On the other hand, underweight is also associated with reduced estrogen, leading to irregular menstrual cycles (Akhter & Jebunnaher, 2012). Women who are obese with body mass index (BMI) of higher than 25 kg/m^2 experience infertility twice as long to achieve pregnancy than those with healthy BMI (Hassan & Killick, 2005).

Stress, environmental toxins, substance abuse, and insomnia also contribute to infertility (Glenville, 2000). The use of some types of vaginal lubricants has a lethal effect on sperm cells and sperm motility, thereby reducing the chances of conception (Kutteh, Chao, Ritter, & Byrd, 1996). The lack of knowledge on when is the most fertile period for couples to time intercourse is also a factor in infertility (Bowers, 2003; Devine, 2003; Neumann, 2003).

Women who consume up to 7 grams or more of caffeine monthly are less likely to become pregnant than women who do not (Hakim, Gray & Zacur, 1998). Increased caffeine consumption raises the risk of endometriosis and tubal problems, which are associated with infertility (Neumann, 2003).

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is a common type of infection in women generally. PID is defined as the inflammatory disease of the pelvic organs due to infection. Sexually transmitted diseases account for 70% of PID cases (Adegbola, 2013). This infection goes unnoticed in some women until such a time when it has caused harm to the pelvic organs, leading to infertility (Adegbola, 2013). This type of infertility is often considered as unexplained infertility.

Chlamydia and Neisseria gonorrhea infections are transmissible through sex, and these infections often lead to PID. Any untreated infection can always develop into PID in women if not adequately treated (Kelley-Weeder & O’Connor, 2006). The CDC (2013) reported that over 1 million women in the United States are diagnosed with PID annually, out of which more than 100,000 end up with infertility issues.

Several studies have shown the association between infertility in women and the history of sexually transmitted diseases (STD) and PID. The number of diagnosed STDs is on the increase annually (Macaluso et al., 2010). Many of these STDs show no symptoms in some women until such a time that complications start to manifest. Black women are eight times more at risk of contracting infections involving chlamydia and gonorrhea, leading to STDs than White women. STDs can lead to tubal scarring and intramural tubal infection-causing infertility (Kelley-Weeder & O'Connor, 2006; Macaluso et al., 2010).

Culture

Culture is the way of life of people. There are cultural differences between different ethnicities across the world. Some cultural practices affect infertility in both sexes, especially when it borders on childbearing (Brown, 2001; Rochebrochard & Thonneau, 2003). For instance, it is normal for couples to agree to postpone childbearing for years after marriage for no significant reason in Western cultures (e.g., the United Kingdom, Canada, and the United States), but this arrangement is almost not acceptable in Africa, especially in Nigeria where delayed pregnancy is undesirable (Adegbola, 2013; Rochebrochard & Thonneau, 2003).

Socioeconomic and Sociodemographic Factors in Infertility

The number of infertile women is increasing rapidly. The 2002 National Survey of Family Growth (as cited in Chandra, Martinez, Mosher, Abma, & Jones, 2005) pointed out that the prevalence of infertility among African American women is 10.4%, 6.4% in White women, and 7% in Hispanic women in the United States.

Educational level is associated with infertility in women. Women with lower educational levels were reported to be less fertile than those with higher degrees (ASRM, 2016). Chinese women also were reported to significantly access fertility treatment services due to their high educational level and income (Jain, 2006).

Access to infertility treatment is expensive worldwide, and most health maintenance organizations and insurance companies do not cover for it. Hence, out-of-pocket treatment is often an alternative considered by those needing treatment. In the US, those who are highly educated and wealthy White infertile women are more likely to have access to fertility treatment than African American Women (Jain, 2006).

Infertility Treatment

Klein and Sauer (2001) defined infertility treatment as an intervention strategy that helps infertile women to achieve pregnancy through assisted reproductive technology. The options for fertility treatment include treating all identifiable conditions in the couple that could inhibit conception, such as treating poor sperm quality, treating infection, surgical removal of blockages in fallopian tubes, myomectomy, correcting hormonal imbalance, enhancing cervical mucus, and utilizing treatment approaches like timed intercourse, intrauterine insemination, in-vitro fertilization, and more modern ART called intracytoplasmic sperm injection (Simonsen, Baksh, & Stanford, 2012).

Timed intercourse is a non-invasive approach that requires the use of medicines such as clomiphene or letrozole to stimulate the ovaries to maturity indirectly and, after that, induce ovulation with human chorionic gonadotrophins.

Timed intercourse happens within 36 hours post-induction of ovulation. This approach is considered for infertile women with an anovulatory problem.

Intrauterine insemination is also a non-invasive treatment approach that is targeted at washing the sperm cells to improve on their motility and count in a man with poor and low sperm quality and stimulating the ovaries of a woman with human menopausal gonadotropin or follicle-stimulating drugs, followed with the induction of ovulation using human chorionic gonadotrophin. This type of treatment is beneficial for women with cervical mucus problems, as it bypasses the cervix with a special catheter to deliver specially prepared sperm into the body of the uterus (Strauss & Barbieri, 2009). This treatment option is not considered for women with blocked fallopian tubes!

In-vitro fertilization is a minimally invasive procedure that requires stimulation of the ovaries with exogenous human menopausal gonadotropin (HMG) or follicle-stimulating hormone (FSH), a collection of eggs (ova), fertilization of the eggs with viable spermatozoa, and transfer of the generated embryos into the uterus. This procedure is the only way to bypass blocked fallopian tubes to treat infertility (American College of Obstetricians and Gynaecologists, 2000). While some couples can take advantage of these options to conceive, other couples are unable to do so because of the cost of treatment, lack of insurance coverage, limited availability of ART, complications from treatment, and location (Letoumeau et al., 2012; Seifer, Frazier, & Grainger, 2008).

Help-seeking behavior of women with infertility varies across ethnicity, educational level, and geographical location. Even with reduced cost, increased insurance coverage, and availability of treatment, some infertile women still do not attempt the procedure, especially Blacks or African Americans, for reasons which are unclear (Seifer et al., 2008). Some may delay accessing care because of stigmatization, lack of awareness, and cultural beliefs (Bitler & Schmidt, 2006; Seifer et al., 2008).

Drug Treatment Protocol for IVF

Chandra et al. (2005) and Zegers-Hochschild et al. (2009) established that stimulation of ovaries is a crucial component of in-vitro fertilization. This procedure requires using gonadotrophic releasing hormones analogs, such as human menopausal gonadotropin (HMG), stimulating follicle hormone (FSH), and estradiol (E2) inhibitors to stimulate the ovaries. The discoveries of these hormones have made it possible for women who could not achieve pregnancy through natural means to become pregnant through assisted reproductive techniques by way of in-vitro fertilization (Chandra et al., 2005; Zegers-Hochschild et al., 2009).

Scholars have posited that different regimens could be used to stimulate the ovaries for in-vitro fertilization (IVF) using gonadotropin-releasing hormone analogs, human menopausal gonadotrophin (HMG), clomiphene citrate (CC), or a combination of HMG, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), clomiphene citrate or a combination of HMG, FSH, and LH (Ali et al., 2012; ASRM, 2014; Chandra et al., 2005; Dakhly et al. 2016; Toftager et al., 2016; Zegers-Hochschild et al., 2009).

According to Ludwig et al. (2000), there are two classes of GnRH analogs: GnRH agonist and antagonist. These classes are used to classify IVF treatment protocols into the following:

1. Long agonist protocol: This requires the introduction of agonist drugs at the mid-luteal phase (Fluker et al., 2001; Ludwig et al., 2000).
2. Short antagonist protocol: This involves the introduction of antagonist drugs on day five or seven of ovarian stimulation or at ovarian follicle size of 14 mm together with the gonadotrophin (Ludwig et al., 2000; Olivennes & Frydman, 1998).
3. Minimal stimulation protocol: This requires the use of CC in combination with FSH and LH for five days starting on day two of a natural cycle (Ferraretti & Gianaroli, 2014; Ibrahim, 2014; Keay, 2002; Mohsen & El Din, 2013).

The purpose of administering gonadotrophins in the IVF cycle is to optimize the number of follicles generated for IVF treatment (Templeton & Morris, 2008). Gonadotrophin analogs inhibit early luteinizing hormone surge, which results in improved oocytes retrieval rate and, therefore, a higher chance for more embryo generation and expected pregnancies in IVF treatment (Templeton & Morris, 2008). The agonists down-regulates the pituitary gland after administration following initial hypersecretion of gonadotrophin, causing desensitization and suppression of the gland. On the other hand, antagonists competitively block gonadotrophin receptors due to the higher affinity for the receptor sites, thus preventing the sudden surge of LH (Vlaisavljevic, Reljic, Lovrec, & Kovacic, 2003). Several studies have demonstrated that long agonist protocol favors more egg production when compared with the antagonist protocol (Albano et al., 2000; Fluker et al. 2001; Olivennes & Frydman, 1998; Williams, Gibbons, Muasher, & Oehninger, 2002).

Most women find the long agonist protocol more favorable because of better luteal phase development and pregnancy outcome (Vlaisavljevic et al., 2003), which is the ultimate aim for stimulating the ovaries of women seeking IVF intervention for infertility. However, the long agonist protocol requires more consumption of gonadotrophins, which is more costly, and the duration of the treatment cycle is more extended (Itskovitz-Eldor, Kol, & Mannaerts, 2000; Templeton & Morris, 2008).

Short antagonist protocol is less costly because it involves few gonadotrophins use, has a shorter treatment duration, and is a good stimulation outcome for women who have reduced ovarian activity and are referred to as poor responders. The minimal stimulation protocol shares the same advantages as short antagonist protocol where fewer gonadotrophins are used, the treatment cycle is very short, and the outcome is equally good (Badrawy, Al-Inany, Hussein, Zaki, & Ramzy, 2005; Ibrahim, 2014; Mohsen & El-Din, 2013; Zhang, Chang, Sone, & Silber, 2010).

Risks Associated With In Vitro Fertilization Treatment

IVF treatment, like any other intervention, is not without risk. The two most pronounced associated risks of IVF treatment are maternal-fetal and neonatal risk (Armour & Callister, 2005; Dunson et al. 2004; Strong, 2003). The most frequently reported associated risks are multiple gestations and ovarian hyperstimulation syndrome, which depend significantly on the type of treatment protocol used, age, and the number of embryos transferred (Gambone, 2006; Onuh, 2017; Rebar & DeCherney, 2004; Schieve et al., 2002; Strong, 2003).

According to Gambone (2006), there has been a steady increase in multiple gestations due to IVF since 1980, with triplet and quadruplet pregnancies accounting for 50% of the IVF gestations and deliveries. The incidence of preterm babies of 33 weeks is significantly higher with IVF treatment (El-Touchy, Bhattacharya, & Akande, 2018). Twenty-two percent of singleton, 14% of twin, and 41% of triplet IVF pregnancies end up as preterm deliveries (El-Touchy et al., 2018). There is a potential risk of low birth weight, cerebral palsy, hyaline membrane disease, respiratory distress, physical disabilities, congenital malformation, and death within the first year of life with preterm deliveries (Gambone, 2006; Kurinczuk, Hansen, & Bower, 2004; Schieve et al., 2002; Strong, 2003).

Also, there are associated maternal risks, such as preterm labor, occurring at the rate of 15%, 40%, 75%, and 99% for a singleton, twin, triplet, and quadruplet gestations, respectively (Strong, 2003). Higher rates of gestational diabetes, pre-eclampsia, early rupture of membrane, cesarean sections, and high maternal mortality were also reported to be associated with IVF treatment (Onuh, 2017; Strong, 2003; Wada, 2015).

Despite these associated risks and consequences, the advent of this technology has made several women pregnant. Some couples are reluctant to use IVF for fear of cost and low success rate (CDC, 2005). The cost of IVF treatment is a big concern because it limits access. Less than 10% of infertile couples participate in IVF treatment (Smith et al., 2003). Many factors are contributing to the reported low success rate of IVF treatment. These factors could be patient-related, personal issues, and the procedure itself. Notwithstanding, successful, favorable clinical pregnancy rates of about 40% and more have been reported for complete IVF treatment cycles that end with embryo transfer (Wright, Schieve, Reynolds, & Jeng, 2003).

Infertility Treatment and Stimulation Influenced by Socioeconomic Status and Demographic Characteristics

Ho et al. (2017) showed that college-educated women presented to fertility clinics approximately 8.4 months earlier than those without a college education. Also, those reporting an income greater than $100,000 often came to fertility clinics six months before those with an income of less than $100,000. The probability of achieving pregnancy was significantly higher for those women with higher incomes and college educations (Datta et al., 2016). Datta et al. (2016) stated that there is evidence of the relationship between socioeconomic status and infertility. Infertility is a common issue among women with higher degrees when compared to those with lower degrees (Datta et al., 2016).

The incidence of infertility was greater amongst women in executive positions, like senior managers, executive directors, and such, compared with those in regular occupations and positions. James et al. (2011) did not find any association between infertility and area-related deprivation at interviews amongst women or men. Improved pregnancy rates were reported as more IVF treatment cycles were performed (James et al., 2011).

In another study, socioeconomic status was not a confounder or effect modifier when the relationship between IVF treatment and perinatal outcomes was examined while adjusting for co-variables, such as age, parity, smoking, gestational diabetes, maternal diabetes, and pre-eclampsia. However, as the socioeconomic status increased, the prevalence of IVF pregnancies also increased: The corresponding percentages were 3.2% and 1.2% for the highest and lowest SES strata, respectively. (Räisänen et al., 2013). Moreover, research conducted by Chethana and Shilpa (2016) stated that due to economic reasons, 47.37% of males amongst couples with primary infertility had not approached the health care facility.

Furthermore, Datta et al. (2016), in their study, found that infertility is associated with demographic characteristics of partners. They found that the statistics of infertile married women or cohabiting partners were higher than in non-married women. Also, women who are older than 35 years at the first time of cohabiting were found with higher infertility when compared with women who are 25 years or younger cohabiting for the first time (Datta et al., 2016).

Dayal et al. (2009), in another study, portrayed that ethnicity did not significantly differ with regards to conception, as African Americans were as likely to have successful conception and deliver a live baby as Caucasians. However, African American women were more likely to come with idiopathic infertility than White women.

Factors Affecting Long Agonist and Short Agonist Protocol in Infertility Treatment

More clinical pregnancy outcomes were reported using a GnRH agonist protocol than clomiphene and the GnRH antagonist protocols combined (Schimberni al., 2016). The same study by Schimberni et al. (2016) also revealed that the total cost of medications for each baby delivered by IVF technology using GnRH agonist was lower compared to the antagonist protocol. However, there was no significant difference for the total amount of FSH administered, days of stimulation, the number of follicles and eggs collected, and embryos transferred (Schimberni et al., 2016). Similar findings were demonstrated by Salat-Baroux et al. (1988). Groups of patients with polycystic ovary disease were treated with GnRH analogs to compare long and short protocols for the hypothalamus and anterior pituitary gland desensitization. Patients were randomly allocated to each group. In the long protocol group (n = 15), decapeptide was administered for 30 days for down-regulation and thinning of the uterine endometrium, followed by stimulation of the ovaries using pure FSH. In the short protocol group (n = 12), buserelin was administered for 15 days, followed by stimulation of the ovaries using pure FSH. Six patients in each of the groups had clomiphene citrate until the induction of ovulation. The most favorable results were recorded from the long protocol. However, significantly lower androgen concentrations were observed on the day of oocyte retrieval in the first group than in the second group (p = 0.031). Still, the pregnancy rate was comparable in the two groups (Salat-Barooux et al., 1988; Shrestha et al., 2015).

Shrestha et al. (2015) concluded that despite the lengthy and costly procedure, GnRH agonist long protocol ensured agreeable outcomes in most women. Also, Engemann et al. (2008) found that the use of the GnRH agonist trigger after the administration of GnRH antagonist, combined with adequate luteal phase and early pregnancy, reduces the risk of oocyte hyperstimulation syndrome in high-risk patients undergoing IVF treatment without affecting nidation of the embryo.

However, Ho et al. (2008) showed that the short GnRH agonist protocol using recombinant gonadotrophins is an effective and relatively cheaper choice for IVF treatment. The total cost of recombinant gonadotrophins was significantly lower (p = 0.025) in the short protocol ($950) compared to the long protocol ($1,580), but there were no significant differences in the rates of term pregnancy between the short and long protocol. Ou, Xing, Li, Xu, and Zhou (2015) demonstrated that regardless of patient's age, the long protocol was superior to the short protocol regarding the number of retrieved oocytes and the implantation and pregnancy rates.

Barut, Agacayak, Bozkurt, Aksu, and Gul (2016) found a significant relationship between socioeconomic status and ovarian reserve parameters, such as the level of Mullerian inhibitory substances and antral follicular number. They also found a highly significant association (p = 0.021) between socioeconomic status and the level of follicle-stimulating hormones.

Factors Affecting the Help-Seeking Behavior of Women Desiring Fertility Treatment

Lam, Broaddus, and Surkan (2013) showed that knowledge of infertility was related to "help-seeking behavior" of infertile women, even after adjusting to socio-demographic variables. Amongst women with only primary school education, literate women's odds of identifying "getting permission" as a barrier to healthcare were 23% less than illiterate women's odds. For married women, the odds of making decisions related to their health were 37% higher in literate than uneducated women. Comparing literate to illiterate women in the subsample with no formal schooling, odds of reporting "getting permission" as a barrier were 35% lower, odds of having decision-making ability were 57% higher, and odds of having sought care for experiences of STI-related symptoms were 86% higher (Lam et al., 2013).

Complementary Alternative Medical Treatment of Infertility

Additional alternative medical (CAM) treatment is any non-drug interventional approach that is perceived to improve the health or total well-being of humans (Olshansky, 2000).CAM involves a wide range of interventions, such as bioenergetics, traditional therapies, mind and body conditioning, and spiritual principles, given healing to the body. CAM varies in efficacy, safety, cost, and outcome (Olshansky, 2000).

Complementary and alternative medicine has, in recent times, gained popularity in infertility treatment. Some women prefer the natural pathway to conception than any new intervention. Such women take responsibility to indulge in lifestyle modifications and practices that improve their health outcomes to treat infertility rather than rely on taking modern medicine and ART to conceive (Coulter & Jenkins, 2005).

Vitamin E, Selenium, and high doses of vitamin C and Zinc are used to improve the quality of sperm motility and morphology, and they count as a treatment for male-related infertility (Coulter & Jenkins, 2005). Vitamin E promotes the zona binding during in vitro fertilization specifically. Anovulatory conditions and oligomenorrhea were reported to have been treated with *Agnus Castus* (Olshansky, 2000)

Coulter and Jenkins (2004) showed that acupuncture improved anovulatory conditions and uterine and endocrine blood flow, which are very important in female fertility. Other studies have also revealed that acupuncture modulates the body’s endocrine system to induce or stimulate ovulatory function 35% of times with significant pregnancy outcomes (Beal, 1999; Hanlon, 2004; Olshansky, 2000). Other benefits of CAM include the physical and psychological well-being of infertility sufferers (Hanlon, 2004).

A proper and balanced diet is an alternative measure to improve female and male fertility (Meletis & Barker, 2004). Food is medicine, and a well-balanced diet with fruits helps to enhance several body systems and metabolic activities, including the female reproductive system (Ogle & Mazzullo, 2002). Choosing from a broad range of foods, as recommended by the American Dietetic Association, using the food pyramid for daily consumption is critical to the healthy eating that promotes conception (Bruce & Thatcher, 2000). On the other hand, alcohol, caffeine, and refined foods with additives half the chance of conception (Hakim et al., 1998). Caffeine notably potentiated the effect of alcohol, and women who consumed higher than 7 g per month of caffeine were more at risk of infertility associated with endometriosis and tubal factors compared to women who consumed the recommended 3 g per month (Grodstein, Goldman, Ryan, & Cramer, 1993)

Some studies also considered reflexology as an alternative, complementary approach to fertility treatment. Reflexology uses the nerve plexus reflexes at the feet and hand nerve endings to control specific organs of the body. Nerves corresponding to a particular organ are identified and manually manipulated to bring about healing and succor to that organ through rejuvenation and restoration of hormonal balance to improve reproductive health (Brown, 1999; Childbirth Index, 2018).

Barriers to Infertility Treatment

IVF has recorded substantial success worldwide (El-Touchy et al., 2018). However, huge barriers have prevented a large population of infertile women from accessing assisted reproductive technology. The existence of these barriers to treatment results in infertility being a chronic condition with attendant emotional distress to many couples (Mohammadi & Kaf, 2010; Mosalanejad, Parandavar, & Abdollahifard, 2013). This situation is prevalent in low-middle income countries like Nigeria (Adegbola, 2013).

Access to IVF treatment can be very daunting, prohibitive, and almost impossible to many infertile women aspiring to conceive in Nigeria, despite the stigmatization, social pressure, adverse effects of living without a child, and the emotional and psychological morbidity they experience. Sadly, the psychological and emotional morbidity associated with childlessness is more in women in Nigeria because of widespread beliefs that attribute the cause of infertility to the woman while ignoring male-related factors (Daniluk, 2005; Kingly, 2017; Peddie, van Teijlingen, & Bhattacharya, 2005).

Income is a strong predictor of access to quality healthcare (Kate, 2014). The financial cost of infertility treatment in Nigeria could be higher than $2,800 per complete cycle in a country where 94.2% of the population live below the poverty line with a daily earning of less than $2 (Devine, Stillman, & DeCherney, 2014; Kingly, 2017). Consequently, most of the women seeking IVF treatment often discontinue treatment and resort to traditional and faith healers. These health-seeking practices are linked to increased maternal mortality rates in Nigeria (Kingly, 2017).

Universal coverage for healthcare as contained in Sustainable Development Goals (SDG) is targeted at promoting the health of the people through equal access to healthcare and improving the financial burden thereof as a result of ill-health. None of the health maintenance organizations in Nigeria pays for infertility treatment, and this development leaves infertile couples to pay out their pockets. A considerable number of couples who cannot afford such treatments are left to their fate.

Countries such as Denmark, Belgium, Germany, Canada, Israel, Australia, and some US states pay for infertility treatment, thereby providing more access to better healthcare (Kingly, 2017). Denmark offers unlimited access to treatment for infertile women and men, while in Belgium, infertile women can access treatment for up to six treatment cycles (Kingly, 2017; Van Dongen, Verhagen, Dumoulin, Land, & Evers, 2010).

Geographical location, long-distance to ART facilities, and lack of adequate ART skills amongst physicians are strong barriers to infertility treatment (Gameiro, Boivin, & Peronace, 2012; Van Dongen et al., 2010). Some infertile women discontinue treatment for fear of daily injection and pain at injection sites. Unwanted side effects of IVF medications and the fear of anticipated treatment failure also contribute to reduced access to treatment (Wada, 2015).

Culture and beliefs have a negative impact on access to infertility treatment. In Nigeria and other developing African countries, married women are often blamed for infertility problems, even when the evidence is contrary (Dyer, Abrahams, Hoffman, & van der Spuy, 2002). Married men are considered fit and usually have reasons not to be present for medical checks and resort to blaming the women for their infertility problems, which is supported by the prevailing cultural norms. The result of such beliefs and cultural practices is delayed infertility (Okoroike, 2009)

However, studies have shown that educational level affects infertility seeking behavior of infertile women (Hammoud et al., 2009; Terava, Gissler, Hemminki, & Luoto, 2008), as more educationally developed infertile women are seen to present early to infertility clinics than the uneducated women. This is not unconnected to the fact that the more educated infertile women are more likely to be aware of the importance of seeking early help to address their infertility status.

Current Trends in Infertility Treatment

Fertility Preservation

Recent studies in infertility treatment now focus on fertility preservation procedures, which require freezing of eggs and, more recently, freezing of whole ovarian tissue. The former technique needs long stimulation of the ovaries with drugs to generate eggs, usually 15-30 for freezing. In most cases, less than 2% will be successfully frozen and saved for use in the future. Freezing of whole ovarian tissue is a new and very promising procedure that is still at the developmental stage. Freezing whole ovarian tissue requires micro-surgically separating the thin outer membrane of the ovary containing eggs to allow for freezing (Wada, 2015). The harvested and frozen tissue, including over approximately 150,000 eggs, can be surgically replaced when the woman is ready to become pregnant to offer younger fertility than the current age of the woman. This makes natural conception possible.

Freezing ovarian tissue is targeted at young women in their 30s who are very conscious of their biological clock (e.g., career women and women diagnosed with cancer who are on chemotherapy and radiation). Women may wish to preserve their fertility until when they are ready to conceive, thus delaying ovarian failure or early menopause, which could pose as a challenge for achieving pregnancy naturally, even with ART.

Preimplantation and Genetic Diagnosis

Pre-genetic diagnosis (PGD) or pre-genetic screening (PGS) is a modern value-added technological approach in ART aimed at improving pregnancy outcomes (Mastenbroek et al., 2007). The argument about whether IVF babies are healthy or not has been and still is a big subject of debate.

PGD, when combined with IVF, allows couples to give birth to offspring that are free from known genetic defects. PGD prevents the babies from carrying recessive mutated genes that may manifest in subsequent generations (Mastenbroek et al., 2007). PGD also provides answers and solutions to miscarriages in healthy and IVF pregnancies in both young and mostly older women (Keskintepe et al., 2009) and could be used for sex selection in IVF procedures, with 99.9% certainty (Danga, 2015). The PGD/PGS is used either to eliminate disease carrier genes or for aneuploidy screening, where the number of chromosomes is being tested (Danga, 2015). Prospective and randomized studies have shown that despite the extra cost, there is no significant difference in the rate of nidation and pregnancy outcomes among older women who did PGD with IVF and infertile women who did only IVF procedure (Mastenbroek et al., 2007).

Literature Gap

Infertility treatment has started gaining momentum and attention from different quarters in Nigeria, with many fertility treatment centers springing up all over the country. However, access to treatment and standard treatment guidelines remain a huge issue of concern, as the number of diagnosed and undiagnosed infertile women in Nigeria is on the rise. Education, ethnicity, age, religion, socioeconomic status, and cost are determinant factors affecting access to treatment (Bitler & Schmidt, 2006; Seifer et al., 2008).

In some instances, insurance coverage was provided to pay for treatment, and the cost was significantly reduced. Yet, the more educated White women seem to make the most of the opportunity by presenting in fertility clinics for treatment while Black American women were reluctant to access treatment for fear of stigmatization, belief, and lack of awareness (Bitler & Schmidt, 2006; Seifer et al., 2008).

No study yet in Nigeria has critically examined the available treatment protocols. Instead, individual protocols were reported. Long agonist protocols are more time consuming, require more drugs, and the rate of treatment cancellation was reported to be high when compared to the short antagonist protocol, which required fewer drugs, is less expensive, required lesser time to complete treatment cycle, and is suitable for poor responders, with minimal cancellation rate (Itskovitz-Eldor et al., 2000; Mohsen & El-Din, 2013; Templeton & Morris, 2008; Zhang et al., 2010;). The treatment outcomes of these protocols, socio-economic status, and other determinant factors were not studied in the reviewed literature during the period of this study.

Therefore, there was a need to resolve the gaps identified in the literature. The focus of this study has been on the Nigerian situation by studying existing data from the 10 fertility centers across the six geopolitical zones. The study critically assessed factors that impact treatment protocol and outcome and to determine which treatment protocol was best for infertile women in Nigeria.

Summary of Literature Review

The purpose of this study was to assess the factors that affect treatment outcomes in women with infertility issues and treatment protocols that are currently being used in IVF procedures. The reviewed literature highlighted the importance of childbirth in every marriage, especially in Africa, where childbirth is considered as necessary in marriage, without which the marriage is considered as not consummated and remains at risk of divorce (Okoroike, 2009). The literature review identified uterine and endocrine factors, infections, and surgeries, amongst other issues as plausible causes of infertility issues in couples.

The advent of IVF technologies since the 80s has ameliorated the biological gap in couples finding it difficult to reproduce (Cristia, 2008; Lundborg et al., 2017). Despite the availability of this technology, determinant factors such as socioeconomic status, social-demographics, culture, and belief have been reported to influence the success of this technology. Still, the know-how has not been adequately studied. Furthermore, the IVF treatment protocols and other non-drug approaches to treatment have not been critically assessed to identify which is more favorable for countries like Nigeria, where access to this technology is challenging because of cost and other behavioral determinant factors. These gaps in knowledge are the fundamental reasons why this study was embarked upon.

The current trends in the treatment of infertility, such as pre-implantation genetic diagnosis, and fertility preservation, were also presented in this chapter. PGD helps to minimize the chances of giving birth to genetically deformed babies by infertile women through IVF, and the fertility preservation technique provides for women to suspend childbirth till a later date. This is useful for career women and women undergoing chemotherapy and radiotherapy due to cancer. The detailed methodological approach used to provide answers to the research questions raised in Chapter 1 is explained in the next chapter.

Chapter 3: Research Method

This study was a retrospective, cross-sectional, quantitative, and nonexperimental study that assessed the relationship between types of fertility treatment protocol and treatment outcome. The secondary data of ART were collected from 10 fertility centers in five states covering the entire six geopolitical zones of Nigeria from January 2015 through December 31, 2017. This observational study required a retrospective collection of data from an existing database of previously completed IVF treatments. Although cross-sectional studies have some limitations, such as lack of representativeness, it was suitable for this study because fertility treatment is not very popular in Africa. This study covered 10 accredited fertility centers in Nigeria.

Research Design and Rationale

This study was quantitatively designed to capture data available in Nigeria on fertility treatment between January 2015 through December 31, 2017, in 10 fertility treatment centers of five states covering the entire six geopolitical zones of Nigeria.

The observational, cross-sectional, retrospective and quantitative study design had many advantages. It was used to provide the odds ratio, relative risk, and absolute risk from a prevalence study. Exposures with multiple outcomes could be conveniently studied, and this type of design avoids a loss to participant follow-up issues, which made it suitable for this study (see Creswell, 2014). Other strengths of this research design included the minimal influence of the investigator or researcher on results and that the findings or research outcomes can be generalized when based on large sample sizes (see Creswell, 2014). Hence, this design was appropriate and efficient to answer my research questions. Also, the plan was relatively cheap compared to experimental design.

Study Area

This study was carried out in Nigeria, located in sub-Saharan Africa. Other West African countries border it: Niger, Chad, Cameroon, and Benin. The south coast of Nigeria hinges on the Gulf of Guinea. It is made up of 36 states and a Federal Capital Territory (see Figure 2).

Nigeria was founded in the year 1914 during British colonial rule. It became a sovereign and independent nation on October 1, 1960. It is popularly referred to as the "Giant of Africa" because of its large population and the size of the economy. It is a highly diversified country, and the estimated population as of the 2006 Census was 185,989,640. Nigeria has over 250 ethnic groups and more than 350 languages (National Population Commission, 2006). The official language in Nigeria is English. Christianity and Islam are the two dominant religious groups in Nigeria.

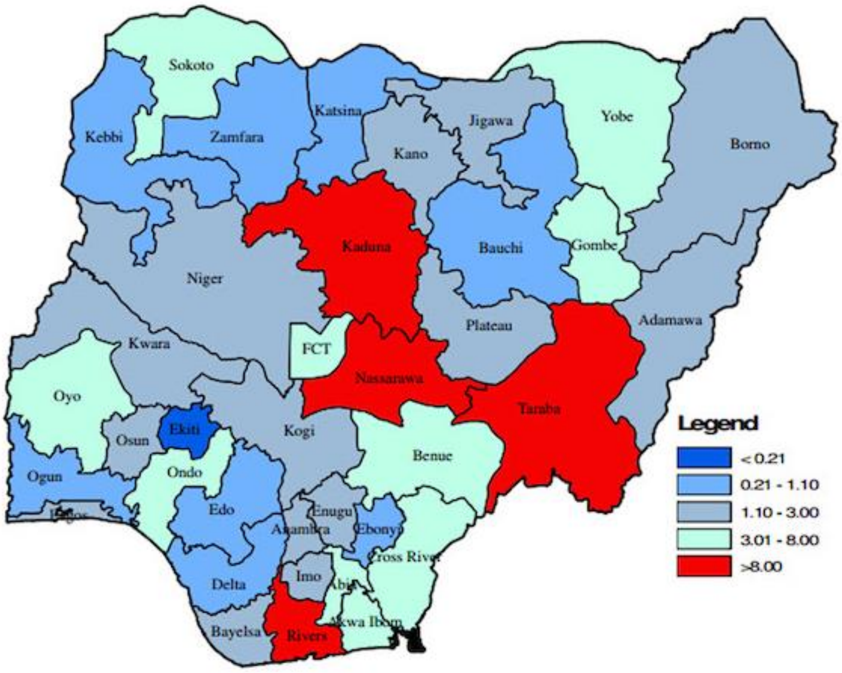

Figure 2. Map showing the 36 states and the federal capital territory in Nigeria.

Study Population

The candidate population for this study was comprised of infertile women who have been enrolled in the enlisted health facilities and have had IVF complete treatment between January 1, 2015, and December 31, 2017. The selected health facilities for this study were composed of all the registered hospitals and clinics with the Nigeria Ministry of Health and Association for Fertility and Reproductive Health, who are licensed to carry out this specialist cadre of treatment, ART (see Table 1).

Table 1

List of Health Facilities

Region	Hospital or clinic
Abuja	• Nisa Fertility and Genetic Center • Fertil Aid Clinic • Deda Hospital • Charitos Bo Hospital
Lagos	• Garki Hospital
Port-Harcourt	• Nisa at Prime Hospital • El-Rapha
Jos	• Kauna Hospital • Fertile Ground Hospital
Enugu	• Alps Hospital

These facilities were selected across Nigeria because they were first- and second-generation fertility treatment centers that are registered by law and are licensed by the relevant authorities and association in Nigeria to carry out IVF treatment. These facilities provide high-quality care with a large clientele base, have official medical records, have standard ICT units, and are easy to access.

Sample Size

In research, studying the entire population is impossible, especially when the population under investigation is significant, hence the need for a representative sample of the population under study. Several factors determine the calculation of the sample size, such as the nature of variables that could be categorical or continuous, the type of test statistics, level of significance, marginal error, and the interrelationship between variables. Fisher's formula was used to compute the minimum sample size for this study (as cited in Abuh, 2013):

$$\boldsymbol{n = z^2pq}/\delta^2$$

Where

n = sample size

z = 1.96

p = proportion or prevalence of the disease or condition in the population under study.

Q = level of precision $(1-p)$

δ^2 = the allowed margin of error or the degree of accuracy.

The prevalence studies showed that the proportion of women who are infertile in Nigeria ranges from 30 to 50%. Hence p is considered at 50% = 0.5

Therefore, values for the parameters are

P = 0.5

$z^2 = (1.96)^2 = 3.8416$

$q = 1\text{-}p = 1\text{-}0.5 = 0.5$

$\delta 2 = (0.05)^2 = 0.0025$

By substituting these values in the formula

$N = 3.8416 \text{ x } (0.5 \text{ x } 0.5) / 0.0025$

$= (3.8416 \text{ x } 0.25) / 0.0025$

$= 0.9604 / 0.0025$

$= 384.16$

$n = 385$ (approximate value)

A minimum of 385 treatment records of infertile women were computed as the sample size for the example above, but 605 records were used in this study.

Sampling Method

Convenience or a purposive nonprobability sampling method was employed in this study. All available medical charts of women accessing infertility treatment in the selected hospitals formed the sampling frame from which the sample size was selected. The medical charts, with complete variables of interest, formed the study's sample size.

Inclusion Criteria

1. The women had primary or secondary infertility as diagnosed by a physician.
2. The age of the participating women was 20 to 50 years.
3. The women had completed at least one fertility treatment cycle between January 1, 2015 and December 31, 2017.

Exclusion Criteria

1. Patients who had timed intercourse, intrauterine insemination, and minimal stimulation.
2. All frozen embryo transfers and surrogacy.

Gaining Access to the Data

Data were accessed following the presentation of the study proposal and Walden Institutional Review Board approval number 0815190326544 to the hospital management, and verbal approval was given to access the data after signing the agreement form.

Operationalizing the Variables

The quantitative independent variables of this study were age, ethnicity, education, religion, tribe, PCOS, endometriosis, a drug used for down-regulation, duration of down-regulation, a drug used for stimulation, and duration of stimulation, while the number of follicles/oocytes retrieved was the dependent variable.

Data Collection

Following the approval of the Walden University Institutional Review Board and the management of the hospitals, data were collected on Microsoft Excel 2010 spreadsheets from the medical records of the selected 10 fertility centers. Ten well-trained research assistants were used for this purpose. The collected data were harmonized, merged, and cleaned using Epidata software and exported to the SPSS Version 25 statistical software for analysis.

Data Analysis Plan

Data were analyzed using SPSS version 25. Descriptive and inferential statistics were performed on the data. Univariate test statistics were used to describe the characteristics of patients, and the results were presented in the forms of tables, figures, and charts. Non-parametric statistics, the Wilcoxon rank-sum, Kruskal-Wallis, and Pearson's correlation tests were used to test the hypotheses. Regression analysis was used to determine which variables were statistically significant predictors of the treatment outcomes. The decision rule was considered at $p < .05$ (Kestin, 2015).

Validity

Validity is to ensure that the result of the study is reliable and trustworthy, and measures up to what it was originally designed to achieve (Golafshani, 2003). However, the impacts of threat were minimized by capturing all the variables of interest and the large sample size for generalization in this study.

Ethical Consideration

Ethical consideration is an essential aspect of every research, especially when the research involves human subjects. Hence, ethical principles of doing no harm, respect, beneficence, confidentiality, and justice for human subjects guided this study, as laid out in *the Belmont Report* (U.S. Department of Health & Human Services, Office for Human Research Protections (2016). All approvals were obtained before data were collected.

Post Data Analysis Plan

The collected data have been pass-word protected and will be saved for a minimum period of 5 years.

Summary

The study is a retrospective and quantitative design. Secondary data from 10 fertility clinics and hospitals across Nigeria were used to answer the research questions. Data were collected following approval from Walden Institutional Review Board and hospital management. The collated data were cleaned and exported to SPSS software version 25 and analyzed. Results were presented in tables and graphs. This marks the end of Chapter 3, and the details of the results are presented in Chapter 4.

Chapter 4: Results

This cross-sectional and retrospective study was conducted using secondary data of women who had completed fertility treatment from 10 selected hospitals across Nigeria between January 1, 2015, and December 31, 2017, to establish the relationship between long and short treatment protocol and to determine which protocol is most favorable for Nigeria. Patient characteristics, including age, medical conditions (PCOS and endometriosis), SES, education, ethnicity, the drug used for down-regulation, duration of down-regulation, the drug used for stimulation, and duration of stimulation were also examined to determine the impact on treatment outcome. As at the time of this report, no researcher had conducted this study in Nigeria.

The research questions and hypotheses that guided this study were as follows:

RQ1: What is the relationship between types of fertility treatment protocol and treatment outcome?

$H_0$1: There is no significant difference in the relationship between fertility treatment protocol and treatment outcome.

$H_1$1: There is a significant difference in the relationship between fertility treatment protocol and treatment outcome.

RQ2: Do patient characteristics (age, education, SES, medical condition, previous IVF, ethnicity) influence the outcome of fertility treatment protocol?

$H_0$2: Patient characteristics have no significant influence on the outcome of the fertility treatment protocol.

H_12: Patient characteristics have a significant influence on the outcome of the fertility treatment protocol.

Summary Description of the Variables

Table 2

Descriptive Statistics of the Variables

Variables	Overall (*N* = 605)
Hospital (%)	
ALPS	60 (9.9)
Charitos	61 (10.1)
Deda	60 (9.9)
Alpha	60 (9.9)
Fertilaid	60 (9.9)
Fertile Ground	59 (9.8)
Garki	60 (9.9)
Kauna	60 (9.9)
Nisa At Prime	60 (9.9)
Nisa Premier	65 (10.7)
Tribe (%)	
Hausa	173 (28.6)
Igbo	184 (30.4)
Yoruba	93 (15.4)
Others	155 (25.6)
Education (%)	
Primary	23 (3.8)
Secondary	168 (27.8)
Tertiary	414 (68.4)
Age (mean (SD))	35.5 (5.2)
Age Group (%)	
20-24	8 (1.3)
25-29	62 (10.2)
30-34	183 (30.2)
35-39	234 (38.7)
40-44	91 (15.0)
45-49	24 (4.0)
50-54	3 (0.5)

Variables	Overall (N = 605)
Religion = Christianity/Islam (%)	429/176 (70.9/29.1)

(table continues)

Variables	Overall (N = 605)
Socioeconomic status (%)	
Low	70 (11.6)
Medium	274 (45.3)
High	261 (43.1)
Polycystic ovary syndrome = No/Yes (%)	366/239 (60.5/39.5)
Endometriosis = No/Yes (%)	368/237 (60.8/39.2)
Treatment protocol = Long/Short (%)	224/381 (37.0/63.0)
The drug used for downregulation (%)	
Buserelin	352 (58.2)
Cetrotide	67 (11.1)
Zoladex	186 (30.7)
GnRH drug = GnRH agonist/GnRH antagonist (%)	538/67 (88.9/11.1)
Duration of downregulation in weeks (%)	
1	34 (5.6)
2	326 (53.9)
3	245 (40.5)
The drug used for stimulation (%)	
HMG	457 (75.5)
FSH	139 (23.0)
FSH & HMG	9 (1.5)
Duration of stimulation in days (median [IQR])	11.0 [9.0, 12.0]
Number of oocytes (median [IQR])	5.0 [2.0, 10.0]

A total number of 605 women's fertility treatment data from 10 accredited fertility hospitals across Nigeria were assessed. The mean age was 35.5, and 38% of the women were within the age group 35 to 39. The women were predominantly Christian, 70.9%. The Igbo women accounted for 38.4%, Hausa 28.6%, Yoruba 15.4%, and other 25.6% of the study sample. Most of the women had a higher degree, 68.4%, and 45.3% of the women were medium-income earners.

PCOS and endometriosis accounted for 39.5% and 39.2%, respectively. Of the participants, 63% of the women had short protocol treatment, and 37% had long protocol treatment. The median duration of stimulation and the number of oocytes were IQR 11.0(9.0, 12.0) and IQR 5(2.0, 10.0).

Research Question 1

What is the relationship between types of fertility treatment protocol and treatment outcome?

$H_0$1: There is no significant difference in the relationship between fertility treatment protocol and treatment outcome.

$H_1$1: There is a significant difference in the relationship between fertility treatment protocol and treatment outcome.

- The independent variable was the type of fertility treatment protocol measured as a nominal variable (values = long, short).
- The dependent variable was treatment outcome measured as the number of eggs (oocytes) - range: 1, 38.

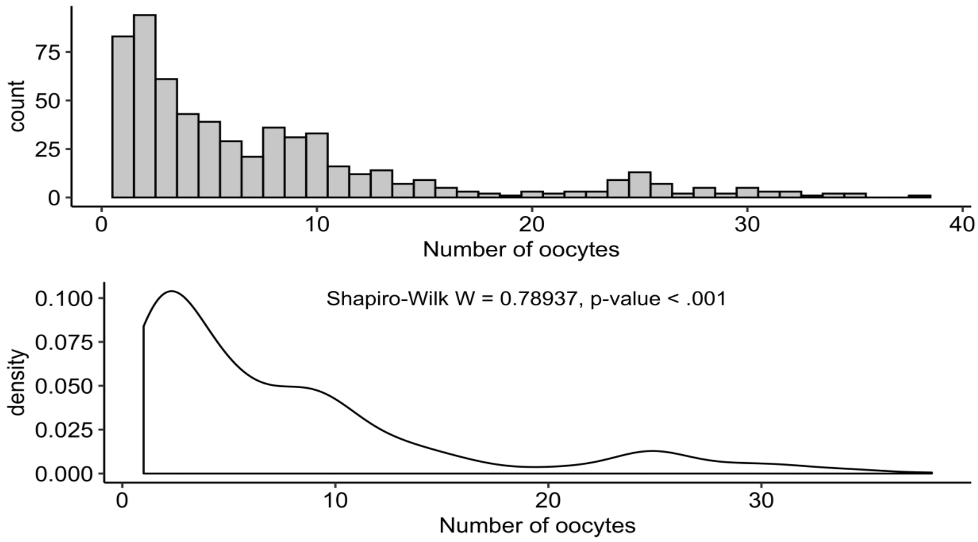

Figure 3. Histogram and density plot of the outcome variable (number of oocytes).

Both the histogram and density plot of the outcome variable presented in Figure 3 show that it right-skewed and is not a normal distribution. Furthermore, I tested the hypothesis for normality using the Shapiro-Wilk Normality test, which showed that the distribution was not normally distributed.

Due to the nonnormal distribution of the outcome variable, the hypothesis that reflected no significant difference in the relationship between fertility treatment protocol and treatment outcome was tested using the Wilcoxon rank-sum test. For RQ1, the median number of oocytes of the long protocol group and the short protocol group were 8 and 4, respectively. The Wilcoxon rank-sum test showed that there is a significant effect of the protocol group ($W = 54503$, $p < .001$) on the number of oocytes (see Figure 4).

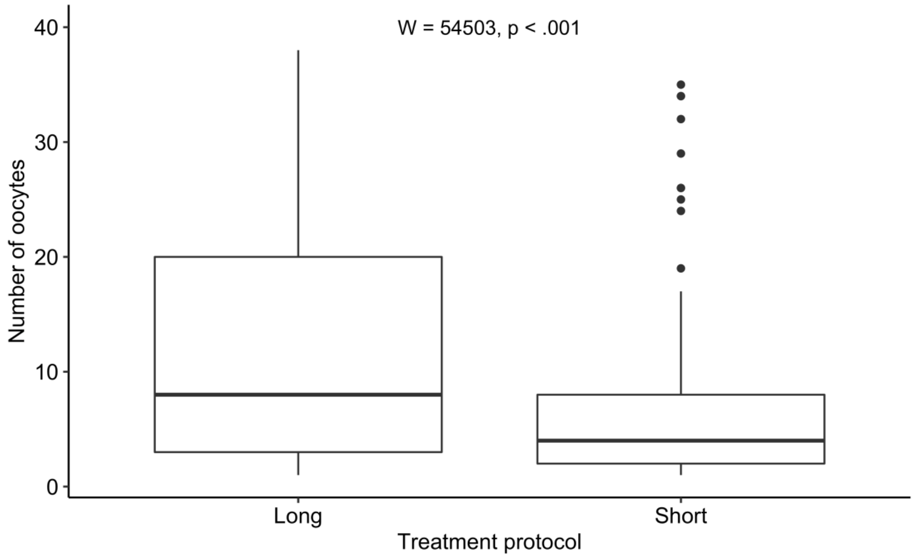

Figure 4. Boxplot of the number of oocytes by the treatment protocol.

The Wilcoxon rank-sum test analysis in Figure 4 showed that there is a statistically significant difference between the numbers of oocytes in the long (median 8) and short (median 4) treatment protocols.

Research Question 2

Do patient characteristics (age, education, SES, medical condition, ethnicity) influence the outcome of fertility treatment protocol?

$H_0$2: Patient characteristics have no significant influence on the outcome of the fertility treatment protocol.

$H_1$2: Patient characteristics have a significant influence on the outcome of the fertility treatment protocol.

The independent variables were

1. Sociodemographic characteristics:

- Age measured both as a continuous variable (age) and as a nominal variable (age group)
- Education measured as an ordinal variable (values = primary, secondary, tertiary)
- SES measured as an ordinal variable (values = low, medium, high)
- Tribe measured as a nominal variable (values = Hausa, Igbo, Yoruba, Other)
- Religion measured as a nominal variable (values = Christianity, Islam)

2. Medical condition:
    - PCOS (values = yes, no)
    - Endometriosis (values = yes, no)
3. Treatment-related factors:
    - The drug used during down-regulation (Buserelin, Cetrotide, Zoladex)
    - Type GnRH drug used (agonist vs. antagonist)
    - Duration of down-regulation in weeks
    - The drug used for stimulation (FSH, HMG, FSH & HMG)
    - Duration of stimulation in days
4. Hospital (This was added to account for a range of effects like the skill of provider, etc.)

The dependent variable was the number of oocytes.

Age.

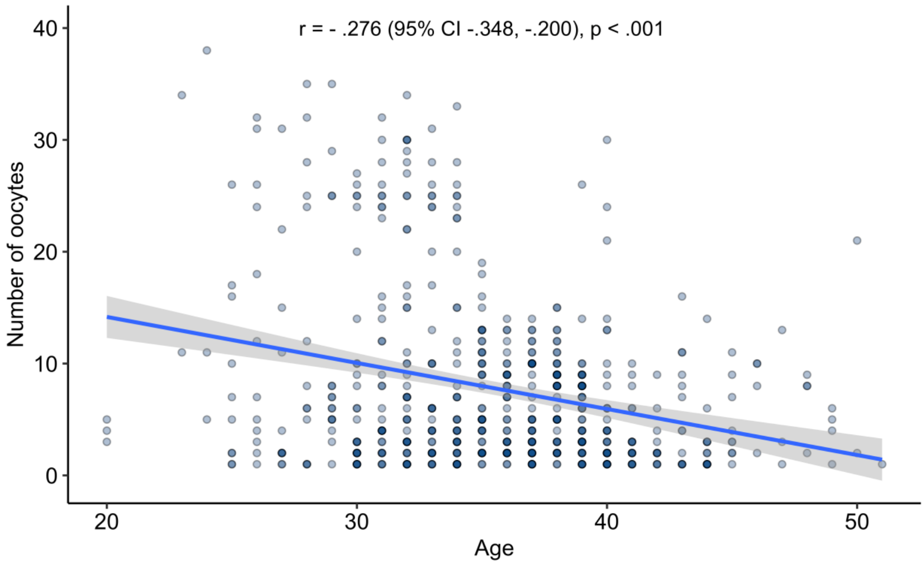

Figure 5. Scatter plot of age versus the number of oocytes.

There is a weak to moderate but statistically significant correlation between age and number of oocytes, $r = -0.276$ (95% CI −0.348, −0.200), $p < .001$. We could also look at how the age groups compare (Figure 6).

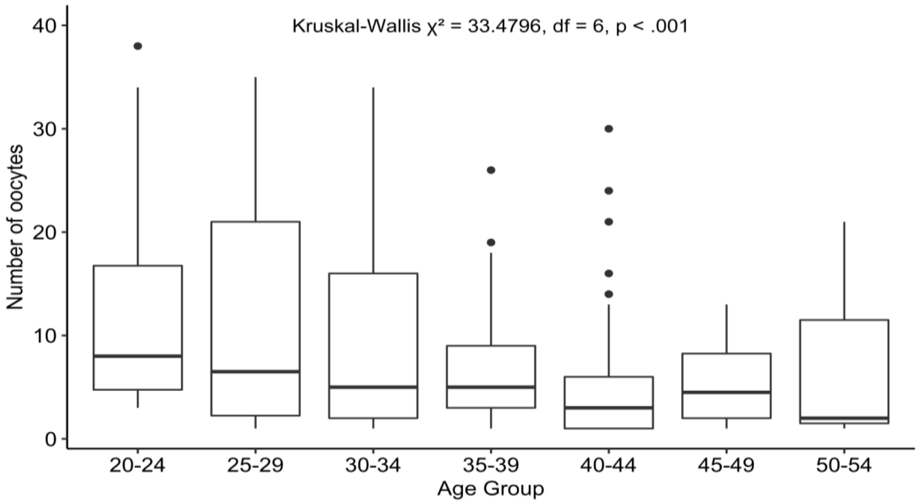

Figure 6. Boxplot of the number of oocytes by age groups.

The Kruskal-Wallis $\chi^2(6) = 33.4796$, $p < .001$ indicates a statistically significant relationship between the Age Group and the Number of oocytes.

Education.

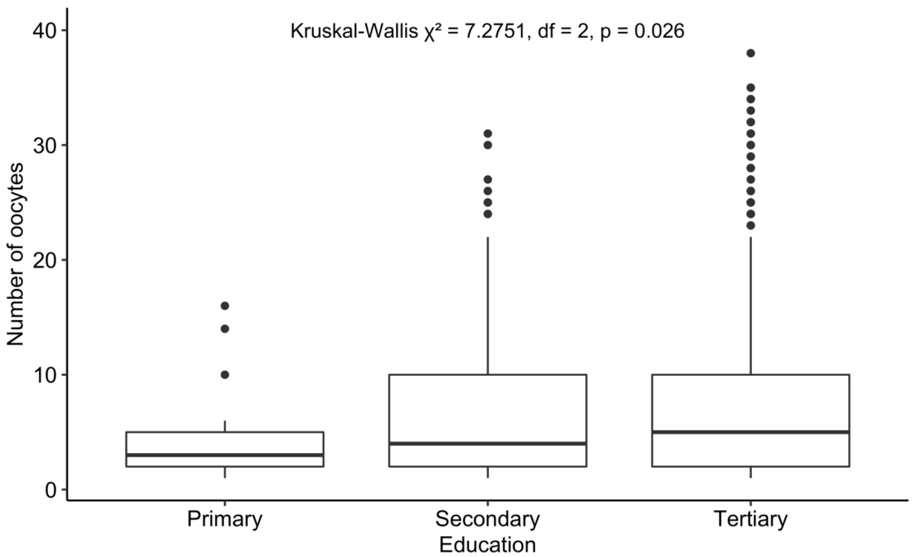

Figure 7. Boxplot of the number of oocytes by education level.

The Kruskal-Wallis, $\chi^2(2) = 7.2751$, $p = .026$, indicates a statistically significant relationship between Education and the Number of oocytes.

Socioeconomic status.

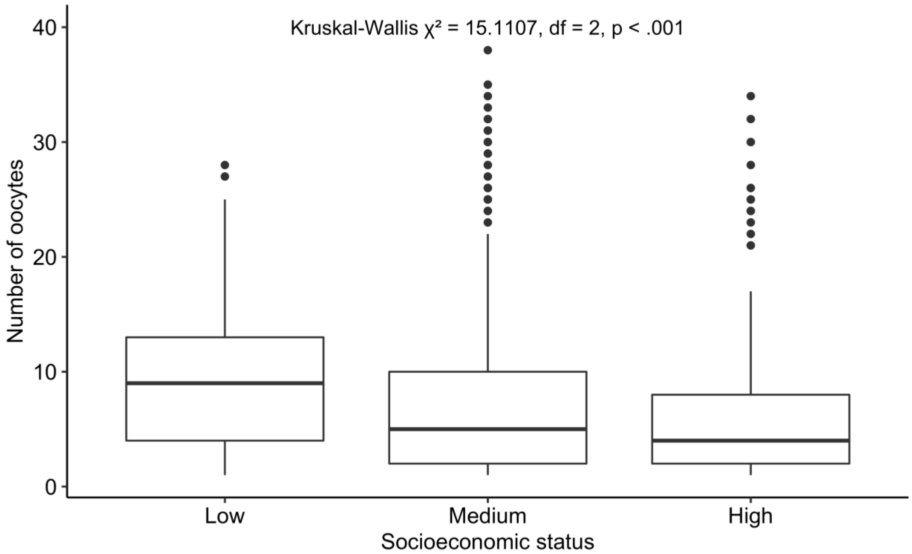

Figure 8. Boxplot of the number of oocytes by socioeconomic status.

The Kruskal-Wallis, $\chi^2(2) = 15.1107$, $p < .001$, indicates a statistically significant relationship between Socioeconomic status and the number of oocytes.

Tribe.

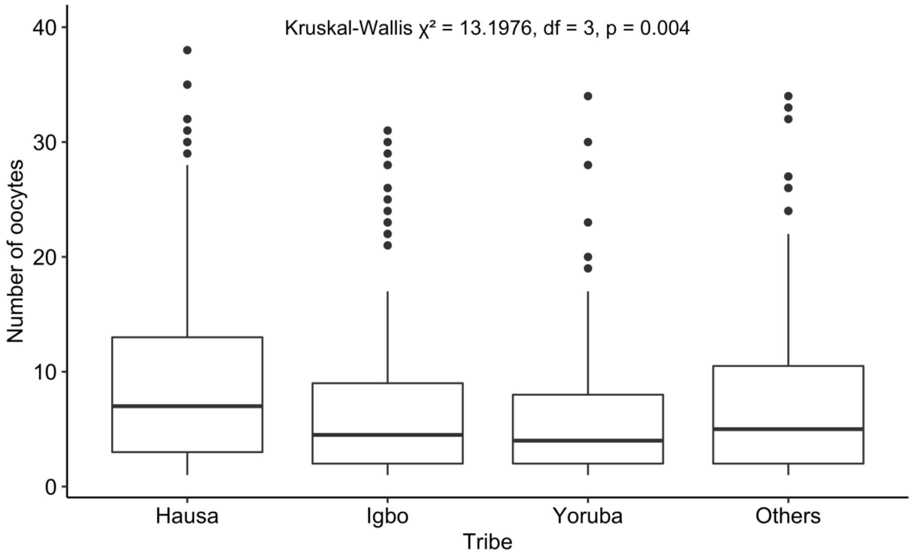

Figure 9. Boxplot of the number of oocytes by the tribe.

The Kruskal-Wallis, $\chi^2(3) = 13.1976$, $p < .001$, indicates a statistically significant relationship between Tribe and the Number of oocytes.

Religion.

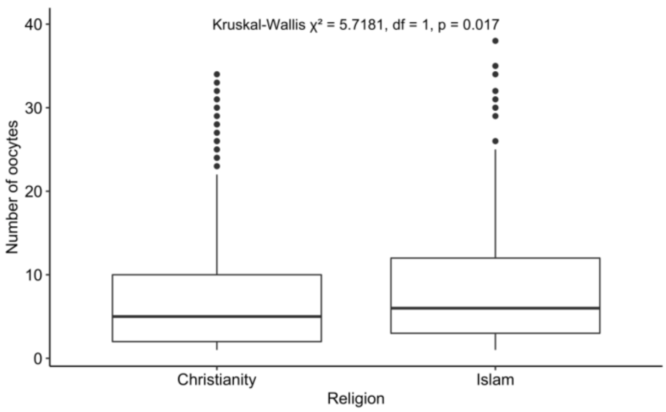

Figure 10. Boxplot of the number of oocytes by religious affiliation.

The Kruskal-Wallis, $\chi^2(1) = 5.7181$, $p = .017$, indicates a statistically significant relationship between Religion and the outcome of the Number of oocytes.

Polycystic ovary syndrome.

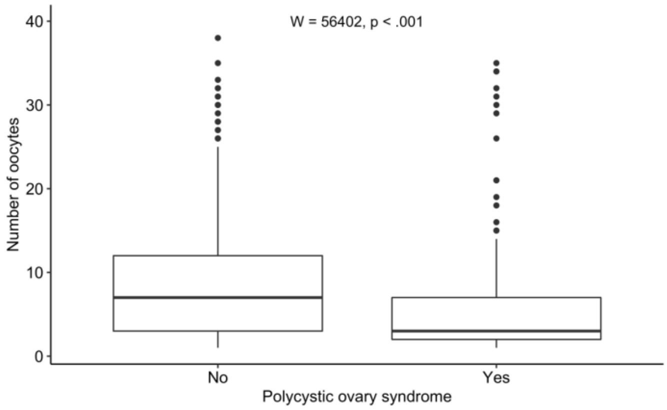

Figure 11. Boxplot of the number of oocytes by PCOS status.

The Wilcoxon rank-sum, $W = 56402$, $p < .001$, indicates a statistically significant relationship between Polycystic ovary syndrome status and the outcome of the Number of oocytes.

Endometriosis.

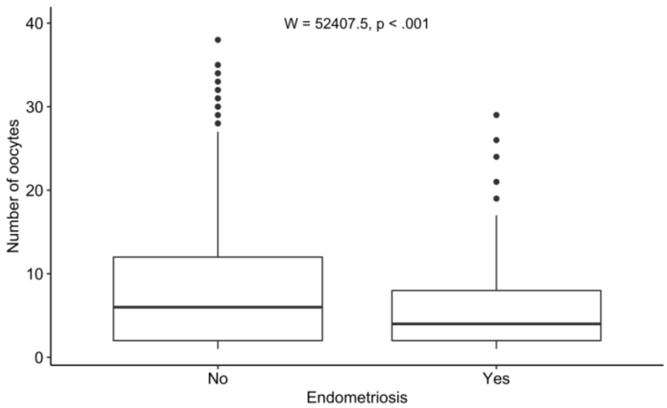

Figure 12. Boxplot of the number of oocytes by endometriosis status.

The Wilcoxon rank-sum, $W = 52407$, $p < .001$, indicates a statistically significant relationship between Endometriosis status and the outcome of the Number of oocytes.

The drug used for down-regulation.

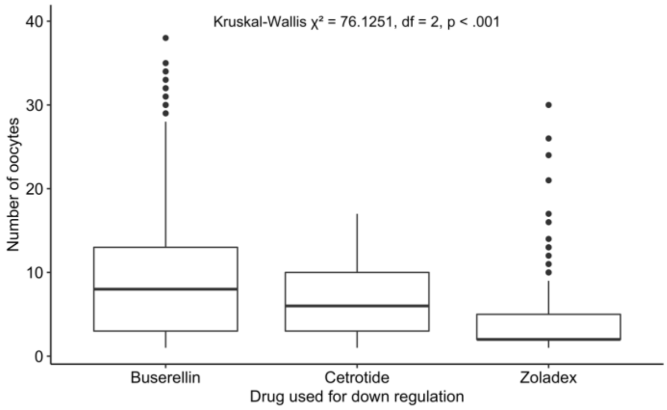

Figure 13. Boxplot of the number of oocytes by drugs used for down-regulation.

The Kruskal-Wallis, $\chi^2(2) = 76.1251$, $p < .001$, indicates a statistically significant relationship between Drugs used for down-regulation and the outcome of the Number of oocytes.

Duration of downregulation in weeks.

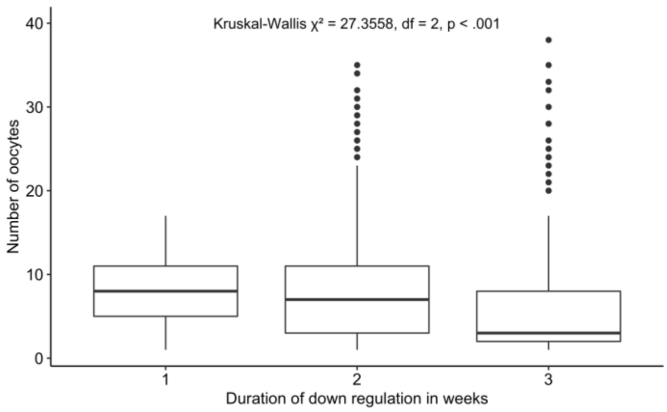

Figure 14. Boxplot of the number of oocytes by the duration of downregulation.

The Kruskal-Wallis, $\chi^2(2) = 27.3558$, $p < .001$, indicates a statistically significant relationship between the Duration of down-regulation in weeks *a*nd the outcome of the Number of oocytes.

The drug used for stimulation.

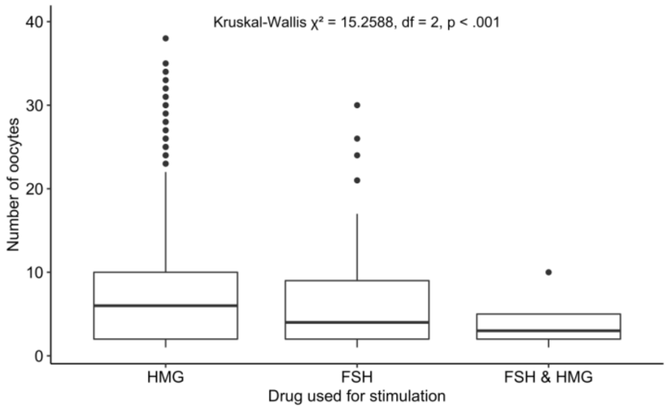

Figure 15. Boxplot of the number of oocytes by the drug used for stimulation.

The Kruskal-Wallis, $\chi^2(2) = 15.2588$, $p < .001$, indicates a statistically significant relationship between Drugs used for stimulation and the outcome of the Number of oocytes.

The dose of the drug used for stimulation.

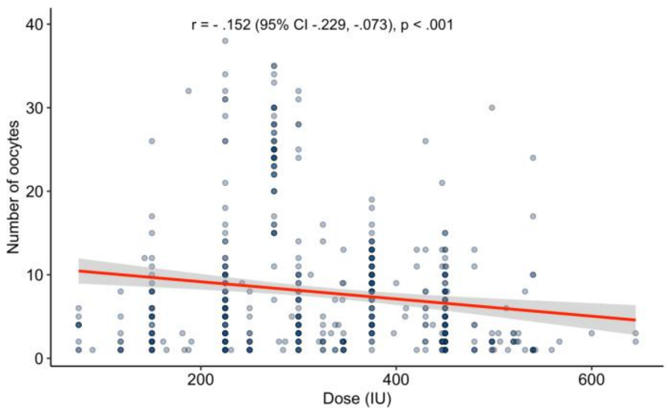

Figure 16. Scatter plot of dose versus the number of oocytes.

As shown in the scatterplot in Figure 16, the Pearson's $r = -.152$ (95% CI $-.229$, $-.073$), $p < .001$ indicates a weak, but statistically significant relationship between the Dose (IU) and Number of oocytes.

Duration of stimulation.

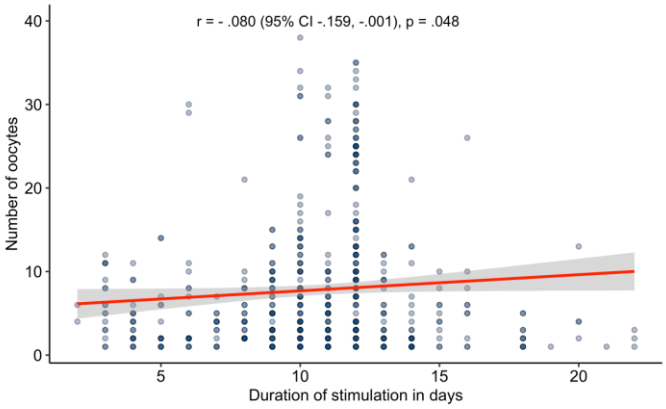

Figure 17. Scatterplot of the duration of stimulation versus the number of oocytes.

The Duration of stimulation in days has a weaker correlation with the Number of oocytes, $r = -.080$ ($-.001$, $-.159$), $p = .048$.

The relationships between these variables and the number of oocytes are summarized in Table 3.

Table 3

Summary of Bivariate Relationships Between Variables and the Number of Oocytes

Variable	Test statistics	*p*-value
Age	$r = -.276$	< .001
Age Group	Kruskal-Wallis $\chi^2(6) = 33.4796$	< .001

Education	Kruskal-Wallis $\chi^2(2) = 7.2751$	.026
Socioeconomic status	Kruskal-Wallis $\chi^2(2) = 15.1107$	< .001
Tribe	Kruskal-Wallis $\chi^2(3) = 13.1976$	.004
Religion	Kruskal-Wallis $\chi^2(1) = 5.7181$	.017
Polycystic ovary syndrome	Wilcoxon $W = 56402$	< .001
Endometriosis	Wilcoxon $W = 52407$	< .001
Drug used for down regulation	Kruskal-Wallis $\chi^2(2) = 76.1251$	< .001
Duration of down regulation in weeks	Kruskal-Wallis $\chi^2(2) = 27.3558$	< .001
Drug used for stimulation	Kruskal-Wallis $\chi^2(2) = 15.2588$	< .001
Dose of drug used for stimulation	$r = -.152$	< .001
Duration of stimulation	$r = -.080$	.048

The results of the relationships between the variables and the number of oocytes are presented in Table 3. The *p*-values < 0.5 show a significant relationship, while *p*-values >0.5 show no significant relationship.

Checking for Confounding

A confounder is related to both the dependent and independent variables but is not an intermediate variable in the causal pathway. The bivariate analyses below show the relationships between the study subjects' sociodemographic, treatment-related characteristics, and the outcome variable. The relationships between these variables and the Treatment protocol group are shown in Figure 18.

Age.

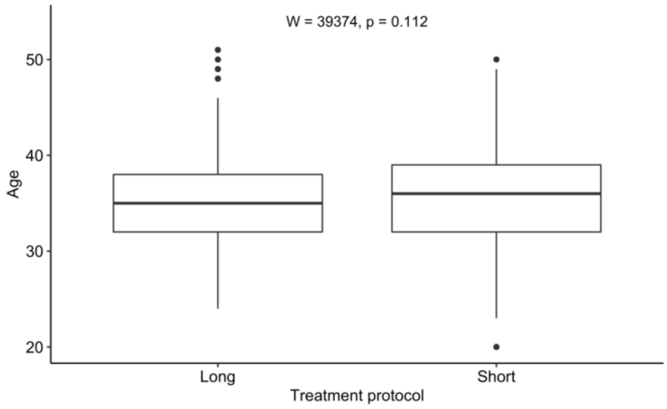

Figure 18. Boxplot of age by treatment protocol group.

The median age for the women who had long and short protocols do not differ significantly (*W* = 39.374, *p* = 0.112).

Age group.

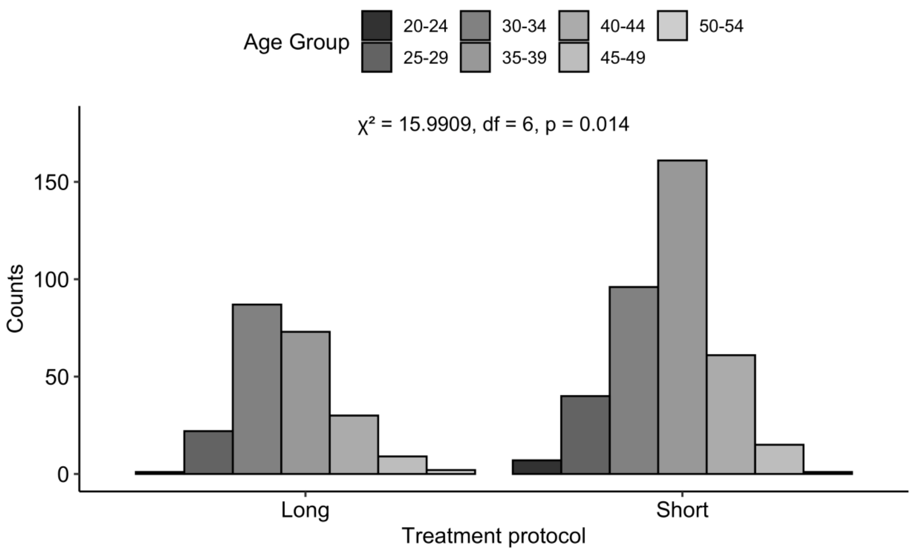

Figure 19. Boxplot of age groups by treatment protocol group.

The Kruskal-Wallis, $\chi^2(6) = 15.9909$, $p < 0.014$, indicates a statistically significant relationship between the Age group and Treatment protocol group.

Education.

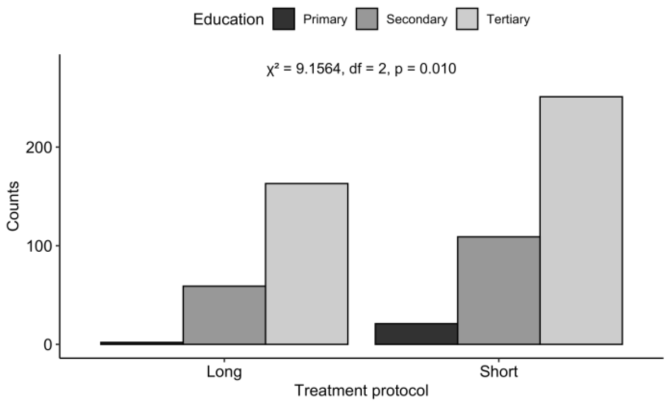

Figure 20. Boxplot of education by treatment protocol group.

The Kruskal-Wallis, $\chi^2(2) = 9.1564$, $p = 0.010$, indicates a statistically significant relationship between Education and Treatment protocol groups

Socioeconomic status.

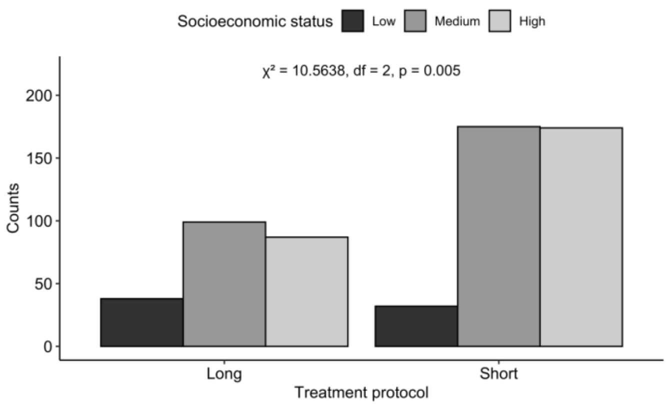

Figure 21. Boxplot of socioeconomic status by treatment protocol group.

The Kruskal-Wallis, $\chi^2(2) = 10.5638$, $p = 0.005$, indicates a statistically significant relationship between Socioeconomic status and Treatment protocol group.

Tribe.

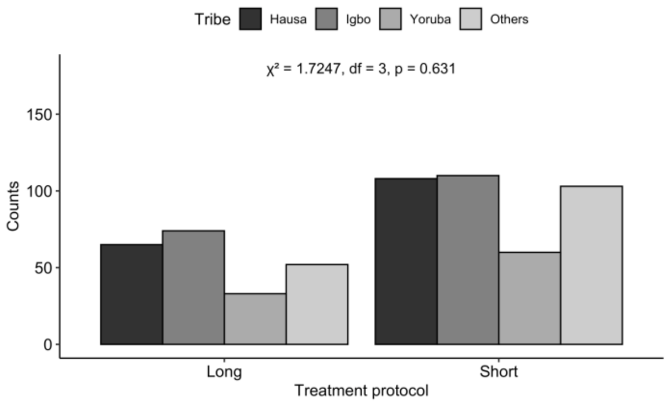

Figure 22. Boxplot of the tribe by treatment protocol group.

The Kruskal-Wallis, $\chi^2(3) = 1.7247$, $p = 0.631$, indicates that there is no statistically significant relationship between Tribe and Treatment protocol.

Religion.

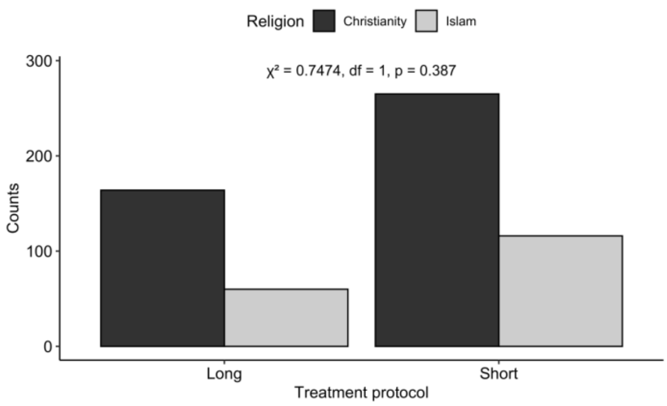

Figure 23. Boxplot of religion by treatment protocol group.

The Kruskal-Wallis, $\chi^2(1) = 0.7474$, $p = 0.387$, indicates that there is no statistically significant relationship between Religion and Treatment protocol group.

Polycystic ovary syndrome.

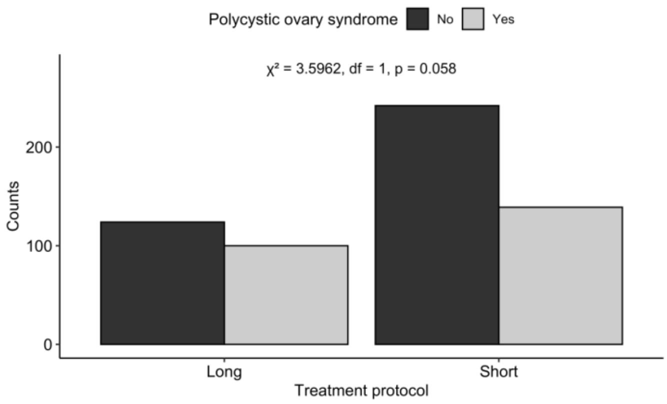

Figure 24. Boxplot of PCOS status by treatment protocol group.

The Kruskal-Wallis, $\chi^2(1)= 3.5962$, $p = 0.058$, indicates that there is no statistically significant relationship between Polycystic ovary syndrome status and Treatment groups.

Endometriosis.

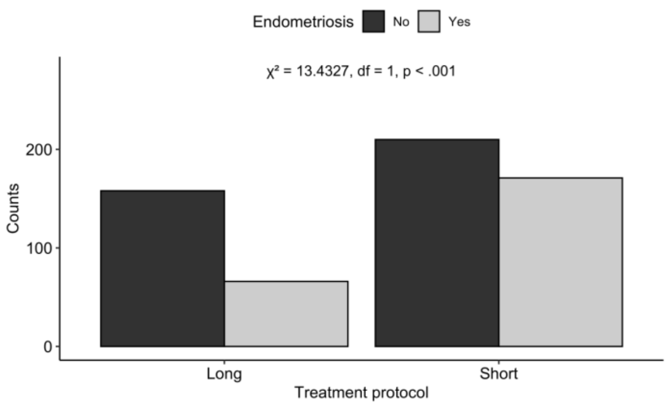

Figure 25. Boxplot of endometriosis by treatment protocol group.

The Kruskal-Wallis, $\chi^2(1) = 13.4327$, $p = 0.001$, indicates a statistically significant relationship between the Endometriosis status and Treatment protocol group.

The drug used for down-regulation.

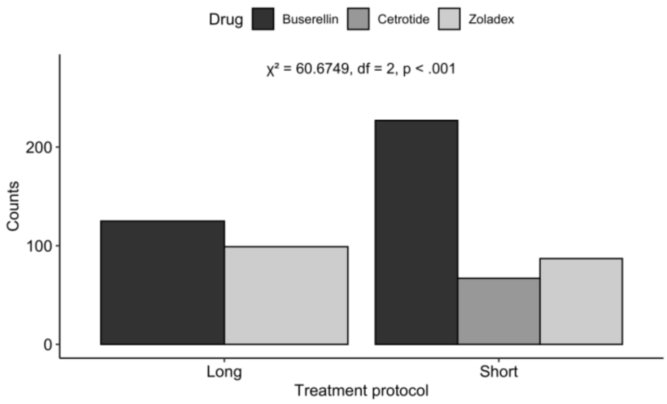

Figure 26. Boxplot of drug used for downregulation by treatment protocol group.

The Kruskal-Wallis $\chi^2(2) = 60.6749$, $p < .001$ indicates a statistically significant relationship between Drugs used for down-regulation and Treatment protocol group.

Duration of down-regulation.

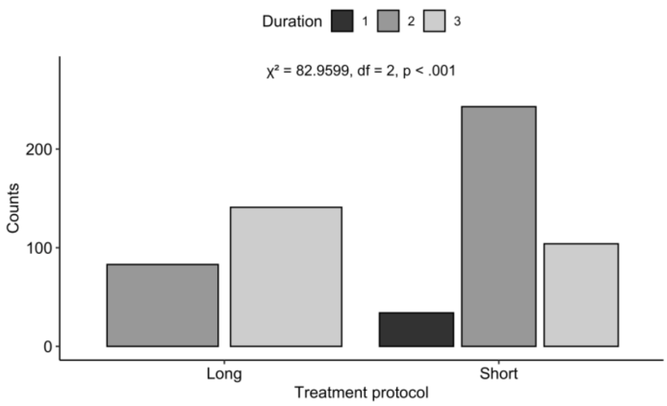

Figure 27. Bar plot of duration of down-regulation by treatment protocol group.

The Kruskal-Wallis, χ^2 (2) = 82.9599, p < .001, indicates a statistically significant relationship between the Duration of down-regulation in weeks and Treatment protocol group.

The drug used for stimulation.

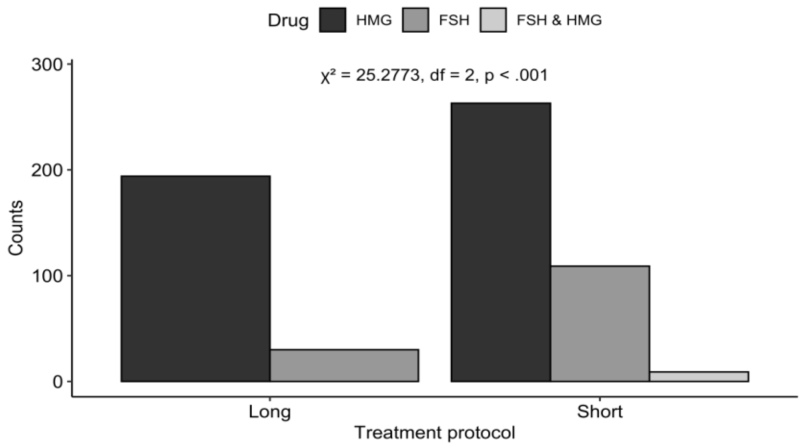

Figure 28. Bar plot of drugs used for stimulation by treatment group.

The Kruskal-Wallis χ^2(2) = 25.2773, p < .001 indicates a statistically significant relationship between Drugs used for stimulation and the outcome of the treatment protocol group.

The dose of the drug used for stimulation.

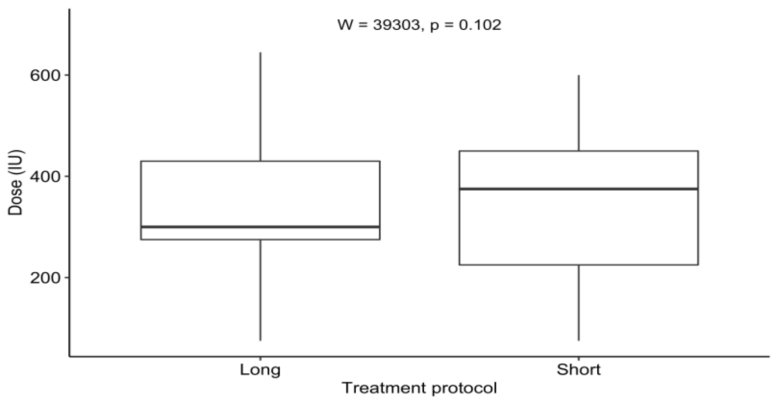

Figure 29. Boxplot of the dose of the drug used for stimulation by treatment protocol group.

The Wilcox on the rank-sum test, $W = 15.2588$, $p = 0.102$, indicates that there is no statistically significant relationship between Drugs used for stimulation and Treatment protocol group.

Duration of stimulation.

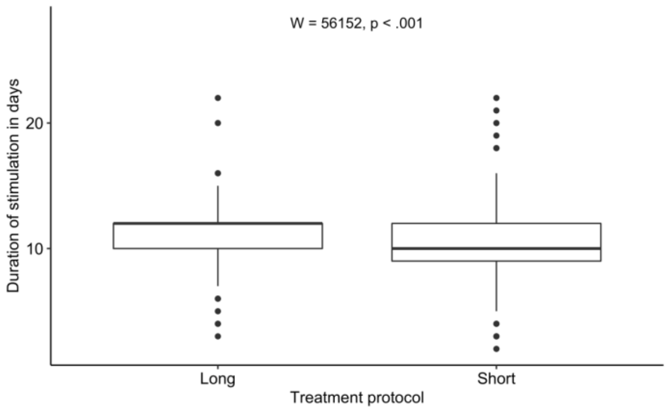

Figure 30. Boxplot of the duration of stimulation by treatment protocol group.

The Wilcoxon rank-sum test, $W = 56152, p < 0.001$, indicates that there is a statistically significant relationship between the duration of stimulation in days and Treatment protocol group.

Table 4

Differences Between Treatment Protocol Groups

	Long (N = 224)	Short (N = 381)	p
Hospital (%)			<0.001
ALPS	33 (14.7)	27 (7.1)	
Charitos	42 (18.8)	19 (5.0)	
Deda	49 (21.9)	11 (2.9)	
Elrapha	19 (8.5)	41 (10.8)	
Fertilaid	41 (18.3)	19 (5.0)	
Fertile Ground	2 (0.9)	57 (15.0)	
Garki	2 (0.9)	58 (15.2)	
Kauna	9 (4.0)	51 (13.4)	
Nisa At Prime	15 (6.7)	45 (11.8)	
Nisa Premier	12 (5.4)	53 (13.9)	
Tribe (%)			0.631
Hausa	65 (29.0)	108 (28.3)	
Igbo	74 (33.0)	110 (28.9)	
Yoruba	33 (14.7)	60 (15.7)	
Others	52 (23.2)	103 (27.0)	
Education (%)			0.010
Primary	2 (0.9)	21 (5.5)	
Secondary	59 (26.3)	109 (28.6)	
Tertiary	163 (72.8)	251 (65.9)	
Age (mean (SD))	35.2 (4.9)	35.6 (5.4)	0.408
Age Group (%)			0.014
20-24	1 (0.4)	7 (1.8)	
25-29	22 (9.8)	40 (10.5)	
30-34	87 (38.8)	96 (25.2)	
35-39	73 (32.6)	161 (42.3)	
40-44	30 (13.4)	61 (16.0)	
45-49	9 (4.0)	15 (3.9)	
50-54	2 (0.9)	1 (0.3)	
Religion = Christianity/Islam (%)	164/60 (73.2/26.8)	265/116 (69.6/30.4)	0.387

Table 4 continued

	Long (N = 224)	Short (N = 381)	p
Socioeconomic status (%)			0.005
Low	38 (17.0)	32 (8.4)	
Medium	99 (44.2)	175 (45.9)	
High	87 (38.8)	174 (45.7)	
Polycystic ovary syndrome = No/Yes (%)	124/100 (55.4/44.6)	242/139 (63.5/36.5)	0.058
Endometriosis = No/Yes (%)	158/66 (70.5/29.5)	210/171 (55.1/44.9)	<0.001
The drug used for down-regulation (%)			<0.001
Buserellin	125 (55.8)	227 (59.6)	
Cetrotide	0 (0.0)	67 (17.6)	
Zoladex	99 (44.2)	87 (22.8)	
GnRH drug = GnRH agonist/GnRH antagonist (%)	224/0 (100.0/0.0)	314/67 (82.4/17.6)	<0.001
Duration of downregulation in weeks (%)			<0.001
1	0 (0.0)	34 (8.9)	
2	83 (37.1)	243 (63.8)	
3	141 (62.9)	104 (27.3)	
The drug used for stimulation (%)			<0.001
HMG	194 (86.6)	263 (69.0)	
FSH	30 (13.4)	109 (28.6)	
FSH & HMG	0 (0.0)	9 (2.4)	
Duration of stimulation in days (median [IQR])	12.0 [10.0, 12.0]	10.0 [9.0, 12.0]	<0.001

The differences between treatment protocol groups were presented in Table 4. The variables with *p*-values of < 0.05 show that there is a significant difference in their relationships, and a *p*-value of > 0.05 indicates that there is no statistically significant difference in their relationships. Those with significant relationships as shown in Table 4 may be due to confounding.

Regression Models

The relationships between the independent variables and the outcome variable can be explored further using regression analyses. Also, the two treatment groups are dissimilar about some of the variables, as seen in Figure 31, and so these will need to be controlled when using regression analyses. The variables with $p \leq .25$ were included in the initial regression model. The most parsimonious models were found using backward stepwise regression.

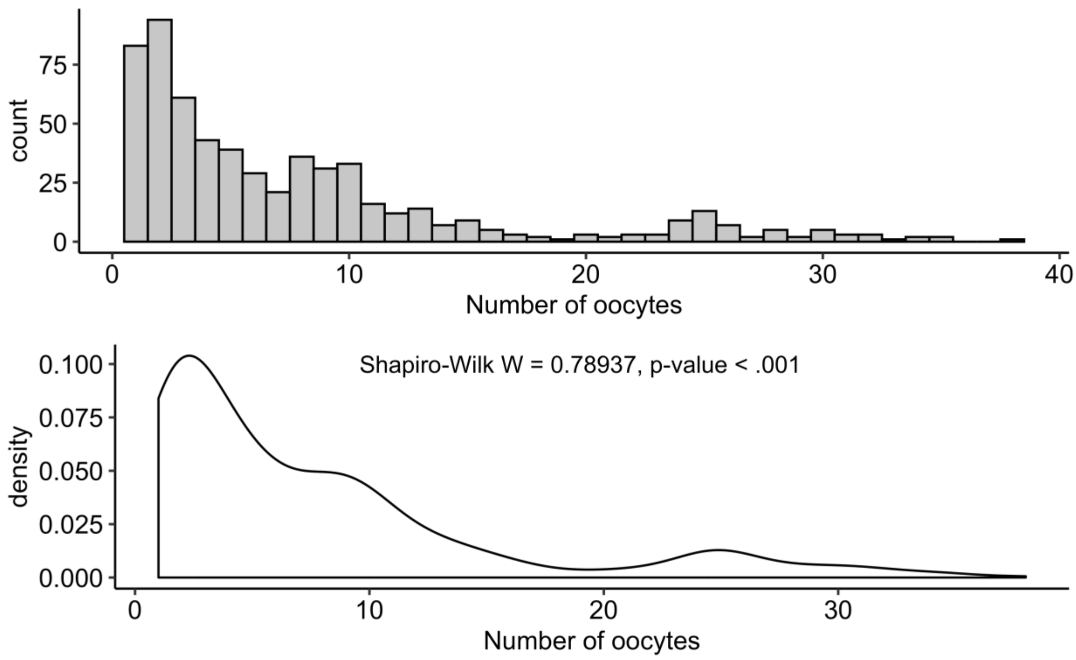

Figure 31. Histogram and density plot of the outcome variable (number of oocytes).

It is apparent from the density plot that the number of oocytes is right-skewed and not normally distributed. This is a deviation from one of the assumptions of linear regression models, which requires the dependent variable to be normally distributed. Since the outcome variable is not normally distributed, the following approaches were explored: (a) linear regression modeling with the log-transformed outcome and (b) generalized linear modeling with a Gamma distribution.

Log Transformation of the Outcome Variable

We can log-transform the outcome variable as the arithmetic mean:

$$\frac{1}{n}\sum_{i=1}^{n} Y_i$$

While the geometric mean is: $\sqrt[n]{\prod_{i=1}^{n} Y_i} = e^{\frac{1}{n}\sum_{i=1}^{n} log(Y_i)}$

So the linear model with the log-transformed outcome is a multiplicative geometric mean model, which is modeling the following:

$$E[log(Y_i)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n$$

Thus

$$Y_i = e^{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n}$$

Which is equivalent to:

$$Y_i = e^{\beta_0} \times e^{\beta_1 X_1} \times e^{\beta_2 X_2} \times \ldots \times e^{\beta_n X_n}$$

Note that $E[log(Y_i)] = \frac{1}{n}\sum_{i=1}^{n} l\,og(Y_i)$ (i.e., the geometric mean). This model is interpretable in terms of the change in the geometric mean. Thus, this model assumes multiplicative effects on the primary outcome by the predictors.

Table 5

Model 1

	β	*SE*	*t* value	*P*
Intercept	2.369	0.0707	33.52	< .001
Endometriosis	-0.234	0.0735	-3.182	.002
Short Protocol	-0.672	0.0787	-8.582	< .001
Cetrotide	0.0538	0.1191	0.4512	.652
Zoladex	-0.888	0.0802	-11.08	< .001

Table 6

Model 2

	B	*SE*	*t* value	*P*
Intercept	1.581	0.1364	11.6	< .001
Endometriosis	-0.1099	0.06557	-1.676	0.094
Short Protocol	-0.3529	0.08355	-4.224	< .001
Cetrotide	0.2732	0.1075	2.541	.011
Zoladex	-0.3237	0.08841	-3.661	< .001
ALPS	-0.03496	0.1409	-0.2481	.804
Charitos	1.412	0.1556	9.075	< .001
Deda	0.05215	0.1469	0.3549	.<.001
Elrapha	0.02513	0.1363	0.1844	.854
Fertilaid	1.233	0.1561	7.897	< . 001
Fertile Ground	0.5081	0.1429	3.557	< .001
Garki	0.3188	0.1405	2.269	< .024
Kauna	-0.06684	0.1358	-0.4921	< .005
Nisa	-0.02962	0.1434	-0.2066	< .001

Model Diagnostics

There are some assumptions of linear regression; these assumptions are:

- Homogeneity of variance (homoscedasticity): The error variance should be constant.
- Linearity: The relationships between the predictors and the outcome variable should be linear.
- Independence: The errors associated with one observation are not correlated with the errors of any other observation.
- Normality: The errors should be normally distributed. Technically, normality is necessary only for hypothesis tests to be valid.
- Model specification: The model should be appropriately specified (including all relevant variables and excluding irrelevant variables).

Other issues of concern are:

- Influence: individual observations that exert undue influence on the coefficients
- Collinearity: predictors that are highly collinear (i.e., linearly related, can cause problems in estimating the regression coefficients).

These assumptions were examined using diagnostic plots (see Figure 32).

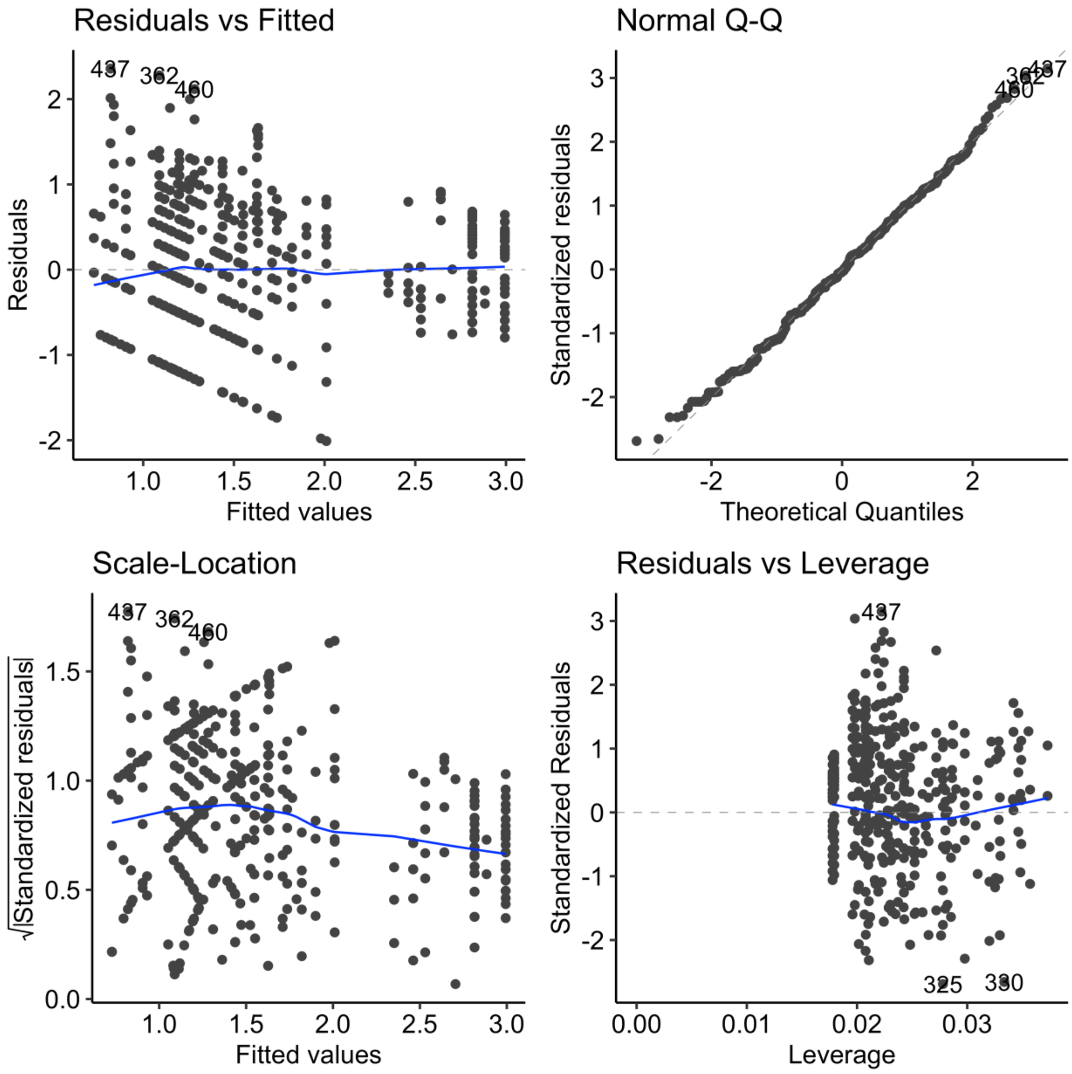

Figure 32. Diagnostic plots.

Model Interpretation

There are essential ways commonly used to assess the performance of the regression model. These ways are the root mean squared error (RMSE), which measures the model prediction error. The RMSE is the average difference between the observed values of the outcome and the predicted values. The lower the RMSE, the better the model. The R^2 is the squared correlation between the observed outcome values and the predicted values. The higher the R^2, the better the model. The F statistic provides the overall significance of the model.

From Figure 32, we see that the better model is:

$$\begin{aligned}\log(\text{Number of oocytes}) \\ = \beta_0 + \beta_1 \times \text{Endometriosis} + \beta_2 \times \text{Short Protocol} + \beta_3 \times \text{Cetrotide} \\ + \beta_4 \times \text{Zoladex} + \beta_5 \times \text{ALPS} + \beta_6 \times \text{Charitos} + \beta_7 \times \text{Deda} + \beta_8 \\ \times \text{Elrapha} + \beta_9 \times \text{Fertilaid} + \beta_{10} \times \text{Fertile Ground} + \beta_{11} \times \text{Garki} \\ + \beta_{12} \times \text{Kauna} + \beta_{13} \times \text{Nisa At Prime}\end{aligned}$$

Which is:

$$\begin{aligned}\log(\text{Number of oocytes}) \\ = 1.581 - 0.110 \times \text{Endometriosis} - 0.353 \times \text{Short Protocol} \\ + 0.273 \times \text{Cetrotide} - 0.324 \times \text{Zoladex} - 0.035 \times \text{ALPS} + 1.412 \\ \times \text{Charitos} + 0.052 \times \text{Deda} + 0.025 \times \text{Elrapha} + 1.233 \times \text{Fertilaid} \\ + 0.508 \times \text{Fertile Ground} + 0.319 \times \text{Garki} - 0.067 \times \text{Kauna} \\ - 0.030 \times \text{Nisa At Prime}\end{aligned}$$

Comparing both models shows much of the variance in the data can be explained by the Hospital variable; the adjusted $\Delta R^2 = .183$. The second model, which incorporates the Hospital, explains 42.2% of the variance in the data compared to the first model, which only explains 23.9%. Therefore, more of the effect on the treatment outcome could be due to factors related to Hospital and not Treatment protocol or patient-related characteristics.

Recall then that the outcome variable is the log-transformed number of oocytes. Therefore, to interpret the coefficients in the model equation, subtract one from this number and multiply by 100 to give the percent increase (or decrease) in the dependent variable for every one-unit increase in the independent variable. For example, the coefficient (β) for Short Treatment Protocol is −0.353, then $(e^{-0.353} - 1) \times 100 = -29.74$: that is, a 29.7% decrease in the Number of oocytes compared to the Long Treatment Protocol

Summary

In Chapter 4, descriptive and inferential test statistics were performed to examine the relationship, if any, on the long and short IVF treatment protocol and patient characteristics on the number of oocytes. Test for normality was conducted on the data to see the distribution curve, which showed right skewness and non-parametric test statistics. Wilcoxon rank-sum test, Kruskal-Wallis, and Pearson correlation test statistics were performed to establish the relationship between the treatment protocols and the influence of patient characteristics on the number of oocytes. The relationships between independent and outcome variables were further assessed using a linear regression model using log-transformed outcomes.

The overall results of analysis showed that there is a significant difference between the long and short IVF treatment protocol and patient characteristics, such as age, education, religion, ethnicity, medical condition, and other variables such as drug used for down-regulation, duration of down-regulation, drug used for stimulation, and duration for stimulation. All influenced the number of oocytes. Details of findings are discussed in Chapter 5.

Chapter 5: Discussion, Conclusions, and Implications

The findings from the results in Chapter 4 are explained in this chapter. The limitations of this study and the implications for future research in infertility treatment in Nigeria are also presented.

Infertility treatment through IVF intervention has continued to advance worldwide with the view of reducing the burden, stigma, anxiety, emotional trauma, and economic losses that are associated with infertility (Okoroike, 2009). In Nigeria, IVF has gained popularity as a means to curb infertility problems as a result of increased awareness, demand, and increased number of fertility treatment centers, despite the relatively high cost of fertility treatment in Nigeria.

Two IVF treatment protocols, long and short protocols, have been widely studied, but at the time of this study, such a study was never done in Nigeria to compare the outcome of both protocols. In this study, I have examined these protocols and patient characteristics, such as age, medical conditions (e.g., PCOS), SES, education, ethnicity, and other factors, like the number of gonadotropins used and duration of treatment and OHSS, using secondary data from 10 fertility centers across Nigeria. Descriptive and inferential statistical analysis was conducted on the data using SPSS Version 25 to establish the IVF treatment protocol most suitable for the majority of infertile women in Nigeria.

At first, a standard distribution test on the outcome variable, which is continuous, using the histogram and density plot was conducted. The result showed a significant right skewness (Figure 1), depicting the nonnormal distribution of the outcome variable, hence the consideration for nonparametric test statistics. The

Wilcoxon rank-sum test was used to test the RQ1 null hypothesis of no relationships between treatment outcome in long and short treatment protocols. The result is as shown in the box plot (Figure 2). The median number of oocytes of the long and short protocol group were 8 and 4 to indicate a significant effect of the protocol group (W = 54503, $p < .001$) on the number of oocytes.

The RQ2 null hypothesis of no relationship between treatment outcome and patient characteristics, such as age, SES, ethnicity, religion, PCOS, and endometriosis, were inferentially tested using the statistics of a bivariate test. The figures for age and age group showed that age significantly affects treatment outcome of protocol group: $r = -0.276$ (95% CI −0.348, −0.200), $p < .001$, and the Kruskal-Wallis, $\chi^2(6) = 33.4796$, $p < .001$. A statistically significant difference was also observed with the level of education and outcome of treatment in the groups, as indicated by the Kruskal-Wallis $\chi^2(2) = 7.2751$, $p = .026$. SES, tribe, religion, PCOS, and endometriosis showed similar results of significant difference in the groups (Figures 3, 4, 5, 6, 7, and 8), with the Kruskal-Wallis of $\chi^2(2) = 15.1107$, $p < .001$; the Kruskal-Wallis of $\chi^2(3) = 13.1976$, $p < .001$; the Kruskal-Wallis of $\chi^2(1) = 5.7181$, $p = .017$; the Wilcoxon rank-sum of $W = 56402$, $p < .001$; and the Wilcoxon rank-sum of $W = 52407$, $p < .001$.

Other factors, such as type of drug used for down-regulation, duration of down-regulation, type of drug used for stimulation, and duration of stimulation, were tested against treatment outcome of protocol group using bivariate statistical analysis, and the results were statistically significant (Figure 25), with the Kruskal-Wallis χ^2 (2) = 76.1251, $p < .001$; drug for stimulation, the Pearson's $r = -.152$ (95% CI −.229,

−.073), $p < .001$; dose of medication for stimulation, the Pearson's $r = −.152$ (95% CI −.229, −.073), $p < .001$; and duration of stimulation, $r = −.080$ (−.001, −.159), $p = .048$. The entire result is summarized in Figures 26, 27, 28, and 30.

The effect of confounding between the dependent and independent variables was also checked using bivariate analysis, and a linear regression model was used to examine the relationships between independent and dependent variables. The result showed that hospital factors accounted for 42.2% of the most effect on the outcome rather than types of protocol and patient characteristics. These results are reflected in Tables 4 and 6.

Interpretation of Findings

The dearth of studies on fertility treatment in Nigeria has made it necessary for findings from this study to be relevant to fertility clinicians and policymakers to reference this evidence-based outcome in their clinical decision related to which fertility treatment protocol should be considered for women seeking fertility treatment in Nigeria.

In RQ1, I assessed a total of 605(*N*) fertility treatment folders of women between ages 20 and 54 (mean age 35.5) from 10 different hospitals across the six geo-political zones in Nigeria. I found that the median number of the oocyte is 8 and 4 for long protocol and short protocol groups, respectively. The Wilcoxon rank-sum test showed that there is a significant effect of the protocol group ($W = 54503$, $p < .001$) on the number of oocytes. This finding is consistent with the study conducted by Jianping et al. (2015). They compared results of a GnRH analog in long and short treatment protocol groups of a 3-year data collection from 2010 to 2013, consisting of

5,662 (*N*) women of various ages, consisting of < 31 to > 40, who have completed IVF treatment cycle. Jianping et al. (2015) found that across all ages of participants, women who received long protocol treatment yielded higher and better quality oocytes than the women who had short protocol ($p < 0.05$). Likewise, Xiao et al. (2013) reported a higher number of and quality of oocyte follicles in the long protocol than in short protocol.

In RQ2, I assessed to see if there is a relationship between patient characteristics and treatment outcomes in the two protocol groups. Age was the first characteristic examined against outcome using the Pearson correlation coefficient. The result showed a significant difference $r = -0.276$ (95% CI −0.348, −0.200), $p < .001$ (Figure 2). The age group was also examined against outcome using the Kruskal-Wallis test statistics; the result was significant at $\chi^2(6) = 33.4796$, $p < .001$ (Figure 3). The result showed that the highest number of oocytes favored women of age < 30 (median 10 and 8), and the oocyte number plateaued at age 30 to 39, after which the number of oocytes declined exponentially in both protocol groups as the age increased, which is consistent with the body's natural physiological process.

This finding is in agreement with retrospective studies by Faitt-Weller (2001) and Tan, Lau, Loh, and Tan (2014). They collected and analyzed 3,412 IVF treatment data from fertility hospitals between January 2008 to December 2010. The age of the women were in order of < 30 years, 30 to 35 years, 36 to 37 years, 38 years, 39 years, 40 to 44 years, and > 45 years and the researchers discovered that age significantly affected the number of yielded oocyte, $p < .001$, and the highest number of oocytes were reported for women < 30 years (mean 18.5 +/- 10.3). Faitt-Weller (2001) also stated that there is a decrease in the number of quality oocyte in IVF treatment as the age of the women increases.

The level of education of women who had IVF treatment from the 10 fertility hospitals was considered as one of the patient characteristics. This was assessed using the Kruskal-Wallis inferential test statistics, and the result on the outcome of treatment was statistically significant at $\chi^2(2) = 7.2751$, $p = .026$. Women with tertiary education showed a better outcome than other women with a lower level of education (median 5). See Figure 4. This is likely because women with higher education were expected to present early for infertility treatment, with the understanding that delay may affect treatment outcome. Shruthi et al. (2014) conducted a 9-year, prospective cohort study with a sample size of 2,569, from 1994 to 2003, and using three fertility clinics in Boston. The influence of the educational level of women on IVF treatment outcome was assessed, and they found that women with a higher education level were able to follow the rules of the treatment protocol better than those with lower education (Shruthi et al., 2014).

The SES was assessed among the patient characteristics that affect treatment outcome using the Kruskal-Wallis $\chi^2(2) = 15.1107$, $p < .001$ (Figure 5), showing a statistically significant association. In this case, women of low SES produced a higher number of oocytes (median 9) than women of medium and high SES class (median 5 and 3), respectively. This finding is in contrast with the reports of Ho et al. (2017), who posited that women with higher income levels are more nourished and financially buoyant. They are more likely to present early at the clinic for fertility treatment, and they still do better with a higher yield of quality oocytes than those of lower-income.

Ethnicity is viewed as a prognostic factor in infertility (Dhillon et al. 2015; Maalouf, Campbell, & Jayaprakasan, 2017). Dhillon et al. (2015) investigated the relationship between ethnicity and IVF outcome, analyzing results of IVF cycles with a sample size of 13,473, comprised of different ethnicities (i.e., White, Black, and South Asian women), age, and BMI; the duration for infertility was adjusted. They compared their findings with 16 published meta-analysis results and reported that White women have better IVF oocytes and embryos than Black and South Asian women: Black versus White (*OR* 0.42 [0.25 to 0.70]; p = 0.001); South Asian versus White (*OR* 0.80 [0.65t o 0.99]; p = 0.04; Dhillon et al., 2015). In my study, the measure of the number of embryos and clinical pregnancy was a direct function of the number of oocytes; hence, a similar relationship between ethnicity and number of oocytes was established after the analysis of tribe (i.e., ethnicity) versus the number of oocytes. The Kruskal-Wallis of $\chi^2(3) = 13.1976$, $p < .001$ indicates a statistically significant relationship between the tribe and the outcome of the number of oocytes, with the Hausa women yielding a higher number of the oocyte (median 8) among the three major languages in Nigeria: Hausa, Ibo, and Yoruba. This finding is strongly associated with age. Hausa women practice early marriage; some marry at menarche and some as teenagers. A typical Hausa family is polygamous and Islamic, and Hausa women who had infertility sought help earlier than the other tribes. The Ibo and Yoruba women were next in that order (median 5 and 4); refer to Figure 6.

Moreover, as observed in this study, religion showed a similar significant influence as an ethnicity on the number of oocytes (Figure 7). Islamic women had a higher number of oocytes (median 8) than Christian women (median 5), reflected by the Kruskal-Wallis of $\chi^2(1) = 5.7181$, $p = .017$. This observation is unconnected to the belief that most Islamic women marry early, and those who have infertility issues sought early intervention. On the side of Christian women, they resort to prayers while waiting for the miraculous, and, as a result, most Christian women sought late intervention. McQuillan (2004) reported a similar fertility pattern, where he observed a higher fertility pattern amongst the Muslim women population than in the Christian women population worldwide.

PCOS and endometriosis were also observed to affect the number of oocytes retrieved in these women significantly. The data showed that the women who had IVF treatment with no medical condition, such as PCOS, did better with the number of matured oocytes (median 8) than those with PCOS (median 3), with a Wilcoxon rank-sum of $W = 56402$, $p < .001$. A similar trend was seen in women with no endometriosis, who did better with the number of matured oocytes (median 7) than those with endometriosis (median 4); the Wilcoxon rank-sum was $W = 52407$, $p < .001$, see also Figures 8 and 9. Similar findings were reported in a study by Hassani et al. (2019), where 60 women were used in a case-control study to assess the impact of PCOS on matured oocytes in IVF treatment. The result showed that women in the case group who had PCOS had a fewer number of matured oocytes than those in the control group who had no PCOS. Likewise, Senapati, Samuel, Morse, and Barnhart (2016) investigated and established the relationship between endometriosis and the number of matured oocytes yield. They analyzed the data of 347,185 IVF treatment cycles from 2008 to 2010 and reported that 11% of these women who had IVF treatment were endometriotic patients, and the number of matured oocytes yielded was significantly lower in this group of women (Senapati et al, 2016).

Other than these patient characteristics as discussed in this section, some factors such as a drug used for down-regulation, duration of down-regulation, the medicine used for stimulation, duration of stimulation, and dose of medication were also assessed to see if these factors impact on the number of oocytes yield in IVF treatment in both protocols.

Results showed that Buserelin, a GnRHa, yielded a higher number of oocytes (median 8) than Cetrotide (median 5) and Zoladex (median 3), The Kruskal-Wallis of $\chi^2(2) = 76.1251$, $p < .001$ showed a statistically significant relationship between Drugs used for down-regulation and the outcome of the Number of oocytes. The duration of down-regulation was assessed, and I observed that a statistically significant relationship also exists between the Duration of downregulation in weeks and the outcome of the Number of oocytes. The Kruskal-Wallis, $\chi^2(2) = 27.3558$, $p < .001$, implies that the faster or shorter the response for optimum down-regulation, the better the number of oocytes, with results of 1-week down-regulation (median 8), 2-week down-regulation (median 7), and 3-week down-regulation (median 4); see Figure 10. This finding indicates that women who took a longer time to achieve optimum down-regulation are more likely not to do better in the stimulation phase of IVF treatment and are regarded as the potential poor responders.

The drugs used for stimulation were HMG, FSH, and a combination of the two. The impact of these drugs on the number of oocytes was assessed, and the result revealed that women who had HMG for stimulation did better (median 8) than those who had FSH (median 5) and a combination of HMG and FSH (median 3); see Figure 11. The Kruskal-Wallis of $\chi^2(2) = 15.2588$, $p < .001$ indicates a statistically significant relationship between Drugs used for stimulation and the outcome of the Number of oocytes. The length of stimulation against the number of oocytes was assessed using a Pearson correlation test statistics, and the result showed a weak positive outcome: $r = -.080$ $(-.001, -.159)$, $p = .048$. This result pointed out that continuous stimulation after 10 days may not impact positively on the outcome.

Findings from this study support the long protocol as the most favorable IVF treatment protocol for the majority of Nigeria infertile women, despite the cost, long duration of treatment, and other side effects that are tolerable. The findings from this study support the Patient-Centered Care Treatment Model framework in IVF treatment, which considers the peculiarity of a patient or group of patients in choosing which IVF treatment protocol would give a much-desired outcome.

Limitations of the Study

This study examined the IVF treatment protocols and the impact of patient characteristics on the number of oocytes. The study population was infertile Nigerian women. Only a few fertility hospitals are available in Nigeria, and these few hospitals are sparsely distributed, with most of them concentrated in Abuja, Federal Capital Territory. Hence, this study only captured the three major ethnic groups of Hausa, Ibo, and Yoruba women in Nigeria, with little consideration of other ethnic groups in Nigeria. Besides, very few fertility physicians are available in Nigeria, which probably accounts for the limited fertility hospitals in Nigeria. In the face of a large number of infertile women presenting for treatments, most physicians were in a hurry and failed to capture some details that may have impacted the study outcome. As a result of pressure on the physician to start treatment by these women, most of the fertility physicians do not assess the patient to see which protocol is the best fit. Instead, treatment protocols are applied randomly. Moreover, some of the physicians use only one protocol for their patients for lack of experience with the other protocols.

Recommendations

The study showed that the median number of oocytes (median 8) generated following IVF treatment was more in the long protocol group than the median number of oocytes (median 5) in the short protocol group, and this difference was statistically significant. Likewise, the patient characteristics were also reported to have a statistically significant influence on the number of oocytes. Hence, the null hypotheses were not accepted.

Though this study used existing secondary data not collected by the researcher; as such, some essential variables that could have impacted positively in this research were missing. Data such as cadre of fertility physician, medical officer or consultant, years of experience with fertility treatment, social lifestyle, previous IVF treatment, and such were not captured in folders. The effect of these variables on the outcome would have been studied. Hence, further study using a mixed-method to have more robust data on IVF treatment for analysis is recommended.

There exist few fertility hospitals and fertility physicians in Nigeria, and most of these fertility centers are in Abuja, FCT. Training and re-training programs in infertility treatment are recommended to stir up interest in owners of hospitals and physicians in Nigeria to consider infertility treatment as a specialty. This way, there would be more fertility centers across the country with a handful of expert physicians in this area of medical practice.

Finally, according to the existing literature, my study is the first in Nigeria that has looked into the current protocol to see which is most favorable to Nigerian women who had IVF treatment. Hence, this study will form the baseline for future research into treatment protocols in Nigeria, though this could be an expensive adventure, as it would involve many hospitals and logistics. However, in the end, it would be a worthwhile adventure.

The Implications for Social Change

The social change implication of this study is that the research findings will assist practicing fertility specialists or intending specialists within or outside Nigeria to initiate treatment on an individual patient basis and the implications of deciding on which treatment protocol befits each who presents at the fertility clinic. Likewise, findings could be applied across a defined population with an understanding of treatment outcomes of the two protocols. These findings would provide evidence that could influence policies on guidelines for fertility treatment in Nigeria.

The study findings showed that women with higher education did better with IVF treatment and that age is also a determinant of treatment outcome; women aged < 35 did better than those women > 35 in this study. These findings could lead to a positive social change through a campaign program that focusses on (a) influencing women to seek improvement in their educational status for better living, (b) women empowerment through Government support or scholarship, and (c) early intervention to address delays in childbearing. The advocacy would educate women who wish to delay marriage or child-bearing to pursue a carrier to consider the option of fertility preservation until a rightful time (Wada, 2015).

Conclusion

The number of women seeking help as a result of infertility has continued to rise in Nigeria, but with not enough fertility centers and requisite expertise to attend to this problem. Instead, many hospitals and physicians take advantage of the demand for infertility in Nigeria to offer care without being properly schooled: no hands-on experience in IVF procedure and stimulation or treatment protocols. Investigations have shown that the high level of treatment failure and chronic infertility experience leading to emotional and psychological distress in these women are the result of lack of experience in IVF procedure and the knowledge gap in the treatment protocol. Although infertility and its treatment protocols have been widely researched globally, in the Nigerian situation, no such study on IVF treatment protocol had been reported at the time of this research.

The need to examine IVF treatment protocols has become imperative to find out which protocol is most favorable to Nigerian women receiving IVF treatment intervention. These findings can help practicing and interested physicians on which protocol would be most impactful to apply in any given situation.

This study used existing fertility treatment data from 10 fertility hospitals across Nigeria, and the analysis of these data showed that of all the treatments assessed, the long fertility treatment protocol offered a more positive number of oocytes than the short protocol. Also, the further assessment showed that age, education, SES, religion, ethnicity, medical condition, a drug used for down-regulation, duration of down-regulation, the medication used for stimulation, and duration for stimulation were shown to influence treatment outcome.

This finding will assist the fertility physicians in making an informed decision on which treatment protocol to consider for a patient or across a given defined population of infertile women seeking treatment. However, there is a need for continuous research in infertility in women, which could lead to the general improvement in reproductive health.

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