GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF OBSTETRICS & GYNECOLOGY

OVARIAN STIMULATION OUTCOMES IN WOMEN CLASSIFIED AS EXPECTED POOR OVARIAN RESPONDERS UNDERGOING AUTOLOGOUS ASSISTED REPRODUCTIVE TECHNOLOGY IN KUMASI, GHANA

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SEPTEMBER, 2024

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THIS THESIS IS SUBMITTED TO THE FACULTY OF OBSTETRICS AND GYNECOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE CONFERMENT OF A FELLOW OF THE GHANA COLLEGE OF SURGEONS (FGCS)

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DECLARATION

I, Dr Mawuse Kanfra, hereby declare that the work presented here is the result of my composition except for other people's work which has been appropriately acknowledged in the reference section. I affirm that neither the whole nor part of this thesis has been presented to any other institution. I am solely responsible for the content of this work.

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ABSTRACT

Introduction: Poor ovarian response (POR) in in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) programs refers to an insufficient response to standard superovulation regimens, resulting in few mature oocytes. This deficiency reduces oocyte yield, embryo yield, cumulative live birth rates, and overall, IVF/ICSI-embryo transfer effectiveness. Managing POR presents challenges in IVF/ICSI-embryo transfer programs, leading to emotional distress and financial burden, especially when IVF/ICSI-embryo transfer is self-funded. Fertility specialists and infertile couples require data to aid in counselling and decision-making for poor ovarian responders, especially for women reliably identified as expected POR. However, knowledge about POR in Africa, particularly in Ghana, is limited. Are the outcomes of OS in women with expected POR different between POSEIDON groups three and four? This study assessed the outcome of ovarian stimulation among women classified as expected POR undergoing autologous IVF or ICSI in Kumasi, Ghana.

Methods: A multicenter prospective study involving 117 consecutively selected women with expected POR undergoing autologous IVF/ICSI-embryo transfer in six fertility centres in Kumasi was conducted from August 2023 to February 2024. The study participants were classified as expected POR using the Patient-Oriented Strategy Encompassing IndividualizeD Oocyte Number (POSEIDON) criteria. A pretested structured questionnaire was used to collect data on participants' socio-demographic characteristics, obstetric and gynecological characteristics, and the outcomes of ovarian stimulation (OS). Data were analyzed and summarized using descriptive statistics including frequencies and percentages. The OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) were compared using chi-square and the students' t-test with a p-value of <0.05 deemed statistically significant.

Results: The proportion of expected POR among women who underwent autologous IVF/ICSI-embryo transfer was 31.6% (n = 117). The age range of participants was 27-48 years, with the mean age being 37.5 (±3.7) years. Over two-thirds (68.4%) of the study participants had primary infertility and a median infertility duration of 6 years. Generally, the total cycle cancellation rate

among the study participants was 38.5%, and out of this, 18.8% of them had their cycle cancelled before oocyte-pick up. About 21.4% of the women achieved clinical pregnancy. There was no statistically significant difference in OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among the two groups of women with expected POR according to the POSEIDON criteria.

Conclusion: The current study found that the proportion of expected POR among women who underwent autologous IVF/ICSI-embryo transfer in the fertility centres in Kumasi was low. Similarly, the proportion of the study participants who achieved clinical pregnancy was low. Additionally, there was a high cycle cancellation rate among the study participants. OS outcomes were similar in the two expected POR groups (POSEIDON groups 3 and 4).

Keywords: Ovarian stimulation; Expected poor ovarian responders; Intracytoplasmic sperm injection; In-vitro fertilization; Kumasi

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LIST OF ABBREVIATIONS

AFC	Antral Follicle Count
AMH	Antimullerian Hormone
ART	Assisted Reproductive Technology
BMI	Body Mass Index
CCCT	clomiphene citrate challenge test
CHRPE	Committee on Human Research, Publications and Ethics
CLBR	Cumulative Live Birth Rate
ESHRE	European Society for Human Reproduction and Embryology
FERSOG	Fertility Society of Ghana
FSH	Follicle Stimulation Hormone
FSHR	Follicle-stimulating hormone receptor
GnRH	Gonadotropin-releasing hormone
GnSAF	gonadotropin surge-attenuating factor
hCG	Human chorionic gonadotropin
ICSI	Intracytoplasmic Sperm Injection
IVF	In vitro Fertilization
LBR	Live Birth Rate
LH	Luteinizing Hormone
ORT	Ovarian reserve test
ORTs	Ovarian reserve tests
OS	Ovarian Stimulation

POR	Poor Ovarian Response
POSEIDON	Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number
SOGOG	Society of Obstetricians and Gynecologists of Ghana
TESE	Testicular sperm extraction
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

CHAPTER ONE

INTRODUCTION

1.1 Background of Study

Several infertile couples have been successfully helped by the advancement of assisted reproductive technology (ART) in the past 40 years.[1] A large number of mature follicles are intended to be recruited and grown through ovarian stimulation (OS), which is essential to the success of in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). This, in turn, leads to the retrieval of a large number of oocytes and the availability of a large number of embryos for transfer. The ovarian response and the success of IVF/ICSI-embryo transfer cycles are significantly influenced by the number of oocytes recovered after OS.[1] This success is also substantially influenced by the quality of the gametes and the quality of the laboratory conditions. Between 10 and 15 oocytes have been shown to be the optimal ovarian response to OS[2] which, in both fresh and cumulative cycles, has the highest likelihood of producing a live birth.[3] However, extremes of ovarian response (poor and excessive response) have been identified as two major concerns with OS in IVF/ICSI-embryo transfer cycles, owing to many reasons that may reduce their success rates. While many fertility doctors continue to prioritize clinical pregnancy,[4] and despite tremendous breakthroughs in ART, treating patients with poor ovarian response (POR) continues to be a challenging task.[5] Specifically, women classified as "poor responders"—those who do not respond effectively to OS continue to have lower IVF/ICSI-embryo transfer success rates.[6] POR is connected not only to a decreased success rate after IVF/ICSI-embryo transfer cycles but also to unfavorable obstetric and perinatal outcomes.[7]

Poor ovarian response suggests an inadequate response to normal superovulation regimens in ART programs.[6] POR is defined as a situation where less than four mature follicles and/or oocytes are obtained following OS with the intention of obtaining higher follicle or oocyte numbers.[8] Although the most crucial factors in determining POR have been the quantity of mature follicles and the number of oocytes recovered following a typical stimulation regimen,[9] the definition has changed over time to include more than just the oocyte retrieval part and now considers variables like low ovarian reserve, advanced maternal age, and prior POR outcomes.[10] It is difficult to effectively manage women who have been categorized as poor ovarian

responders.[11] While several OS regimens have been proposed to enhance the ovarian response in poor responders, none have shown to be more successful.[12–14] Compared to normal responders, POR women are less likely to have more recovered oocytes during standard OS, which makes it less likely that oocyte retrieval from them will result in the generation of high-quality embryos. As a result, there is usually a high cycle cancellation rate and a low clinical pregnancy rate.[15] In Italy, a study reported that women with POR had a 6% live birth rate (LBR) per cycle.[15] The cumulative life-birth rate (LBR) was found to be approximately 8%, 13%, and 19% when 1, 2, and 3 oocytes were obtained in the first IVF cycle, respectively, in a study carried out in Belgium to evaluate the LBR for at least two years from either fresh or frozen embryo transfer cycles.[15] Given that women typically have many IVF/ICSI-embryo transfer cycles, evaluating the cumulative LBR may be important for predicting the long-term result in specific groups.[7]

Poor ovarian response rates vary across the globe with a prevalence rate of 5.6% to 35.1% reported by different studies.[16–18] One of the factors that contribute to the variations in the response rates can be attributed to the use of different definitions for POR. In 2011, the Bologna criterion was developed to standardize the definition of POR by the European Society for Human Reproduction and Embryology (ESHRE).[11] The ESHRE consensus on the definition of POR states that at least two of the following three characteristics must be present: (1) women who are older than 40 years or who have any other risk factors for POR, (2) a POR in the past (cycles cancellation or fewer than 3 oocytes retrieved using a standard procedure) and (3) abnormal ovarian reserve test (i.e. AFC <5 – 7 follicles or AMH <0.5 – 1.1 ng/ml).[11] Despite the enormous effort to standardize the definition of POR, the Bologna criteria have drawn some criticisms. The absence of precisely defined risk factors for POR as utilized in the definition is one of the main critiques leveled against the Bologna criteria.[19] Therefore, there is a very significant chance that distinct subgroups will be identified if these risk variables are used to identify people with POR.[20] It was also noted by Younis *et al.* that several pairings of two of the three parameters can result in distinct subgroups of POR as opposed to a single, easily identifiable group.[19] The adoption of a cut-off of three or fewer oocytes without taking age into account, the question of oocyte number versus quality, and other elements that can lead to diminished ovarian reserves were among the numerous criticisms levelled against the Bologna criteria.[19,21]

Recently, the Patient-Oriented Strategy Encompassing IndividualizeD Oocyte Number (POSEIDON) has also been developed to divide women who have a decreased chance of a successful IVF/ICSI-embryo transfer into four groups according to their age, ovarian reserve indicators like AMH and/or AFC, and response to previous IVF/ICSI-embryo transfer cycle.[22] The POSEIDON criteria for "low prognosis" patients have been developed as a measure of ovarian resistance to gonadotropin stimulation (i.e., hypo-responsiveness).[23] The four groups of POSEIDON patients are described as ‘‘Group 1: Young patients < 35 years with sufficient ovarian reserve parameters (AMH ≥ 1.2 ng/mL; AFC $\geq$ 5) and with an unexpected poor or suboptimal response/poor ovarian response in a previous autologous IVF/ICSI’’. They are further classified under ‘’subgroups 1a (<4 oocytes) or subgroup 1b (4-9 oocytes) after standard ovarian stimulation. Group 2: Older patients ≥ 35 years with sufficient ovarian reserve parameters (AMH ≥ 1.2 ng/mL; AFC $\geq$ 5) and an unexpected poor or suboptimal response/poor ovarian response in a previous autologous IVF/ICSI’’. They are also further classified under subgroups 2a (<4 oocytes) or subgroup 2b (4-9 oocytes) after standard ovarian stimulation. Group 3: Young patients < 35 years with poor ovarian reserve pre-stimulation parameters (AMH < 1.2 ng/mL; AFC <5) and Group 4: Older patients aged ≥ 35 years with poor ovarian reserve pre-stimulation parameters (AMH < 1.2 ng/mL; AFC <5)’’.[23] Thus POSIEDON groups 1 and 2 are known as “unexpected POR” whilst POSIEDON groups 3 and 4 are known as “expected POR’’ to exogenous gonadotropin stimulation. The ‘’unexpected POR’’ are hypo-responders whose ovarian response to exogenous gonadotropin stimulation is low. Women with a low ovarian reserve are considered ‘’expected POR’’ women because they have a significantly poorer prognosis due to a rise in oocyte aneuploidy with age.[23]

POR is linked to a lower oocyte yield, a higher risk of cycle cancellation, and a much lower chance of becoming pregnant.[9] Assessing clinical and laboratory outcomes of OS among women with POR can inform and aid fertility specialists in improving their management. Generally, the number of metaphase 11 oocytes at ICSI, cycle cancellation rate (before oocyte pick up), and clinical pregnancy rates are among the six key performance indicators for ovarian stimulation in IVF/ICSI-embryo transfer cycles that were agreed upon by the Maribor consensus.[24] These key performance indicators are essential for objectively tracking ovarian stimulation and assessing clinical work in ART.[24] Additionally, two reference indicators that are directly linked to the caliber of clinical practice were defined in the Vienna consensus: the percentage of retrieved

oocytes and the percentage of mature metaphase II oocytes at ICSI.[25] Addressing the expectations of couples undergoing IVF/ICSI-embryo transfer cycles classified as expected POR is important because of the predicted low success rates. Discussing the accumulated live birth rates over several treatment cycles with couples as well as the likelihood of success in the first IVF/ICSI-embryo transfer cycle may bolster their confidence and lower drop-out and disappointment rates following the first IVF/ICSI-embryo transfer cycle. The management of women classified as expected POR can be challenging for fertility specialists since there is no conclusive proof of how to enhance outcomes.[12,14] Options available to women who record POR during their OS cycles may be to proceed with oocyte pick-up and utilize the limited quantity of oocytes available, or choose to end the cycle and repeat ovarian stimulation using a higher dosage of gonadotropins in the hopes of receiving a sufficient response. Some POR women may also opt for donor oocytes or the adoption of a child.[26–32] Notwithstanding the aforementioned difficulties, POR women choosing autologous IVF/ICSI-embryo transfer would have to balance these difficulties against expected results and live birth success rates. This necessitates thorough investigation and thorough research on the topic.

1.2 Problem Statement

Since the POSEIDON criteria were released a decade ago, several papers have chosen to evaluate various reproductive outcomes amongst the four categories of low-prognosis women that the criteria define[7]. Previous studies that utilized the POSEIDON criteria have reported better IVF/ICSI-embryo transfer outcomes in POSEIDON groups 1 and 2 than in groups 3 and 4.[20,33] In Iran, Eftekhar *et al.* in a retrospective study found a higher clinical pregnancy rate in POSEIDON groups 1 and 2 than in groups 3 and 4.[33] A similar trend was also observed in a study in Korea that also utilized the POSEIDON criteria.[20]

Poor ovarian response is linked to unfavourable IVF/ICSI-embryo transfer outcomes.[30] Many countries do not offer insurance for IVF/ICSI-embryo transfer treatments.[34] Also, in addition, the process is expensive and time-consuming.[35] Because there are emotional and financial costs associated with oocyte retrieval failure or the unavailability of an embryo for transfer, cycle cancellations can be extremely traumatic. Though poor IVF/ICSI-embryo transfer outcomes have been documented in expected POR women,[7,20] many of such women may still want to undergo

autologous IVF/ICSI-embryo transfer. Adequate fertility counselling which addresses patients' expectations and also informs individualizing of treatment strategies is very important in managing expected POR women. This approach cannot be over-emphasized especially in countries including Ghana where IVF/ICSI-embryo transfer is not state-sponsored.

Data is needed by both fertility specialists and infertile couples to advise, plan for, and decide on the management of the couples with expected POR. There is a dearth of knowledge on autologous IVF/ICSI-embryo transfer outcomes among expected POR women in Africa, particularly in Ghana. In Nigeria, a 16.9% prevalence of POR among women undergoing autologous IVF/ICSI-embryo transfer was reported in a study.[36] In South Africa, Senaya utilized retrospective data to assess the prevalence of POR and the outcome of autologous IVF/ICSI-embryo transfer, using the Bologna criteria to identify POR women.[37] In that study, a prevalence rate of POR of 3.6% and clinical pregnancy and live birth rates of 10% and 5% respectively were reported.[37]

To the best of the author's knowledge, and at the period this research was conducted, no study in Africa has utilized the POSEIDON criteria to evaluate the outcome of autologous IVF/ICSI-embryo transfer in POR women and for that matter, those reliably classified as expected POR. Using this criterion can guide fertility specialists in counselling and offering individualized treatments to women with expected POR in the POSEIDON subgroups since the demographic features in Ghana may be different from other jurisdictions like Korea and Iran which utilized the POSEIDON criteria.[20,33] Notably, most studies that were conducted in Africa on POR utilized a retrospective approach to assess the outcome of IVF/ICSI-embryo transfer in women with expected POR. Utilizing a prospective study design is justifiable in its ability to assess causality and also reduce recall bias.[38] Additionally, there is limited data on studies that specifically assessed OS outcomes in women with expected POR according to the POSEIDON criteria. This study adopted a prospective design to assess the outcomes of OS among women classified as expected POR undergoing autologous IVF/ICSI-embryo transfer in six fertility centres in Kumasi, Ghana.

1.3 Justification of the Study

This study provides data on the proportion of expected POR among women undergoing autologous IVF/ICSI-embryo transfer and the outcome of OS among this group undergoing IVF/ICSI-embryo transfer in all six fertility centres in Kumasi, Ghana. This is the pioneer study to assess the outcome of OS in women with expected POR undergoing autologous IVF/ICSI-embryo transfer using the POSEIDON criteria in Kumasi, Ghana and will serve as reference data for future research into POR in Ghana and beyond. This study provides data to guide fertility specialists in counselling women with expected POR undergoing autologous IVF/ICSI-embryo transfer.

1.4 Research Questions

1. What is the proportion of expected POR among women undergoing autologous IVF/ICSI-embryo transfer in Kumasi?
2. What is the cycle cancellation rate among women with expected POR undergoing autologous IVF/ICSI-embryo transfer in Kumasi?
3. What is the clinical pregnancy rate among women with expected POR undergoing autologous IVF/ICSI-embryo transfer in Kumasi?
4. What is the difference in the outcomes of OS (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among the two groups of women with expected POR (POSEIDON group 3 and group 4) undergoing autologous IVF/ICSI - embryo transfer in Kumasi?

1.5 Research Hypothesis

Null hypothesis (H0): The OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among women in expected POR group 3 are the same as among women in expected POR group 4.

Alternative hypothesis (H1): The OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among women in expected POR group 3 are significantly different from that among women in expected POR group 4.

1.6 Study Objectives

1.6.1 Main objective

This study assessed the outcome of OS among women classified as expected POR undergoing autologous IVF/ICSI-embryo transfer in Kumasi.

1.6.2 Specific objectives

1. To determine the proportion of expected POR among women undergoing autologous IVF/ICSI-embryo transfer in Kumasi.

2. To determine the cycle cancellation rate among women with expected POR undergoing autologous IVF/ICSI-embryo transfer in Kumasi.

3. To determine clinical pregnancy rates among women with expected POR undergoing autologous IVF/ICSI-embryo transfer in Kumasi.

4. To compare the outcomes of OS (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among the two groups of women with expected POR (POSEIDON group 3 and group 4) undergoing autologous IVF/ICSI-embryo transfer in Kumasi.

CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

This chapter discusses literature based on the specific objectives of the study. A literature search was conducted using databases including Google Scholar, PubMed, Wiley Online Library, Hindawi and Web of Science to review the literature. The literature search was done using the keywords and themes derived from the study topic and objectives.

2.1 Etiologies and Diagnosis of Poor Ovarian Response and Patients' Classification

2.1.1 The etiologies of poor ovarian response

Even though the exact etiology of POR is uncertain, studies have shown that decreased responsiveness to ovarian stimulation is the first indication of the condition.[39] It is linked to advanced maternal age which results in availability of few genetically normal embryos for transfer, and in younger women, insufficient ovarian reserve is the most common etiological cause.[40] Pelvic adhesions, endometriosis, and previous ovarian surgery are linked to inadequate ovarian reserve.[41–43] Some studies have reported that a low ovarian reserve can occasionally be the result of iatrogenic causes like post-radiotherapy or chemotherapy[44,45] and it can also be influenced by high body mass index or heavy smoking.[43]

The follicular response to exogenous gonadotropins may also be altered by specific circumstances, such as obesity,[46] underlying genetic polymorphisms[47–50] or autoimmune disorders.[17,43] All of these factors contribute to the complexity of the ovarian response to stimulation, highlighting the importance of individualized treatment plans in the field of reproductive health.

Inadequate ovarian response is a primary cause of infertility and is controlled by several factors.[51] Ovarian response to follicle-stimulating hormone (FSH) is a critical factor in the success of ART and this response can vary considerably among women, leading to differences in treatment outcomes. Granulosa cells, crucial for follicular development, may have fewer FSH receptors, reducing their sensitivity to FSH and hindering follicular maturation. Even if FSH

receptors are present, defective signaling pathways within granulosa cells can prevent appropriate responses to FSH binding, leading to inadequate follicular growth.[52]

In addition to controlling follicular selection and the early beginning of atresia, proper vascularization is necessary for hormone delivery and follicular growth.[53] Gonadotropin distribution to follicles may be restricted by inadequate vascular networks, which may impact follicle development. Some individuals can develop autoantibodies directed against granulosa cells, which can disrupt regular cell processes and affect the growth of follicles. Normal follicular development depends on the proper regulation of angiogenesis, and angiogenic factor and their suppression can reduce the growth of preantral and antral follicles as well as ovulation.[54] The most significant angiogenic agent controlling follicular angiogenesis and follicular cell activity is vascular endothelial growth factor (VEGF). The elements that make up the VEGF system include both angiogenic and antiangiogenic components. The VEGFxxxb isoforms, the VEGF receptor-1, and soluble versions of VEGF receptors 1 and 2 are the antiangiogenic members, whereas the angiogenic members are VEGFxxx isoforms (where xxx is the number of amino acids in the protein) and VEGF receptor 2.[54] While binding VEGFxxx isoforms to VEGF receptor 2 promotes angiogenesis by stimulating endothelial cell migration, proliferation, and survival, binding VEGFxxx isoforms to VEGF receptor-1 results in poor receptor phosphorylation, which lessens the action of the receptor on endothelial cells.[54] Excessive activity of vascular endothelial growth factor receptor-1 (VEGFR-1) can disrupt normal ovarian function, contributing to a poor ovarian response.[53] Follicle development can also be inhibited by blocking vascular endothelial growth factor (VEGF), VEGF receptor-2, vascular endothelial cell factor cadherin, or interfering with the angiopoietin system.[53] Insulin-like growth factors I and II play crucial roles in ovarian function, and abnormal levels of these factors can disrupt follicular development and hormone regulation.[55]

Circulating gonadotropin surge-attenuating factor (GnSAF) regulates the release of gonadotropins. Reduced bioactivity of GnSAF can lead to excessive gonadotropin release, which may negatively affect follicular development. Understanding these mechanisms is essential for developing targeted strategies to enhance ovarian response and fertility outcomes in individuals experiencing infertility.[56]

Recent research has highlighted the role of genetic variations, particularly in the FSH receptor (FSHR) gene, in influencing ovarian response to FSH stimulation.[57] The Ser680Asn variant is one of the most thoroughly studied polymorphisms of the FSHR gene.[55] This polymorphism has been linked to differences in FSH receptor function and ovarian response to FSH. Specifically, women with the Ser/Ser genotype tend to have FSH receptors that are more resistant to FSH action, which may result in a suboptimal ovarian response during ART procedures.[52] Understanding these genetic variations is crucial, as they could potentially serve as genetic markers for predicting ovarian response and optimizing FSH dosing in ART protocols. By using these markers, one may be able to forecast the ovarian response, choose the right dose of FSH, and reduce any risks related to FSH stimulation.[56] These insights highlight the importance of personalized medicine in optimizing fertility treatment outcomes. By tailoring treatment approaches based on individual genetic profiles, healthcare providers can enhance the effectiveness and safety of ovarian stimulation procedures, ultimately improving the chances of successful fertility treatment.

Ovarian response variability has also been linked to genes in the estrogen pathway, in addition to the FSHR gene. Genetic differences in genes related to estrogen may affect the ovarian response to FSH stimulation. Estrogen is essential for folliculogenesis and ovarian function.[56] By identifying these genetic markers, clinicians may be able to personalize ART protocols based on an individual's genetic profile, potentially improving treatment outcomes and reducing the risk of adverse effects associated with ovarian stimulation.

According to Lashen and Ledger, the ovarian response differs greatly between people and even within the same person.[58] Due to their limited ovarian reserves, older women and individuals with elevated basal FSH are known to respond poorly to ovarian stimulation; in fact, a POR may be the first sign of early menopause.[59,60] A study by Oehninger *et al.* has emphasized that oocyte aneuploidy is linked to advanced maternal age.[61] The same authors also described abnormalities in the zona pellucida of oocytes from people who responded poorly.[61] People who have low ovarian reserves or normal ovarian reserves but who are inherently less responsive to gonadotrophin may not be good responders.[58] Although no specific explanation could be identified, variations in exogenous FSH metabolism may be blamed for the variable ovarian response.[62]

Poor ovarian response to stimulation can be an unexpected complication in relatively young patients.[40] In many of these situations, the true etiology of the POR is unknown, while in a few cases “ovarian failure” might have an immunological cause.[4] A few endocrine-related disorders have been noted which include FSHR polymorphisms, a reduction in the number of FSH receptors (FSHR) in granulosa cells,[63] and poor signal transduction following FSHR binding.[64,65]

2.1.2 Diagnosis of poor ovarian response

The effectiveness of ART has been largely attributed to OS. However, many patients do not always respond to OS protocols in the same way or as anticipated. When given the recommended dosages of gonadotropins during ovarian stimulation for IVF/ICSI-embryo transfer, some women develop relatively few eggs. Poor ovarian responders are the term used to describe these women.[9,11] As a result, there is a decrease in oocyte yield, high cycle cancellation rates, and an overall decreased likelihood of becoming pregnant.[3,66,67]

To identify poor ovarian response, a variety of factors are taken into consideration. These include the number of mature follicles on the day of the hCG trigger, the total or daily gonadotropin dose, the duration of gonadotropin administration, the number of oocytes retrieved, the AMH levels, the AFC, the peak estradiol levels, and the number of IVF/ICSI-embryo transfer cycles that were previously cancelled due to poor ovarian response.[9] The term "poor responders" lacks a consensus definition, and many studies from different settings have documented several criteria to define this circumstance.[51,68,69] It is difficult to categorize the diverse group of women with POR.[70] One of the first POR classifications was done by Garcia *et al*.[69] Polyzos and Devreoy found in a noteworthy comprehensive study that 47 research on POR used 41 different classifications.[14] They also found that different interpretations were used by the same authors in different tests and that no more than three trials utilized the same definition.[14]

The number of mature follicles generated and the number of oocytes recovered after a standard stimulation regimen are the most important variables.[11] Various writers have recommended varying amounts, which might be as little as three to five mature follicles seen on ultrasonography the day of the hCG trigger, or as little as three to five retrieved oocytes.[14,71]

The term "POR" was first used in 1983 to characterize a condition in which fewer oocytes were recovered and, consequently, fewer embryos were produced when inadequate follicle growth and a peak estradiol concentration of less than 300 pg/mL were coupled with a typical OS regimen.

Loutradis *et al*. classified a patient as a poor responder if they met any of the following criteria: three or fewer recruited follicles or collected oocytes; a serum estradiol concentration at the time of hCG trigger of less than 300 pg/mL (if one follicle) or 500 pg/mL (if two or three follicles). This study focused on alternative strategies for managing patients who did not respond well to ovarian stimulation.[72,] Hence, it is thought that peak estradiol levels of lower than 300 to 500 pg/ml are essential for identifying a subpar reaction.[9]

Some have proposed that the total gonadotropin dose given, the daily stimulation dose and the duration of stimulation might be used to identify poor responders.[73–75] According to Murat *et al.* when poor responders are undergoing OS using the microdose technique, there is no need to use dosages of recombinant FSH above 300IU to increase the likelihood of conception.[75] Yang *et al.* discovered that in both normal and poor responders, the length of stimulation appears to have a varied effect on oocyte maturation, clinical pregnancy rates, and LBR in ICSI-ET cycles. Additionally, they discovered that although both groups experienced pregnancies, the mean stimulation length was lower in poor responders (7.8 ± 2.2 vs. 9.2 ± 1.6 days, $p < 0.01$) than in normal responders.[73] Although Yang *et al*. offered other criteria, such as the determination of the FSH/LH ratio, an additional criterion is an increase in baseline serum FSH on day three (≥7 to ≥15 mIU/mL).[74]

Women's ovarian reserve declines with age, and this has been widely documented.[68,76–78] Sallam *et al.* classed patients as poor ovarian responders if they underwent therapy with ICSI, IVF, or TESE/ICSI and obtained less than 5, 6, or 8 oocytes.[79] Additionally, patients who use more than 300 IU of FSH per day but do not create more than three preovulatory follicles or who consume more than 3000 IU of FSH to recruit fewer than four follicles are considered poor ovarian responders, according to Kailasam *et al*.[80] There have occasionally been claims that the cause is noticeably old age (≥40 years).[81–83] Some publications combine the aforementioned parameters.[9,14,59] Nevertheless, it is necessary to have at least one cancelled IVF/ICSI-embryo transfer cycle after a failed standard ovarian stimulation procedure before confirming a POR.[67,69]

The most difficult grouping of patients to treat is the "poor ovarian responders" subgroup because they are more likely to respond inadequately to IVF/ICSI-embryo transfer, which may result in fewer pregnancies and live births.[7] Even worse OS outcomes occur in women who are predicted to be expected POR.[20] The group of women who are POR are not homogeneous, but rather a subpopulation with a variety of characteristics, thereby making it challenging to define or identify them.[22,67,84] Some standardization has however been achieved in categorization, thanks to the Bologna criteria and the POSEIDON criteria that followed.

2.1.3 Classification of women with poor ovarian response

ESHRE devised the "Bologna" criteria in 2011 intending to standardize the POR definition.[69] Women with POR are defined as those who satisfy two out of the following criteria: 1) AFC of less than 5-7 follicles and serum AMH levels of less than 0.5-1.1 ng/ml are indicators of a low ovarian reserve. 2) Other risk factors for poor ovarian response include advanced maternal age (≥40 years old), and 3) earlier cycle cancellation brought on by poor ovarian response.[85,86] If a woman has had two previous poor ovarian responses, she is also considered a poor ovarian responder.[9]

The "Bologna" criteria for POR diagnosis was used in around half of the interventional trials that were registered on clinicaltrials.gov since 2011, according to a comprehensive review and meta-analysis.[17] While recording at least two instances of POR in response to standard OS being adequate for its classification when other criteria are lacking, the diverse nature of women with POR has made applying the "Bologna" criteria in clinical practice challenging. The Bologna criteria's vague definition of POR's risk factors makes it conceivable for there to be multiple subgroups of these risk factors, which complicates the process of classifying women according to this criterion. A few of these risk factors included "chromosome instability, unexplained infertility, short menstrual cycles, single ovary, chemotherapy, radiotherapy, chronic smoking, and family history of premature menopause. This complexity has posed difficulties in effectively categorizing patients with POR, despite the efforts of ESHRE in standardizing the classification.[86]

A new method to classify patients; the POSEIDON classification system is designed to help categorize patients undergoing autologous IVF/ICSI-embryo transfer, particularly those with

POR. This classification system was devised in 2016 and classified POR women into "expected" or "unexpected" POR. The POSEIDON criteria for "low prognosis" patients have been developed as a measure of ovarian resistance to gonadotropin stimulation (i.e., hypo-responsiveness).[23] The POSEIDON group proposed this categorization intending to give patients with diminished ovarian reserve or unexpectedly insufficient ovarian response to exogenous gonadotropins a treatment-focused definition of ART.[85,87,88]

To deliver more individualized treatment plans and enhance IVF/ICSI-embryo transfer outcomes, four categories are used in the classification: one for the mother's age and expected aneuploidy rate; another for the ovarian reserve biomarkers, such as anti-mullerian hormone (AMH) and antral follicle count (AFC); and a third for the ovarian response in previous cycles following ovarian stimulation treatments.[22] Many studies have shown a positive association between the number of oocytes retrieved after a standard IVF/ICSI-embryo transfer cycle and CLBR with higher oocyte numbers correlating with better outcomes.[89–91] Women belonging to the POSEIDON groupings have a lower prognosis in autologous IVF/ICSI-embryo transfer programs compared to normal responders due to the decreased number of oocytes generated which will decrease the number of embryos available for transfer.

Group 1 comprises individuals who are younger than 35 years old, have adequate ovarian reserve characteristics (AMH > 1.2 ng/mL; AFC ≥ 5), and have had a previous autologous IVF/ICSI cycle with an unexpectedly poor or unsatisfactory response. They are further divided into "subgroups 1a (<4 oocytes) or subgroup 1b (4-9 oocytes)." Group 2 comprises older individuals who are at least 35 years old, have adequate ovarian reserve characteristics (AMH > 1.2 ng/mL; AFC ≥ 5), and have had a previous autologous IVF/ICSI cycle where their ovarian response was unsatisfactory. Subgroups "2a (<4 oocytes)" and "Subgroup 2b (4-9 oocytes)" are also used to further categorize them following standard ovarian stimulation. Group 3 consists of young patients under 35 years old with poor ovarian reserve pre-stimulation parameters (AMH < 1.2 ng/mL; AFC <5), and Group 4 consists of older patients over 35 years old with poor ovarian reserve pre-stimulation parameters (AMH < 1.2 ng/mL; AFC <5).[23] Therefore, in response to exogenous gonadotropin stimulation, POSIEDON groups 1 and 2 are referred to as "unexpected" POR, whereas POSIEDON groups 3 and 4 are referred to as "expected" POR. Those with a poor ovarian response to exogenous gonadotropin stimulation are known as hypo-responders, and they

are the unexpected POR responders. Due to a rise in oocyte/embryo aneuploidy with ageing, women with limited ovarian reserve are considered anticipated POR women and have a significantly worse prognosis compared with normal responders.[23]

The POSEIDON group's classification introduces a novel method to assist physicians in achieving the necessary oocyte yield to identify at least one euploid embryo suitable for embryo transfer. This approach aims to offer a practical endpoint for doctors in determining clear lines of therapy for poor prognosis patients in IVF/ICSI-embryo transfer cycles, ultimately improving the chances of successful outcomes.[20] The POSEIDON concept also serves as an important counselling tool to aid fertility practitioners in first identifying and classifying women who have an increased risk of low response to OS and thus individualize treatment protocols with emphasis on optimizing follicle-to-oocyte ratio (FOI) to achieve higher success in autologous IVF/ICSI-embryo transfer programs. Understanding the different POSEIDON groups and their associated outcomes is crucial because it allows clinicians to tailor treatment strategies to individual patients. For example, patients in POSEIDON groups 1 and 2, who typically have better ovarian reserve and are younger, may require different treatment approaches than those in groups 3 and 4, who have lower ovarian reserve and are older. Clinicians might modify treatment strategies to enhance outcomes by identifying individuals who are more susceptible to respond poorly to standard ART protocols.

The importance of considering ovarian reserve, age, and embryo morphology in predicting IVF/ICSI-embryo transfer success as highlighted by the POSEIDON classification system. An important consideration in predicting the outcome of IVF/ICSI-embryo transfer is a woman's ovarian reserve or the quantity and quality of her eggs. Due to their increased propensity to generate quality eggs, younger individuals with a higher ovarian reserve (POSEIDON 1) may fare better. However, because they are more likely to have fewer high-quality eggs, older patients with a reduced ovarian reserve (POSEIDON 4) may have lower success rates following OS.

The variations in results between ethnic groups imply that environmental and genetic factors might also affect the success rates of IVF/ICSI-embryo transfer cycles. Factors such as genetic predisposition to certain conditions or environmental factors such as diet and lifestyle may influence the response to IVF/ICSI-embryo transfer treatments.[92] Therefore, personalized

approaches to IVF/ICSI-embryo transfer cycles that take into account patient characteristics and demographic factors could be essential for optimizing outcomes.

In conclusion, the POSEIDON classification system provides a valuable framework for categorizing patients undergoing IVF/ICSI-embryo transfer cycles and tailoring treatment strategies to improve outcomes. By considering ovarian reserve, age, and other factors, clinicians can better predict and optimize IVF/ICSI-embryo transfer success rates, ultimately helping more couples achieve their goal of having a child. [37,93,94]

2.1.4 Ovarian reserve

Ovarian reserve is a complex clinical syndrome that is influenced by age, genetics, and several environmental factors.[95] It has historically been used to characterize a woman's capacity for reproduction, particularly the number and quality of oocytes she has[95] because subfertile women need to become pregnant after receiving fertility treatment.[96] It is well recognized that a woman's ovarian reserve decreases permanently, and there is wide variation in the rate at which women lose primordial follicles. There is also significant variation in the timing of the menopausal transition or the onset of sterility.[9] Consequently, women of reproductive age who exhibit decreased ovarian reserve are those whose fecundity or reactivity to ovarian stimulation is lower than that of women of similar age.[95,97]

Ovarian reserve tests give an indirect estimate of a woman's residual follicular pool, and the conclusions drawn from these tests help clinicians differentiate between people who may respond well, badly, or hyper-reactively to ovarian stimulation.[96] Many fertility centres regularly monitor ovarian reserve using different ovarian reserve tests to help with counselling by predicting the response and outcome in couples before IVF/ICSI-embryo transfer.[76,96] Additionally, it can detect females who might not react well to gonadotropin-stimulated ovaries.[76,97] Nevertheless, assessing the ovaries' response to gonadotropin stimulation is a procedure that can only be carried out after the ovaries have undergone OS. It would be wonderful to be able to accurately predict, before beginning treatment, which women will not respond well to IVF/ICSI-embryo transfer cycles. An ovarian reserve test suggestive of a reduced response to OS does not always connote a woman's inability to conceive, therefore they

should not be the only criteria to deny women ART programs like autologous IVF/ICSI-embryo transfer.

An optimal ovarian response test needs to be easy to administer, reproducible, and capable of differentiating between individuals with a normal ovarian response and those without.[76,97,98] It should be inexpensive, non-invasive, easy to interpret, allow for reproducibility, and show little variation both inside and between cycles of the menstrual cycle.[76,95,99] Furthermore, it ought to be able to identify the ovarian reserve reduction early enough to allow for the possible investigation of timely treatments. Lastly, from a clinical standpoint, a test should not be considered abnormal for decreased ovarian reserve unless a high specificity threshold is reached.[76,95,99] By doing this, the number of patients with normal ovarian reserve who are mistakenly classified as having impaired ovarian reserve would be reduced. Crucially, this would prevent patients with normal ovarian reserve from undergoing needless therapies, and patients who ought to be able to conceive naturally would not be advised to donate or adopt oocytes.

Although there are several ovarian reserve tests available, they are considered proxy markers of ovarian response and none is optimal due to several limitations such as the limited predictive accuracy for fertility potential and the lack of standardization in different assays, thresholds and interpretation criteria. The ovarian reserve has been determined by biological (age), biochemical, biophysical, and histological testing. Follicle-stimulating hormone (FSH) was initially presented in 1988. Other tests that were added later were the gonadotropin-releasing hormone (GnRH) agonist (1989), the clomiphene citrate challenge test (CCCT) (1989), inhibin B (1997), the AFC (1997), and AMH (2002).[95] However, the majority of these measurements have low predictive value, either as a result of their high intra- or intercycle variability (e.g., FSH) or their indirect nature as indicators of ovarian reserve (e.g., CCCT, GnRH agonist).[100] The provocative tests (GnRH agonist and CCCT) have essentially been abandoned because they are expensive, time-consuming, and require additional patient visits. In clinical practice, additional procedures including ovarian vascularity assessment, histological testing, and ultrasound assessment of ovarian volume have been used to try and forecast the possibility of an ovarian response to gonadotropin stimulation.[39,76,96,101] In addition to chronological age, the available data suggests that AFC and AMH are the most helpful markers of ovarian reserve.[97,102,103] Additionally, AMH can be utilized to detect ovarian reserve decline in people of all ages before it reaches a critical

level that treatment cannot be effective.[104] This could help women decide whether to postpone getting pregnant by providing them with information to enhance their decision.

In recent times, it has become evident that ovarian reserve tests are more accurate at predicting the ovarian response to stimulation than they are at predicting the occurrence or outcome of pregnancy, despite preliminary data suggesting that several of these tests have a high predictive value for pregnancy.[96] The lack of consistent threshold values to indicate abnormal outcomes and classifications for poor or hyper-responders further complicates the interpretation of these results.[76] In more recent times, researchers have also investigated the usefulness of ORTs in anticipating hyper-response and, consequently, employing safe stimulation regimens to prevent OHSS, a potentially fatal iatrogenic ART consequence.[76,96,97,103] It is still unclear how they should be used to evaluate ovarian reserve in subfertile women in general and identify individuals who may have decreased ovarian reserve.[96,99] It's also important to emphasize that ovarian reserve tests are not perfect and shouldn't be the main criteria used to deny someone access to alternative treatments like IVF/ICSI-embryo transfer.[103,105] Evidence of diminished ovarian reserve does not always imply an inability to conceive; rather, it may suggest a lower likelihood of achieving clinical pregnancy.[102]

2.1.4.1 Anti-Mullerian hormone

AMH is a dimeric glycoprotein that belongs to the transforming growth factor-b superfamily. Granulosa cells in the early-developing follicles of the ovary are the only cells in females that generate it..[76,106] When follicles move from the primordial to the primary stage and eventually reach the antral stages, with sizes ranging from 2 to 6 mm, AMH production begins.[76,96,104] The size of the primordial follicle pool is correlated with the quantity of tiny AFs. Age-dependent, AMH is almost undetectable during the menopausal years and reaches its maximum values around menarche. AMH is unique in that, as shown by Marca and associates, its blood levels are not cycle-dependent.[96,102,104] Unlike other biochemical indicators, it does not exhibit intercycle fluctuation and can be assessed at any point during the cycle.[96,107] Thus, there is minimal clinical significance to AMH changes.[108]

According to sensitivity and specificity analyses, the AMH is the most ancient and sensitive ovarian reserve test available. It has a substantial association with the primordial follicle pool

and an inverse relationship with chronological age,[106] accurately estimating the ovarian response during ART.[109,110] AMH values 0.5–1.26 ng/ml are thought to signal perimenopausal transition within 3–5 years, which helps forecast when menopause will begin.[111] Moreover, AMH stands out among the other ovarian reserve tests in that it can be used as a screening tool for a wider subfertile population.[112]

AMH levels decrease with age in fertile women's longitudinal studies, and it is the first marker to demonstrate a reduction in young women[106] presenting this as a potential screening tool for expectant mothers who want to delay childbirth. Nomograms are used to measure the physiological decline in AMH levels that occurs with age and, as a result, ovarian reserve. The use of abnormal aberrations in these numbers can help couples decide whether or not to delay having children.[113] Additionally, this would allow individuals to pursue efficient treatment options while their chances of becoming pregnant are fairly high.[114,115] The evidence that is currently available does not support the use of serum AMH as a marker to forecast pregnancy.[96] On the other hand, follicles with higher amounts of AMH in their oocytes have a better potential for fertility than follicles with lower levels of AMH, according to the study of follicular fluid AMH.[116]

Serum AMH measurements can be taken at any point during the menstrual cycle because they exhibit little intra- and inter-cycle variation.[106] Compared to other indicators like AFC, it exhibits clear age-related reductions at a very young age.[69,76,103] The only ovarian reserve test that has been proven to help assess the remaining ovarian reserve in young women receiving chemotherapy or radiation therapy for cancer is AMH.[117]

However, an AMH value obtained using one assay cannot be compared to another AMH result obtained using a different assay, which is the primary disadvantage due to the lack of a universally defined test and the unpredictability of results from different laboratories.[76,96] The AMH test is time-consuming and labour-intensive, and it also needs particular storage conditions. Nonetheless, progress has been made in automating AMH testing such that it can be completed quickly.[118] Even though certain investigations showed significant intra- and inter-cycle variance and a high degree of AMH variability in the population,[119] AMH are a very accurate measure of the ovarian response to ovarian stimulation and the possibility of cycle cancellation.[110] However, its accuracy in predicting pregnancy is not reliable[120]. There are

different threshold values (0.2–1.26 ng/ml) that have been employed with 80–87% sensitivity and 64–93% specificity to identify poor responders.[9,96]

The AMH and AFC have been shown to have more clinical utility than follicle-stimulating hormone (FSH) in a substantial body of research.[76] AMH declines years before FSH increases, making it an earlier and more accurate real-time indicator of ovarian reserve. During early folliculogenesis, cumulus and mural granulosa cells from preantral and tiny antral follicles directly produce AMH. Compared to indirect markers like FSH and ovarian markers (estradiol and inhibitor B) produced by follicles during late folliculogenesis, it has a stronger association with the primordial follicle pool.[106]

There is a strong association between basal AFC and AMH levels measured by transvaginal ultrasonography.[107] AMH showed a high negative association with age ($r = -0.844$, $P<0.001$) and a slight positive correlation with AFC ($r = 0.400$, $P<0.001$), according to research by Jain *et al.* on the link between AFC and AMH in infertile women in India.[107]

2.1.4.2 Basal Follicle-stimulating hormone

The most popular ORT for evaluating the ovarian response to stimulation for nearly 20 years has been basal FSH levels, which are determined on the third day of the menstrual cycle.[96,103] Because it is based on the feedback regulation of FSH pituitary production by ovarian hormones, it is an indirect indicator of ovarian reserve. It was suggested more than 30 years ago that the ovarian response to IVF may be predicted using early follicular phase (basal) FSH as a measure of ovarian reserve.[76] Basal FSH levels in the blood rise as a result of ovarian ageing and follicle depletion; women with basal FSH levels above 25 mIU/ml have been demonstrated to have poorer ovarian response and reproductive outcomes than women with serum FSH levels of 15 mIU/ml.[103] Even though basal FSH is inexpensive and easy to measure, there isn't a commonly accepted threshold for determining inadequate ovarian response.[102] The test is still often used in many fertility centres despite the low reliability caused by inter- and intra-cycle changes in FSH levels. This is probably because the test has a long history of development and usage, is simple to perform, and requires little sample preparation.[76,101,102]

FSH as a screening test for counselling will only be helpful for a small subset of women since it can only reliably predict an unfavourable reaction at very high levels in women with regular

menstrual cycles.[96] Using meta-analyses and systematic reviews, it has not been possible to ascertain any combination of specificity and sensitivity for baseline FSH as a test of poor response or for a non-pregnancy prediction.[96] Because ovarian ageing might start in some individuals years before elevated FSH levels are observed, a normal test cannot completely rule out a POR.

Since high basal estradiol can indicate DOR even when FSH is within the normal range, combining it with estradiol is more significant. Premature FSH elevations in the early follicular phase may cause earlier higher estradiol levels in women with diminishing ovarian reserve. As a result, aberrant FSH elevation that would normally suggest inadequate ovarian reserve may be concealed by an increase in the negative feedback on pituitary FSH output. Consequently, measuring FSH and estradiol on the third day of the cycle could help reduce the quantity of false-negative tests.

Basal FSH can be used in conjunction with other indicators to guide couples considering a substandard response, but it should not be utilized as a means of disqualifying women who cycle regularly from ART. However, it's unclear if basal FSH is helpful in a population that is often infertile or if increased levels are helpful in young women who cycle regularly.[96,102]

2.1.4.3 Antral follicle count

During the early follicular phase, antral follicle counts are determined with transvaginal ultrasound. The total AFC is calculated by adding the number of follicles in both ovaries and taking the mean of two perpendicular readings. For a very long time, ovarian reserve has been measured using AFC.[77,97] AFC is a simple procedure that produces immediate results. When evaluated with high-resolution ultrasound equipment and the required knowledge, it has a robust intercycle and good interobserver reliability. However, when using numerous sonographers, obesity compromises its accuracy.[96,97]

In common IVF trial populations of people with low and high risk of DOR, the inadequate ovarian response is very specific (73–97%) when predicting low AFC cut-off points of 3-5 follicles (both ovaries combined).[121] It is thought that a count of 8–10 indicates a typical response. There is debate over the size of the antral follicles, which is a reliable indicator of ovarian reserve.[76,96] While the number of 7–10 mm antral follicles stays stable with age, the

number of 2-4 mm follicles decreases and is linked to other indicators like FSH and CCCT, suggesting that the former is a more accurate indicator of ovarian reserve..[76] On day three of the cycle, the total ovarian volume and the baseline serum levels of FSH, E2, and inhibin B are thought to have the best discriminating power for a poor ovarian response.

Nevertheless, AFC lacks the specificity and sensitivity to identify the absence of pregnancy.[77,102] Antral follicle counts are often performed using 2D ultrasound; however, the more recent 3D ultrasound has certain benefits as well, such as a shorter scanning time and the ability to store data for post-procedure analysis.[122] However, it doesn't appear that the 3D imaging for AFC offers any appreciable advantage in terms of AFC measurement[96] and as a result, using real-time 2D ultrasound in clinical settings is sufficient for measuring AFC.[96]

Even though AFC is widely used, several writers have expressed concerns regarding its utility in ovarian reserve assessment in ART. Due to intracycle variance, AFC must be performed at the start of each cycle. Additionally, it is inherently variable due to interobserver variability and technology. There has been a noticeable variance in AFC between and among centres. This variety could be brought about by variations in the training of the operators, the number of sonographers, the methodology, the standards for measuring antral follicles, and the advancements in ultrasound technology (e.g., the resolution of ultrasound machines). In fact, only antral follicles that are visible with ultrasonography are measured by sonographers in determining AFC. There is not enough data to support the idea that the antral follicles observed on ultrasonography are possibly healthy and contain competent oocytes, despite some attempts to standardize the measurement of antral follicles. Additionally, there are differences in the clinical standards and technical techniques used in follicle counts.[114]

The main drawback of utilizing the AFC to calculate ovarian reserve is that it must be done during the early follicular phase of the menstrual cycle; nonetheless, it is comparable to the AMH in terms of forecasting the ovarian response to gonadotropins.[9,76,96]

Nonetheless, it has been shown that AMH and AFC are comparable in this respect in terms of ovarian response prediction in normal, poor, and hyper-responders to OS, with similar sensitivity and specificity.[123] All ovarian reserve tests (ORTs) showed a strong correlation with each other when Thomas *et al*. looked at the link between four markers of ovarian reserve and ovarian

response as well as live birth rates after assisted reproduction. The highest association was seen between AFC and AMH ($r = 0.71$, $p < 0.0001$), leading them to conclude that the optimal model for predicting ovarian response consisted of combining AMH, AFC, and age [103]

It is ineffective to try to use many markers rather than just one basal marker to boost the prediction power of ORTs.[76] The available data makes it abundantly evident that ORTs should only be used as screening tests rather than diagnostic ones for low ovarian reserve, however, the best diagnostic method for determining a poor response is still the initial IVF attempt.[76,114] Even though there are many other ORTs available, age remains the most reliable predictor of pregnancy, even if women's fertility falls at varying rates with age.[124] The limited predictive value of ovarian reserve testing may be explained by the possibility that factors other than age also affect the likelihood of pregnancy after IVF/ICSI-embryo transfer.

2.2 Ovarian Stimulation Among Poor Responders Undergoing Autologous IVF/ICSI-embryo transfer using the POSEIDON Criteria.

To improve POR women's OS outcomes, several documented procedures and guidelines have been established.[125] A meta-analysis of pituitary suppression regimens using GnRH agonists and antagonists has not revealed any appreciable differences in the incidence of ongoing pregnancies between the agonist and antagonist groups.[126–128] According to Sunkara *et al*. in expected POR, the antagonist regimen appeared to be friendlier and may eventually lower the high drop-out rate observed in the POR population, even if the lengthy agonist protocol raised the number of developed oocytes by one in comparison to the antagonist protocol.[126]

The 2019 guidelines on OS for women with poor ovarian response published by the European Society of Human Reproduction and Embryology (ESHRE) state that there is not enough evidence to support the use of one type of gonadotropin over another in this population. Furthermore, recombinant follicle-stimulating hormone (r-FSH) doses greater than 300 IU have no beneficial effects on live birth rates and may potentially be harmful to the patient.[125] These guidelines emphasize the importance of individualized treatment approaches and caution against high doses of gonadotropins in POR patients.

To improve the results of autologous IVF/ICSI-embryo transfer for women who have poor ovarian response, a variety of protocols and interventions have been investigated. These include

natural cycle IVF/mild stimulation, double stimulation in the same ovarian cycle, and the use of adjuvants such as androgens, growth hormones, coenzyme-Q and antioxidants.[129,130] Though the use of the modified natural cycle IVF and minimal stimulation IVF may lower the cost of IVF/ICSI-embryo transfer by reducing the dose of gonadotrophin required as well as offering a milder approach to OS than the conventional OS, outcomes of OS in terms of egg yield are lower.[131] Accumulation of embryos through this approach may increase live birth rates by decreasing the risk of lacking an embryo to transfer in POR women.[132] Whilst there has not been any reported significant improvement in pregnancy rates or live births with the use of growth hormone, there have also been inconsistent results and no conclusive evidence of the use of dehydroepiandrosterone.[133] Additionally, treatment with intraovarian injection of autologous platelet-rich plasma (PRP) has been investigated with some studies suggesting improvement in ovarian response and pregnancy rates among POR women.[134,135] Whilst some international infertility societies recommend against routine use of growth hormone, dehydroepiandrosterone and androgen supplementation among POR women,[133] others have suggested considering the role of platelet-rich plasma and coenzyme-Q in improving ovarian response but emphasize the need for an individualized approach which takes into account the evaluation of individual patient needs, discussion of the potential benefits and risks of these add-ons as well as monitoring OS outcomes and staying updated on emerging evidence in the use of these ad-ons.[18,133]

While these approaches show promise, larger randomized studies are needed to validate their effectiveness. The results of smaller trials have been inconclusive, highlighting the importance of further research to establish the efficacy of these therapy methods in improving ART outcomes for women with POR. Emerging treatment modalities like ovarian fragmentation and in-vitro activation of gametes as well as stem cell therapy may revolutionize the management of POR women.[136–138]

2.2.1 Oocyte yield and embryo rates in poor ovarian responders

Previous research has highlighted how important the quantity of recovered oocytes is in determining live birth rates.[66,139] The number of recovered oocytes is an important factor in a typical IVF/ICSI-embryo transfer cycle since it indicates the ovarian response and has a direct impact on the success rate of ART.[140] POR is dependent upon the amount and quality of oocytes, as they are essential for attaining clinical pregnancy.[141,142]

Several studies have focused on the number of oocytes recovered among POR women undergoing autologous IVF/ICSI-embryo transfer. Abdullah *et al*. for example, reported a mean number of retrieved oocytes of 4.32 ± 1.20 and 3.51 ± 2.54 between POSEIDON groups three and four, respectively.[141] Though Abdullah *et al.* found significant difference in the number of oocytes aspirated among women in the four POSEIDON groups, they did not report on its effect on clinical pregnancy and live birth rate. However, the importance of oocyte quantity in the success of IVF treatments (clinical pregnancy and live birth rate) for women with POR have been documented in a study in China by Wang *et al.*[91]

The number of high quality embryos obtained are crucial in the management of women with POR,[19] as the success of IVF or ICSI treatments partly depends on the transfer of high quality embryos, which also contribute to live birth rates.[143,144] Clinical pregnancy rates resulting from the transfer of high quality embryos have been reported to be as high as 70%, with implantation failure rates of up to 30%, which may also be influenced by the occurrence of miscarriages.[145]

The failure of having a successful IVF/ICSI-embryo transfer outcome from transfer of high quality embryos has been attributed, in part, to endometrial receptivity issues.[146] Abdullah *et al*. compared the number of high quality embryos retrieved among POSEIDON groups three and four and discovered that there was significant difference in the number of high quality embryos obtained between the two groups.[141]

2.3 Prevalence of Poor Responders Accessing ART

A lot of couples faced with the issue of infertility now have hope due to ART. Fertility specialists work hard every day to ensure the success of ART. However, women with POR have a low success rate following autologous IVF/ICSI-embryo transfer due to their poor response to OS and are often referred to as 'poor responders'.[30] Women classified as poor responders generally have diminished ovarian reserve because of the ageing factor and inadequate number of follicles receptive to the stimulation of FSH.[30]

Globally, studies that have assessed women undergoing ART show a marked-up burden of women with POR.[40,147–149] The reported prevalence of poor ovarian response varies widely. There have been reports of prevalence rates between 9 and 26%.[10,20,148] The variations in

prevalence rates of poor responders may be explained by the population's heterogeneity. Also, in a multi-country study involving Brazil, Vietnam, and Turkey, it was found that four out of ten (40%) women undergoing autologous IVF/ICSI-embryo transfer were poor responders.[148] Among these women, two out of ten (20%) were classified into POSEIDON groups 3 and 4 (expected POR). The participants' older age was cited by the authors as the reason for the increased prevalence of POR in this study.[148] These findings highlight the substantial impact of POR on women undergoing IVF/ICSI-embryo transfer, emphasizing the need for tailored approaches to improve outcomes in this population.

Research from South Africa, Egypt, and Nigeria has revealed that among women undergoing ART, a significant proportion of them have poor ovarian response.[37,93,94] In Nigeria, POR was reported in 16.9% of 166 women (mean age 35.2 ±4.3) undergoing IVF/ICSI-embryo transfer.[93] In South Africa, Senaya reported a POR prevalence of 3.6% among 1120 IVF/ICSI-embryo transfer cycles.[37] In the South African, study, the median age of the women with POR was 40 years with majority (52.5%) of them being 40 years and above.[37] A study in Egypt found a high prevalence of POR, at 48.6%, among 216 women (mean age 29.4 ±3.5) who underwent IVF/ICSI-embryo transfer.[94]

Additionally, a study in Ghana investigated the variations in AMH levels with age in women accessing ART. They found that very low AMH levels (0.94 ± 0.73 ng/ml) were prevalent among women older than 40 years.[150] These findings highlight the significant burden of POR in sub-Saharan Africa and underscore the importance of further research and tailored interventions to improve ART outcomes in this region.

2.4 Cycle Cancellation Rates Among Poor Ovarian Responders

Cycle cancellation in IVF/ICSI-embryo transfer can have a devastating effect on women. Failure of the ovaries to respond appropriately to gonadotropin stimulation is a primary cause of cycle cancellation. This can lead to poor embryo development, empty follicle syndrome, poor fertilization, or the recovery of a few oocytes following OS.[10,24,151] Though cycle cancellation is often an unexpected outcome from a OS cycle, this may not be surprising among expected POR women.[36,98,131]

Cycles may be cancelled during OS if the ovaries do not respond well, or after the trigger but before the embryo transfer if issues such as poor embryo quality or endometrial factors arise. Though a previous cycle cancellation due to poor ovarian response may be associated with a high rate of cancellations in subsequent cycles,[78] the outcome may be favourable in certain cases.[68] Having two consecutive cycles terminated owing to a poor ovarian response, however, essentially guarantees the occurrence of another poor ovarian response.[24,68,78,135,152]

It has been observed that cycle cancellation between oocyte pick-up and embryo transfer is an unreliable indicator of clinical outcome in IVF/ICSI-embryo transfer due to its potential correlation with a variety of biological factors (e.g., sperm failure), factors associated with oocyte activation and fertilization capacity, or factors specific to the clinic.[24] The projected cancellation rate between oocyte pick-up and embryo transfer is 14% (weighted average) according to data that has been published from 14 research.[24]

On the other hand, cycle cancellation that occurs before oocyte pick up after a conventional OS can be attributed to insufficient ovarian response or other elements such as early ovulation or mistakes in gonadotropin administration.[36] It was decided that the key metric to evaluate ovarian stimulation effectiveness was cycle cancellation before oocyte pick-up in the 2020 report of the European IVF-monitoring collaboration for ESHRE.[24]

The cycle cancellation rate before oocyte pick-up is determined by the population treated; estimates range from 3% for high responders, 20% for the general population, and 40% for poor responders.[24] In Japan, an 11.5% cycle cancellation rate was reported by Sugimoto *et al*. in a study among poor responders who underwent autologous IVF/ICSI.[135] In a multi-centre study involving Brazil, Vietnam and Turkey, 0.23% of POR women who underwent autologous IVF had their cycles cancelled before oocyte pick-up.[148] The differences in cycle cancellation rates reported in these studies could be due to several factors including variations in IVF/ICSI-embryo transfer technologies adopted for treatments and study populations.

Long-term stimulation is necessary for POR-affected women, which means higher gonadotropin dosages and higher costs. Cancellation rates are still high despite this.[134,135] Because IVF/ICSI-embryo transfer therapy entails significant emotional and financial investments, it can be highly upsetting to have a cycle terminated due to unsuccessful egg retrieval or an embryo not viable

enough for transfer. This is why it's so important to give women POR thorough fertility counselling that considers their goals and modifies the optimal course of treatment.

2.5 Pregnancy Rates Among Poor Ovarian Responders

Although neither biochemical nor clinical pregnancy is the ultimate goal of autologous IVF/ICSI-embryo transfer, they (especially clinical pregnancy) are the frequently used criterion for assessing its efficacy. A pregnancy that is confirmed on ultrasonography by showing one or more gestational sacs or clear signs of pregnancy is referred to as a clinical pregnancy. It encompasses both intrauterine pregnancy and an ectopic pregnancy with clinical documentation.[8]

Biochemical pregnancy constitutes one of the outcomes of autologous IVF/ICSI-embryo transfer where an initial assessment of pregnancy test results indicates conception but does not result in clinical pregnancy. An exceptionally early miscarriage that occurs in the first few days of pregnancy is known as a "biochemical pregnancy." The embryo does not develop into a clinical pregnancy, but it does release enough hCG for the hormone associated with pregnancy to be observed on the first pregnancy test.[153] When taken at face value, a biochemical pregnancy appears to be a "false positive" result, meaning that the patient was not pregnant. To the patient, this can become very worrisome considering that she had tested positive with a pregnancy test and may ask questions including ‘How can I be pregnant and later not pregnant again within a short time’. This may cast doubt about their belief in any other test results which may be different from their initial assessment. The fact is that biochemical pregnancy is a true conception but results in an early miscarriage.

The American Society of Reproductive Medicine and the Society for Assisted Reproductive Technologies distinguished between biochemical pregnancies and clinical pregnancies, which involve unexplained miscarriages. Contrary to the widely accepted outcomes of clinical pregnancy, such as induced and spontaneous miscarriages, ectopic pregnancy, and delivery, the brief rise in β-hCG characterizes a biochemical pregnancy. When β-hCG levels in the urine or serum fall quickly, the onset of the next menstrual period doesn't significantly delay, and these characteristics help distinguish a biochemical pregnancy from a clinical pregnancy. Ultrasonography isn't necessary to identify biochemical pregnancies.[154]

Poor ovarian responders frequently have a lower pregnancy rate than normal ovarian responders, while the number of oocytes and the age of the female may have a significant influence on the outcome.[20,155] Fewer oocytes in the poor responders may result in fewer high-quality embryos available for transfer, which could explain their lower pregnancy rates,[10,58,156,157] Therefore, a key factor influencing the outcome of IVF/ICSI-embryo transfer for individuals with low ovarian response is the availability of high-quality embryos for transfer.

When it comes to patients with low ovarian response, younger women have better outcomes than older women.[82] This is because younger women have higher-quality eggs than their older counterparts increasing their success rates.[82] However, because there are fewer oocytes and hence fewer high-quality embryos available for transfer in POR women, the pregnancy rate is lower than anticipated even though the younger poor ovarian responder has a better prognosis.[20,33,82]

Despite numerous attempts to develop effective ovarian stimulation protocols for women with POR, none have emerged as clearly superior. Studies indicate that most cycles using these protocols have resulted in unfavorable outcomes, including reduced conception and live birth rates.[5,158,159]

For instance, a study conducted in Israel among women with POR who underwent IVF/ICSI-embryo transfer reported clinical pregnancy and live birth rates of 9.1% and 5.3%, respectively. It's interesting to note that in this study, women under 40 had a far greater clinical pregnancy rate than women over 40. Similarly, an earlier study in Tokyo reported a clinical pregnancy rate per cycle of 12.1% among women with POR. Another study in Shanghai reported a 7.1% clinical pregnancy rate out of 5243 IVF/ICSI-embryo transfer cycles among women with POR, with a clinical live birth rate after six consecutive IVF cycles of 14.9%.[62,158,160,161] Also, in China, a study found a biochemical pregnancy rate of 36.0% among expected POR women with 23.4% and 12.6% in both expected POR groups three and four women respectively.[141]

These findings underscore the challenges and complexities fertility practitioners face in managing POR in autologous IVF/ICSI-embryo transfer settings. They highlight the urgent need for further research and the development of innovative approaches to improve outcomes for women with POR undergoing autologous IVF/ICSI-embryo transfer. Because most women with

POR may not become pregnant in the first IVF/ICSI-embryo transfer cycle, it is crucial to address the low pregnancy rate with the prospective couple early in the therapy of the poor ovarian responder.

2.6 Comparison of OS Outcomes Among Women with Expected POR (3 and 4)

According to the POSEIDON criteria, women with reduced ovarian reserve are classified as having expected POR.[66,97] Previous studies have focused more on comparing outcomes of OS among women with both unexpected (POSEIDON groups 1 and 2) and expected (POSEIDON groups 3 and 4) POR. These studies have reported better outcomes of OS in women with unexpected POR than those with expected POR.[7,20,66,141] Generally, women classified as expected POR by the POSEIDON criteria have undesirable outcomes following autologous IVF/ICSI-embryo transfer as compared to unexpected POR.[155]

Among women with expected POR, there are few studies that have focused mainly on comparing outcomes of OS (that is those in POSEIDON groups 3 and 4). A few of the studies have compared outcomes of OS among POSEIDON groups 1 to 4.[20,141] In Turkey, a study that compared clinical pregnancy rates among the four POSEIDON groups found a relatively higher clinical pregnancy rate in women with expected POR group 3 (16.2%) than group 4 (12.2%).[162] A similar finding was also observed in a study by Abdallah *et al*. where a relatively higher clinical pregnancy rate was reported in women with expected POR group 3 (21.3%) than those in group 4 (10.3%) in China.[141] Abdallah *et al.* in that same study observed a relatively higher biochemical pregnancy rate among women POSEIDON group 3 (23.4%) than those in group 4 (12.6%).[141] However, there was no statistically significant difference in terms of biochemical pregnancy rate among women in the two POSEIDON groups.[34] It is worth noting that all these studies did not focus only on outcomes of OS in those in POSEIDON groups 3 and 4 but all of them (1 to 4). The authors attributed these findings to diminished ovarian reserve among women with expected POR. Women with expected POR in POSEIDON groups 3 and 4 are similar in all characteristics (both have low ovarian reserve) except their ages which are different.

Also, the median number of matured oocytes retrieved has been reported in a previous study to be the same in both women with expected POR in POSEIDON groups 3 and 4 (medians: 2 vs 2).[162] However, in that same study, the median number of oocytes retrieved was relatively higher

in women with expected POR in POSEIDON group three (median: 4) than in group four (median:2).[162] Also, a relatively higher mean number of oocytes retrieved was reported in women with expected POR in POSEIDON group 3 (mean: 4.32 ± 1.20) than in group 4 (mean: 3.51 ± 2.54).[141] The authors attributed this finding to the difference in age among women with expected POR with those in POSEIDON group three having relatively younger age than those in group 4.

2.7 Summary of Important Findings

Through the review of the literature, it was found that the prevalence of POR varies across the globe and these are influenced by factors including the difference in definition for POR, type of treatment regimen, quality of embryo used etc. Despite being widely criticized, the BOLOGNA criteria were the initial attempt to define the term. The POSEIDON criteria, which popularized the "low prognosis concept," is now the most widely utilized standard for evaluating OS outcomes in women with POR. While several therapeutic approaches, such as the use of adjuvants, have been suggested to improve the OS outcome for this particular group of women, none of them have shown to produce superior results. OS results for POR are still poor, and they are considerably worse for women who are consistently categorized as predicted poor ovarian responders. Also, the cycle cancellation rate is high among women with expected POR and this is a result of their low or poor ovarian reserve. Women with expected POR generally have low chances of achieving clinical pregnancy due to their low ovarian reserve.

CHAPTER THREE

METHODS

3.0 Introduction

This chapter focused on the study setting, design, study population (both inclusion and exclusion criteria), data collection and procedure, data analysis and ethical considerations.

3.1 Study Setting

This study was carried out in six fertility centres in Kumasi, Ghana. Six (6) hospitals in Kumasi offer ART to the general public. They include Trust Care Specialist Hospital and Fertility Centre, RUMA Fertility and Specialist Hospital, Hallmark Medicals, Aniniwaah Medical Centre – Diagnostic and Fertility Clinic, Adiebeba Specialist Hospital and OAK Specialist Hospital. Most infertility treatment options including IVF, ICSI, gamete donation, surrogacy, and freezing of gametes and embryos are offered by these fertility hospitals. A wide variety of patients access fertility treatment in these centres. The 2022 annual report (unpublished data) of the six fertility centres in Kumasi indicated that 502 women underwent autologous IVF/ICSI-embryo transfer in Kumasi. Out of the 502 women who underwent autologous IVF/ICSI-embryo transfer in 2022 in all the fertility centres in Kumasi, 130 of them were women with POR.

Trust Care Specialist Hospital and Fertility Centre is situated in the Kwadaso sub-metropolitan district of the Kumasi Metropolitan Assembly, Ghana. With a 30-bed capacity, it is well-known for its cutting-edge amenities, highly skilled staff, and first-rate services. A robust administration supports a team of seasoned experts who work at the hospital, including professors, consultants, specialists, nurses, biomedical (laboratory) scientists, and support personnel.

RUMA Fertility and Specialist Hospital started operating in March 2014 after obtaining legal registration in November 2013. It presently employs about 120 people in eight departments, and twelve units. This clinic won an award in 2016 for being the nation's best-assisted conception facility. The clinic is supervised by the Kwadaso Municipal Health Directorate.

Hallmark Medicals is situated in the Oforikrom Municipal area of the Kumasi Metropolitan Area. Specifically, it is located at Ahinsa Estate and shares a wall with Kumasi High Senior High

School and Kwame Nkrumah University of Science and Technology. It provides other services as well, including maternal and child health.

Aniniwaah Medical Centre was founded in 1992 as a medical centre and on December 15, 2004, it was organized as a limited liability company under the Companies Code, 1963 (Act 179). It is located at Emena on the Boadi junction-Appiadu road in the Ashanti Region. The hospital offers a wide range of specialized services and has a cutting-edge diagnostic centre to serve the needs of patients.

Adiebeba Specialist Hospital started operating in 1991 and is located at Ahodwo. The hospital offers services including obstetrics and gynecology, internal medicine, child health, mental health and general surgery. It has a bed capacity of 15 beds and is endowed with well-trained and dedicated health professionals.

OAK Specialist Hospital is located in the centre of Fankyenebra in the Kumasi Metropolis, Ashanti Region. It's a cutting-edge medical facility with subspecialties including cardiology, neurology, infectious diseases, hematology, nephrology, urology, and gastrointestinal, they have highly qualified consultants and specialists in the fields of obstetrics & gynecology, pediatrics, and internal medicine.

3.2 Study Design

This was a multi-centre prospective study that involved women classified as expected POR using the POSEIDON criteria undergoing autologous IVF/ICSI-embryo transfer in six fertility centres in Kumasi, Ghana. Study participants were recruited at the start of OS and followed up until clinical pregnancy was confirmed or otherwise. The POSEIDON classification for expected POR is POSEIDON group 3 (women < 35 years with poor ovarian reserve pre-stimulation parameters defined as AMH < 1.2 ng/ml; AFC <5), and POSEIDON group 4 (women aged ≥ 35 years with poor ovarian reserve pre-stimulation parameters defined as AMH < 1.2 ng/ml; AFC <5.

3.3 Study Population

The target population for this study were all women with expected POR and accessing autologous IVF/ICSI-embryo transfer in six fertility centres in Kumasi. The selection of study participants into the study was based on satisfying the inclusion criteria. All women with expected POR who did not meet the inclusion criteria were excluded from the study.

3.3.1 Inclusion criteria

1. Women aged < 35 years with poor ovarian reserve pre-stimulation parameters (AMH < 1.2 ng/mL; AFC <5).
2. Women aged ≥ 35 years with poor ovarian reserve pre-stimulation parameters (AMH < 1.2 ng/mL; AFC <5).
3. Women having both ovaries present and adequately visualized on transvaginal ultrasound and who met the POSEIDON criteria for expected POR.
4. Women who met the POSEIDON criteria for expected POR and provided informed consent.

3.3.2 Exclusion criteria

1. Women with expected POR who underwent OS with mild or minimal stimulation protocols, used alone or in combination with oral anti-oestrogens or aromatase inhibitors were excluded from the study.
2. Women with expected POR who had preimplantation genetic testing were also excluded from the study. These women were excluded from the study because of all the fertility centres, only one of them used this technology for determining embryo euploidy before embryo transfer.

3.4 Sample Size Estimation

The two proportions sample size estimation formula was used to estimate the sample size for this study.[163]

$$SS = \frac{(Z_{\alpha/2}+Z_{\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2))}{(P_1 - P_2)^2}$$

Where SS is the sample size, $Z\ \alpha/2 = 1{\cdot}96$ at type 1 error of 5 %, $Z_\beta = 0{\cdot}84$ at 80% power, P_1 is the proportion of women with expected POR group three who achieved clinical pregnancy rate, and P_2 is the proportion of women with expected POR group four who achieved clinical pregnancy rate. $P_1 - P_2$ is the difference in the prevalence of women with expected POR group three and expected POR group 4 who achieved clinical pregnancy rate following IVF/ICSI-embryo transfer. Based on an earlier study, Lee *et al.*[20] reported that 16.7% and 4.8% of women in expected POR groups three and four achieved clinical pregnancy respectively. This study was used as the comparator for estimating the sample size because among the studies conducted in sub-Saharan Africa, none of them used the POSEIDON criteria and this was the closest and also compared OS outcomes using the POSEIDON criteria.

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$$= \frac{(1.96 + 0.84)^2 \text{ x } (0.167\ (1 - 0.167) + 0.048\ (1 - 0.048))}{(0.167 - 0.048)^2} = 102$$

Using a 10.0% contingency rate, a minimum of 112 women with expected POR who underwent autologous IVF/ICSI-embryo transfer had more than 80.0% power to detect the difference in OS outcomes between the two groups of women with expected POR based on the POSEIDON criteria.

3.5 Sampling Technique

A consecutive sampling technique with a proportional allocation was employed to recruit 112 women classified as expected POR accessing autologous IVF/ICSI-embryo transfer in the six fertility centres in Kumasi. The proportional allocation of the sample size was used to ensure that the number of women who were recruited from each fertility centre was based on the number of sampling units in each facility. However, in each fertility centre, the women were consecutively recruited until the estimated number per facility was obtained. The proportional allocation of the sample size to the size of each fertility centre was determined by dividing the average number of women with expected POR who accessed IVF/ICSI-embryo transfer in 2022 by the number of women with expected POR who accessed autologous IVF/ICSI-embryo transfer in 2022 in all the six fertility centres in Kumasi and multiplied by the estimated sample size. The estimated sample size for each fertility centre has been presented in Table 3.1. In each fertility centre, all women who met the inclusion criteria and provided informed consent were included in the study

until the desired sample size was attained. However, a total of 117 women who met the inclusion criteria were recruited into the study. During the study period, in addition to the 117 women with expected POR who were recruited, a further 253 women underwent autologous IVF/ICSI-embryo transfer.

Table 3.1: Sample size for each fertility centre.

Facility	Sample size
Trust Care Specialist Hospital and Fertility Centre	16
RUMA Fertility and Specialist Hospital	44
Hallmark Medicals	21
Aniniwaah Medical Centre – Diagnostic and Fertility Clinic	21
Adiebeba Specialist Hospital	1
OAK Specialist Hospital.	14
Total	**117**

3.6 Data Collection and Procedure

In all the fertility centres, a list of all women presenting for autologous IVF/ICSI-embryo transfer was reviewed. Informed consent was obtained from all women who met the inclusion criteria (patients who fell within POSEIDON groups 3 and 4) and these women were then given a unique study identification number which was used throughout data collection. A pretested structured questionnaire was administered to study participants by research assistants in English or the local Twi language (for those who could not understand English) through a face-to-face interview. The questionnaire was uploaded on a smartphone with the aid of Kobo-Collect. Three research assistants with a background in embryology, public health and nursing were trained by a biostatistician and fertility specialist for three days on informed consent, data collection instruments and questionnaire administration. Information was collected on their socio-demographic, obstetric and gynecological characteristics like age, parity, type of infertility, duration of infertility, previous IVF/ICSI-embryo transfer and its outcome as well as the history of chronic medical conditions or any pelvic surgeries. Clinical data were also retrieved from participants' medical records, and this included AFC and serum AMH (ng/ml) levels. During the period of data collection, all women undergoing autologous IVF/ICSI-embryo transfer were

routinely screened for ovarian reserve (AFC and AMH) before OS. Data on OS outcomes and parameters like type of OS protocol used, type of gonadotropin and dosage used for stimulation, duration of gonadotropin stimulation, method of fertilization whether fresh or frozen embryos were also collected. The OS outcomes included total follicles ≥18mm at the time of trigger, the total number of oocytes retrieved, total mature metaphase 11 oocytes retrieved, the total number of embryos formed and their grade, the number of women who had their cycles cancelled before oocyte pick-up and those whose cycle were cancelled before embryo transfer stage, number of embryos transferred, positive pregnancy test and clinical pregnancy rates.

3.7 Ovarian Stimulation (OS) Protocol

During the study, all patients received normal OS treatments. In all the fertility centres, patients underwent pituitary suppression using either the long agonist protocol or the short agonist/flare protocol. The practice of batching cycles was implemented at all the fertility centres. To facilitate batching of cycles, all women received combined oral contraceptive pretreatment. In the long agonist protocol, pituitary suppression was achieved by giving GnRH agonist depot injection (Goserelin/Zoladex 3.6mg, AstraZeneca, UK) in the mid-luteal phase of the cycle preceding the stimulation cycle. Gonadotropin administration was initiated with highly purified urinary FSH (Fostimon, IBSA, Switzerland), recombinant FSH (Gonal-F, Serono, Switzerland) and/or HMG (Menopur, Ferring pharmaceutical, NJ, USA) on the second day of withdrawal bleeding when pituitary desensitization was confirmed as demonstrated by the absence of ovarian follicles larger than 5 mm and endometrial thickness less than 5.4 mm on transvaginal ultrasound examination. Gonadotropin dosages varying between 300IU to 450IU daily were used by the various fertility specialists. Under the terms of the short agonist/flare protocol, a short-acting GnRH agonist injection (Buserelin/Suprecur 0.25mg, Neon Healthcare Ltd, UK) was started on the second day of menstrual bleeding and continued till the day of hCG trigger while gonadotropin administration was commenced on day three of withdrawal bleed and continued until the day of hCG trigger.

The ovarian stimulation protocol and the initial exogenous gonadotropin dosing regimen were individualized and determined by the various fertility consultants in the study sites based on the women's age, BMI, ovarian reserve tests (AMH and AFC) and the outcome of any past OS. In

all OS cycles done across the study sites, subsequent exogenous gonadotrophin was administrated in variable doses and further adjusted according to individual ovarian response based on transvaginal ultrasound scan and/or serum estradiol measurements. Transvaginal ultrasound assessment of follicular growth and endometrial thickness was performed serially to monitor ovarian response and serum estradiol levels and progesterone determinations were recorded according to individual practices at each fertility centre.

When the leading follicular cohort reached a diameter ≥18 mm, final follicular maturation was induced with hCG (Choriomon, IBSA, Switzerland). A transvaginal ultrasound-guided oocyte retrieval was conducted 34-36 hours after the ovulation trigger under anesthesia. After oocyte retrieval, insemination of mature oocytes either by conventional IVF or ICSI was performed based on sperm quality. Normal fertilization was identified by the presence of two pronuclei (2PN) and two polar bodies at the time of fertilization assessment, 16 to 19 hours after insemination. Luteal support was initiated on the evening of oocyte pick up and consisted of vaginal and intramuscular progesterone as pertain to the practice at the various centres.

Embryo culture, assessment and final embryo grading were done by trained embryologists. Embro grading was done using the Gardner embryo grading system and in all the fertility centres, the resulting embryos were transferred in a fresh cycle or vitrified according to individual centres' policies. Day five embryo transfer was performed in all fertility centres. Pregnancies were confirmed with urinary pregnancy tests or serum beta-hCG levels measured 14 days after embryo transfer. Clinical pregnancy was confirmed by visualization of an intrauterine gestational sac with or without a fetal pole four weeks after embryo transfer.

3.8 Pretesting of Questionnaire

The questionnaire was pretested among ten women with expected POR and accessing autologous IVF/ICSI-embryo transfer in one fertility centre in Kumasi. These women were not included in the final study. This was done to ensure that there was no ambiguity and difficulty in understanding the data collection instrument for the study participants. After the pretest, all the necessary corrections were made to the questionnaire before it was used to collect the final study data.

3.9 Study Variables

This study variables were made up of both dependent (outcome) and independent (predictor) variables.

3.9.1 Dependent variable

The primary outcome of the study was the proportion of clinical pregnancy among women with expected POR undergoing autologous IVF/ICSI-embryo transfer in Kumasi. A pregnancy that is confirmed on ultrasonography by showing one or more gestational sacs or clear signs of pregnancy is referred to as a clinical pregnancy. It encompasses both intrauterine pregnancy and an ectopic pregnancy with clinical documentation.[8] The secondary outcomes were the number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, a positive pregnancy test result and the proportion of expected POR. The International Glossary on Infertility and Fertility Care defined cycle cancellation in ART as ‘‘an ART cycle in which ovarian stimulation or monitoring has been initiated, with the intention to treat, but which did not proceed to follicular aspiration or in the case of a thawed or warmed embryo did not proceed to embryo transfer’’.[8] The cycle cancellation rate in this study was measured as the total number of cycles cancelled before oocyte pick-up and embryo transfer divided by the estimated sample size and expressed as a percentage.

3.9.2 Independent variables

The independent variables included socio-demographic characteristics (such as age, educational qualification, and marital status), clinical characteristics (such as body mass index, parity, duration of infertility, and cause of infertility), results of ovarian reserve tests (AFC, serum AMH) and OS characteristics such as stimulation protocol used, type and dosage of gonadotrophin used, and total duration of gonadotrophin stimulation.

3.10 Data Quality Control and Analysis

Data was exported from Kobo-Collect into an Excel spreadsheet for data quality control. Data cleaning was done by two research assistants independently and compared to improve the quality of the data before analysis.

Data were analyzed using Stata version 16. Continuous variables were analyzed and presented using means and standard deviations (for normal distribution data) or medians and interquartile ranges (for skewed data). Categorical variables were analyzed and presented using frequencies and percentages. Categorical variables were compared using the Chi-square test while continuous variables were also compared using the student's t-test. The clinical pregnancy rate, positive pregnancy rate and cycle cancellation rate among the POSEIDON groups three and four were compared using the Chi-square test with a p-value <0.05 considered statistically significant. Also, the Student's t-test was used to compare the means of the number of oocytes retrieved, number of M11 oocytes retrieved and number of embryos obtained among POSEIDON groups three and four women.

3.11 Ethical and Legal Considerations

This study adhered to all ethical and legal considerations in research that involves human participation. Written approval to commence research was sought from all the fertility centres. Ethical clearance was also sought from the Committee on Human Research, Publications and Ethics, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi with reference number; CHRPE/AP/769/23. Patient recruitment and data collection was commenced after this clearance was obtained.

Written informed consent was taken from all study participants before recruitment into the study. This was done by explaining the purpose of the study to the participants as well as all the benefits, and risks involved in taking part in the study. The study participants were made to understand that their involvement or rejection to participate in the study would not in any way affect their welfare or the quality of service they would receive at the facility. All prospective study participants were encouraged to ask questions for clarification. All those who agreed to take part in the study were made to either sign or thumbprint a written informed consent before being recruited into the study. The study period was for seven months (August 2023 to February 2024).

CHAPTER FOUR

RESULTS

4.0 Introduction

This chapter focused on the results of the study including the demographic characteristics, clinical and cycle characteristics as well as the objectives of the study.

4.1 Demographic, Clinical and Cycle Characteristics of Study Participants

4.1.1 Demographic characteristics of study participants

Table 4.1 shows the socio-demographic characteristics of the study participants. The age range of participants was 27-48 years, with a mean age of 37.5 (±3.7) years. The majority (75.2%) of the study participants were at least 35 years old. Over 96.6% of the study participants were married while the remaining 3.4% were cohabiting. A majority (95.7%) of the study participants were employed, over three-quarters (79.5%) of them were Christians and 47.0% of the study participants had tertiary education. Five of the women reported that they take alcohol (Table 4.1).

Table 4.1: Socio-demographic characteristics of study participants

Characteristics	Frequency, N = 117	Percentage, %
Age group (years)		
< 35	29	24.8
≥ 35	88	75.2
Mean age (±SD)	37.5 (±3.7)	-
Marital status		
Married	113	96.6
Cohabiting	4	3.4
Employment status		
Employed	112	95.7
Unemployed	5	4.3
Religion		

Christian	93	79.5
Muslim	24	20.5
Level of education		
Basic	16	13.7
Secondary	46	39.3
Tertiary	55	47.0
Ethnicity		
Akan	85	72.6
Northern tribes	25	21.4
Others	7	6.0
Smoke		
Yes	0	0.0
No	117	100
Drink alcohol		
Yes	5	4.3
No	112	95.7

Source: Field Data, 2024

SD: Standard deviation

4.1.2 Clinical characteristics of study participants

Table 4.2 shows the clinical characteristics of the study participants. A majority (74.4%) of the study participants had never given birth. Over two-thirds (68.4%) of the study participants had primary infertility. The median duration of infertility was 6 years (interquartile range: 8, 3). Female factor (63.2%) was the major indication for ART. Of those whose infertility was due to a female factor, over half (62.2%) of them were due to tubal causes. Over 45.3% of the women had undergone pelvic surgery of which over half (54.7%) of them had myomectomy (Table 4.2A).

Nine (7.7%) of the study participants had chronic medical conditions. Less than a quarter (15.4%) of the study participants had previous autologous IVF/ICSI-embryo transfer and twelve of them had recorded a previous poor response to OS. The mean BMI of the study participants was 29.7 (±5.4) with a range of 18.9 and 51.8. Over 44.4% of the women were obese (Table 4.2B).

Table 4.2A: Clinical characteristics of study participants

Characteristics	Frequency, N = 117	Percentage, %
Parity		
0	87	74.4
1	22	18.8
2+	8	6.8
Type of infertility		
Primary	80	68.4
Secondary	37	31.6
Duration of infertility (years)		
< 5	50	42.7
5 – 10	48	41.0
11+	19	16.3
Median duration (IQR)	6 (8, 3)	-
Indication for ART		
Both male and female factor	22	18.8
Female factor	74	63.2
Male factor	15	12.8
Unexplained	6	5.2
Female factor (n = 74)		
Tubal	46	62.2
Ovulatory	26	35.1
Others*	2	2.7
Had pelvic surgery before		
Yes	53	45.3
No	64	54.7
If yes, type of surgery (n = 53)		
Myomectomy	29	54.7
Laparotomies	11	20.8
Cesarean section	7	13.2
Salpingectomy	5	9.4
Ovarian cystectomy	1	1.9

Source: Field Data, 2024
IQR: Interquartile range
*Others include advanced age and prolonged infertility, endometriosis

Table 4.2B: Clinical characteristics of study participants

Characteristics	Frequency, N = 117	Percentage, % [Range]
Diagnosed of endometriosis		
Yes	5	4.3
No	112	95.7
Chronic medical condition		
Yes	9	7.7
No	108	92.3
If yes, medical condition (N = 9)		
Hypertension	3	33.3
Diabetes	1	11.1
Others[a]	6	55.6
On long-term medication		
Yes	10	8.5
No	107	91.5
Take herbal medication		
Yes	8	6.8
No	109	93.2
Had previous IVF treatment		
Yes	18	15.4
No	99	84.6
Number of IVF treatments in the past (n = 18)		
1	11	61.1
2	6	33.3
3	1	5.6
Had previous poor response to OS (n = 18)		
Yes	12	66.7
No	6	33.3
Number of oocytes retrieved for previous poor response to OS (n = 12)		
< 3	5	41.7
4 – 9	7	58.3

Achieved pregnancy for oocytes <3 in previous OS (n = 5)		
Yes	1	20.0
No	4	80.0
BMI		
Normal	26	22.3
Overweight	39	33.3
Obese	52	44.4
Mean BMI (±SD)	29.7 (±5.4)	-
Antral follicle count, median (IQR)	5 (5, 3)	-
Antimullerian hormone, median (IQR)	0.8 (1.02, 0.31)	-

Source: Field Data, 2024
IQR: Interquartile range
BMI: Body mass index
[a]Others include HIV, hepatitis B, psychiatric, Asthma, & subclinical hyperthyroidism

4.1.3 Cycle characteristics of study participants

The long agonist protocol was used in over two-thirds (67.5%) of the study participants and in more than half (51.3%) of the women, highly purified FSH was the gonadotropin of choice for OS. The mean duration of stimulation was 11.2 (±2.1) days with a range of 5 to 14 days and the median estimated follicle count at the time of trigger was 7 (interquartile range: 11, 4). Over 44.4% of the study participants had between 4-9 follicles counted on transvaginal ultrasound at the time of trigger. Approximately 56.0% of the embryos were grade A on the day of transfer. A majority (80.6%) of the study participants had a fresh embryo transfer. The median total gonadotrophin dosage used per cycle was 3900 IU (interquartile range: 4500 IU, 3375 IU). Over 23.6% and 34.6% of the study participants had single and double embryos transferred respectively. Approximately 80.0% of the study participants' method of fertilization was IVF. (Table 4.3).

Table 4.3: Cycle characteristics of study participants

Characteristics	Frequency	Percentage, %
OS protocol used		
Long agonist	79	67.5
Short agonist/flare	38	32.5
Type of gonadotrophin used for OS		
Both FSH and hMG	36	30.8
Highly purified FSH	60	51.3
Recombinant FSH	21	17.9
Starting dose of gonadotrophin (IU)		
300	56	47.9
375	54	46.1
450	7	6.0
Total gonadotrophin dosage used per cycle (IU), median (IQR)	3900 (4500, 3375)	-
Duration of stimulation (days), mean (±SD)	11.2 (±2.1)	-
Estimated follicle count at the time of trigger		
≤3	20	20.2
4 – 9	44	44.4
10+	35	35.4
Estimated follicle count at the time of trigger, median (IQR)	7 (11, 4)	-
Number of oocytes retrieved (n =95)		
≤3	30	31.6
4 – 9	47	49.5
10+	18	18.9
Number of oocytes retrieved, median (IQR)	5 (8, 2)	-
Number of M11 oocytes (n = 73)		
≤3	43	58.3
4 – 9	28	38.9
10+	2	2.8
Number of M11 oocytes, median (IQR)	5 (8, 2)	-
Blastocytes number, median (IQR)	2 (3, 1)	-
Morula number, median (IQR)	2 (3, 1)	-
8-cell number, median (IQR)	2 (2, 1)	-
4-cell number, median (IQR)	1 (2, 1)	-
Number of embryos formed, median (IQR)	3 (5, 2)	-
Method of fertilization (n = 75)		
ICSI	15	20.0
IVF	60	80.0
Embryo grade on the day of transfer (n=25)		
Good (Grade A)	14	56.0
Fair (Grade B)	6	24.0
Poor (Grade C)	5	20.0
Frozen embryo transfer (n = 72)		
Yes	14	19.4
No	58	80.6

Number of embryos frozen, mean (±SD), range	3.1 (±1.1), 1 – 5	
Fresh embryo transfer (n = 72)		
Yes	58	80.6
No	14	19.4
Number of embryos transferred (n = 55)		
1	13	23.6
2	19	34.6
3+	23	41.8
Day 5 embryo transfer (n = 72)		
Yes	72	100.0
No	0	0.0

Source: Field Data, 2024
FSH: Follicle-stimulating hormone
AMH: Antimullarian hormone
M11: Metaphase 11

4.2 Proportion of Expected POR Among Women Who Underwent Autologous IVF/ICSI-Embryo Transfer

During the recruitment period, in addition to the n=117 women with expected POR, a further 253 women underwent autologous IVF/ICSI-embryo transfer. Hence the proportion of women with expected POR was 31.6% (Figure 4.1). Of those who were women with expected POR (n = 117), over three-quarters (75.2%) of them belonged to the POSEIDON group four while the remaining 24.8% of them were in POSEIDON group three (Figure 4.2).

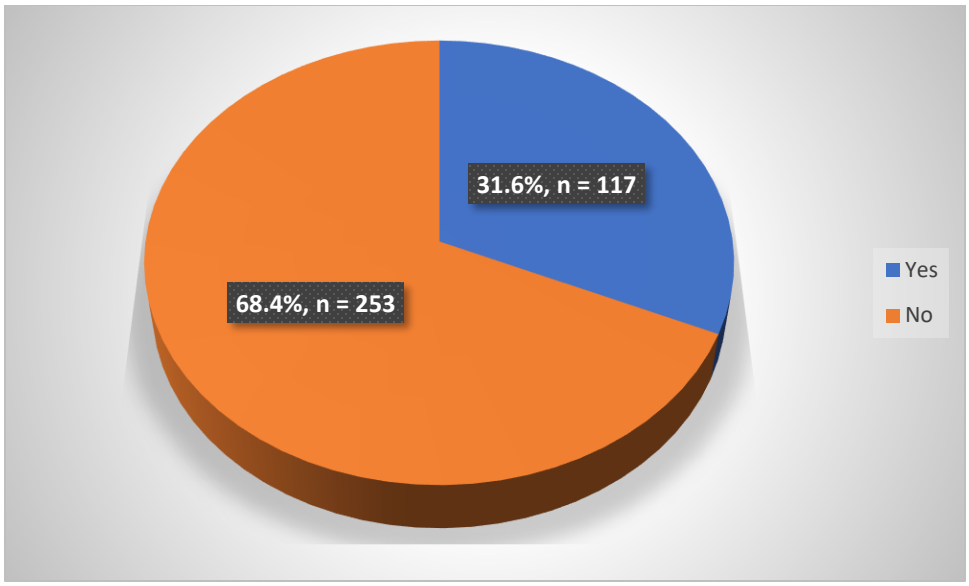

Figure 4.1: Proportion of expected POR among the women who underwent autologous IVF/ICSI-embryo transfer

Source: Field Data: 2024

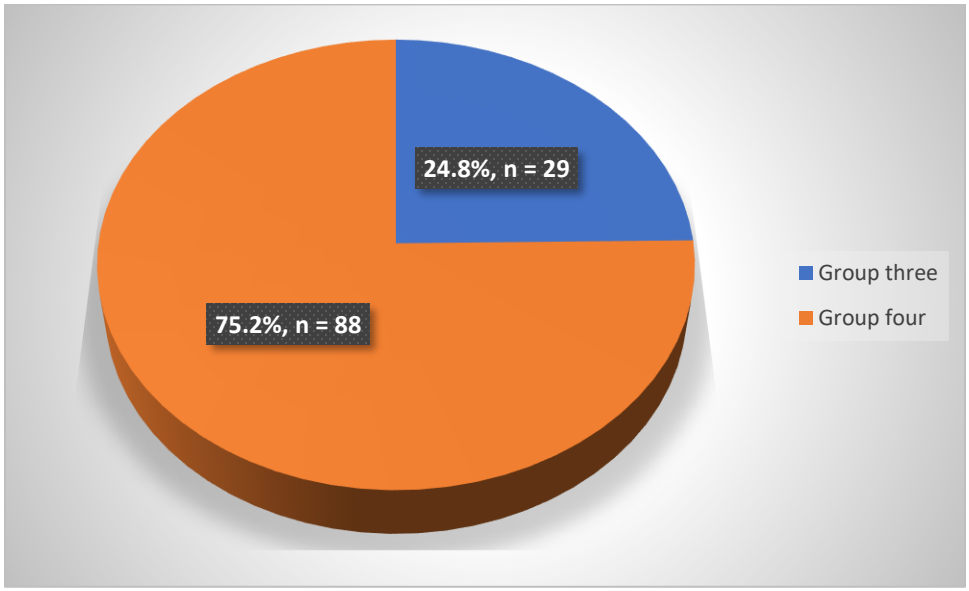

Figure 4.2: Proportion of POSEIDON groups three and four

Source: Field Data: 2024

4.3 Cycle Cancellation Rates Among Study Participants

Figures 4.3, 4.4 and 4.5 show the total cancellation rate, cancellation rates before oocytes pick up and cycle cancellation rate before embryo transfer respectively among the study participants. Generally, the total cycle cancellation rate among the study participants was 38.5% (Figure 4.3). Of the 117 study participants, 22 (18.8%) of them had their cycles cancelled before oocyte pick-up (Figure 4.4). Of the 95 study participants who continued their treatment after oocyte pick-up, 23 (24.2%) had their cycles cancelled before embryo transfer (Figure 4.5).

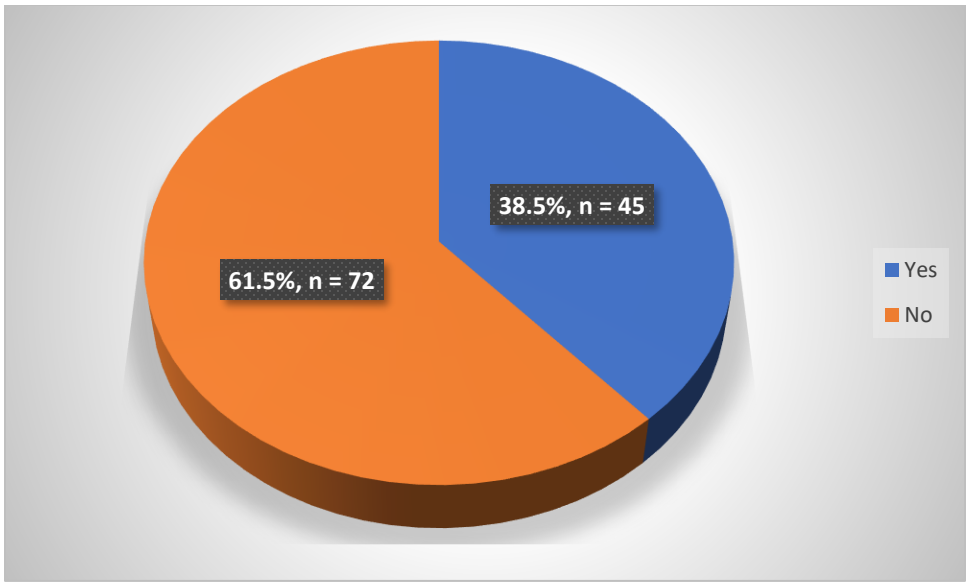

Figure 4.3: Total cycle cancellation rate among study participants

Source: Field Data, 2024

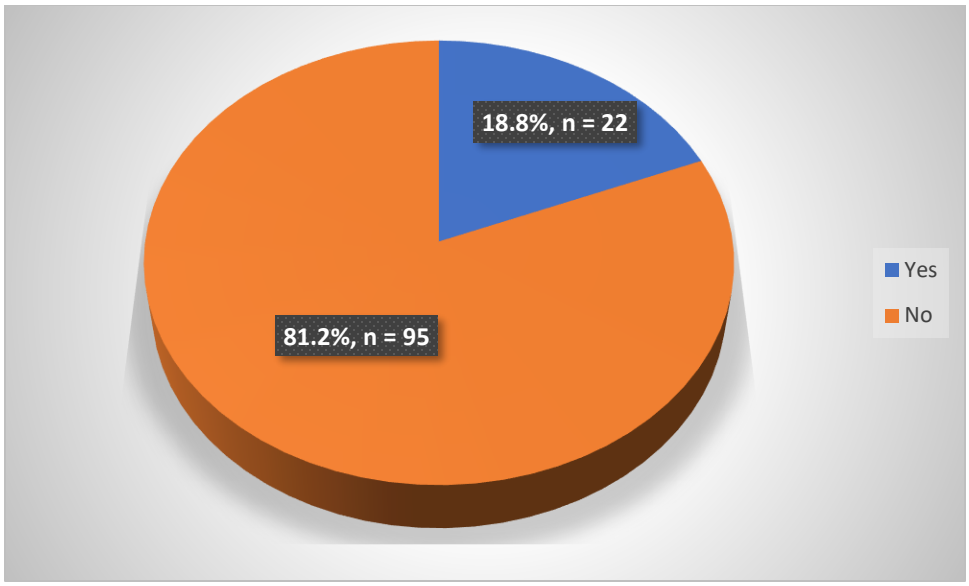

Figure 4.4: Cycle cancellation rate before oocytes pick up among study participants

Source: Field Data, 2024

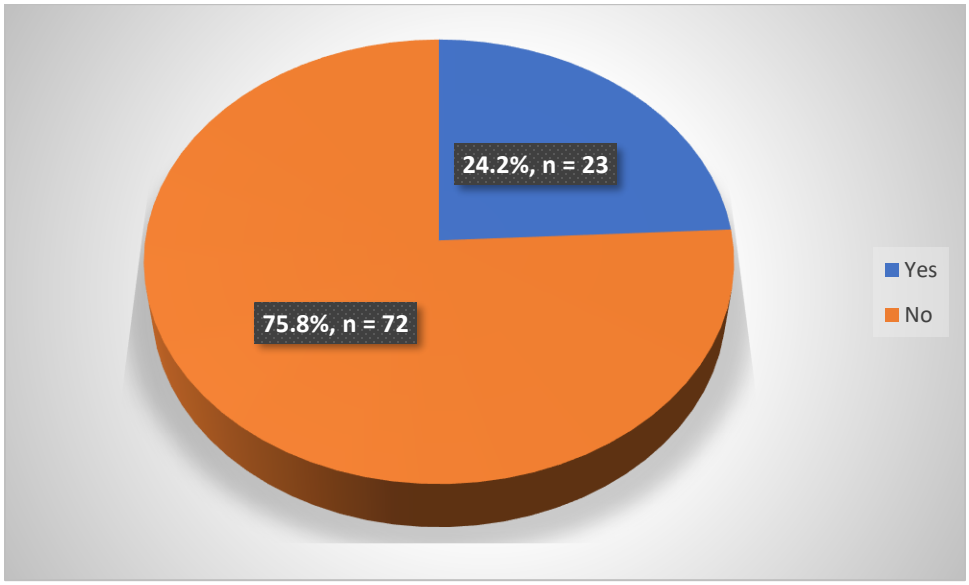

Figure 4.5: Cycle cancellation rate before embryo transfer among study participants

Source: Field Data, 2024

4.4 Positive Pregnancy Test and Clinical Pregnancy Rates Among the Study Participants

Figures 4.6 and 4.7 show the positive pregnancy test and clinical pregnancy rates respectively among the study participants. Of the 117 study participants, less than a quarter (24.8%) of them had a positive pregnancy test (Figure 4.6). Over 21.4% of the study participants achieved clinical pregnancy while the remaining 78.6% did not (Figure 4.7).

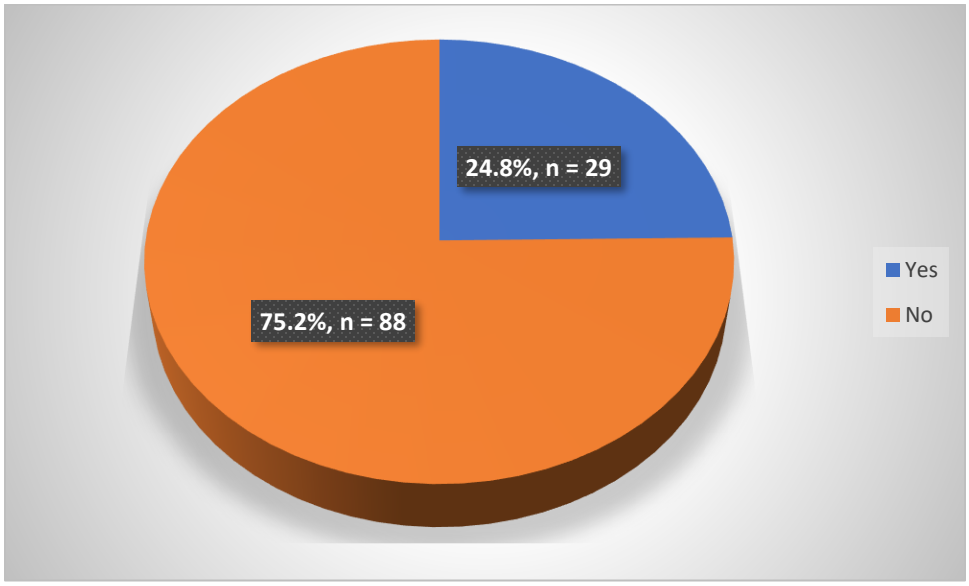

Figure 4.6: Positive pregnancy test rate among study participants

Source: Field Data, 2024

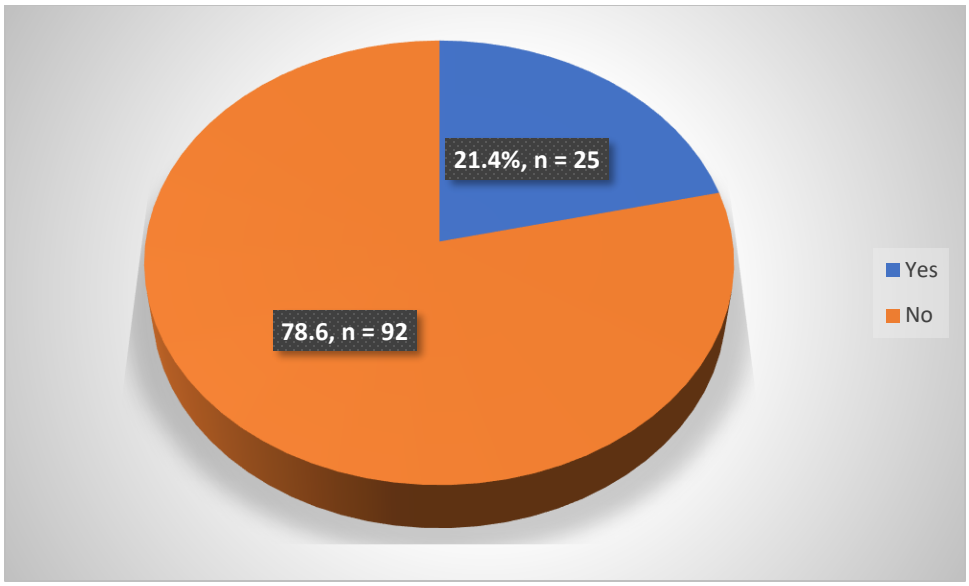

Figure 4.7: Clinical pregnancy rate among study participants

Source: Field Data, 2024

4.5 Comparison of Outcomes of OS Among Women in Expected POR Groups 3 And 4

Table 4.6 shows the comparison of outcomes of OS among women in expected POR groups 3 and 4. Approximately 31.0% of the women in POSEIDON group three had a positive pregnancy test while 22.7% of the women in POSEIDON group four also had a positive pregnancy test. However, there was no statistically significant difference in achieving positive pregnancy tests among the two POSEIDON groups of women with expected POR. Similarly, six and nineteen women in POSEIDON groups 3 and 4 achieved clinical pregnancy respectively (20.7% vs 21.6%, p = 0.918). More women in POSEIDON group three cancelled their cycle than those in group 4 (41.4% vs 37.5%, p = 0.710). The mean number of oocytes retrieved among women in POSEIDON group three was 6.5 (±4.1) while the mean number of oocytes retrieved among women in POSEIDON group 4 was 5.6 (±4.2). However, there was no statistically significant difference in number of oocytes retrieved among women in the two POSEIDON groups. The mean number of metaphase 11 oocytes among women in POSEIDON group three was similar to the mean number of metaphase 11 oocytes among women in POSEIDON group four (4.0 (±3.1) vs 3.9 (±3.0), p-value = 0.832) (Table 4.4).

Table 4.4: Comparison of outcomes of OS among women in expected POR groups 3 and 4

Variables	POSEIDON		p-value
	Group Three	Group Four	
	n = 29 (%)	n = 88 (%)	
Positive pregnancy test rate[a]			0.369
Yes	9 (31.0)	20 (22.7)	
No	20 (69.0)	68 (77.3)	
Clinical pregnancy rate[a]			0.918
Yes	6 (20.7)	19 (21.6)	
No	23 (79.3)	69 (78.4)	
Total cycle cancellation[a]			0.710
Yes	12 (41.4)	33 (37.5)	
No	17 (58.6)	55 (62.5)	
Number of oocytes retrieved[b]	6.5 (±4.1)	5.6 (±4.2)	0.379
Number of M11 oocytes[b]	4.6 (±3.6)	3.9 (±3.0)	0.832
Number of embryos formed[b]	4.0 (±3.1)	3.6 (±2.3)	0.446
Blastocytes number[b]	2.5 (±2.1)	2.0 (±1.6)	0.847
Morula number[b]	2.4 (±1.2)	2.1 (±1.0)	0.315

Field Data, 2024
[a]Analyzed using the Chi-square test
[b]Analyzed using student t-test

CHAPTER FIVE

DISCUSSIONS

5.0 Introduction

This chapter focused on the discussion of the study's significant findings. The current study's findings were discussed by comparing them with earlier studies across the globe. Explanations were given in instances where there were variations between the findings in the current study and previous ones.

5.1 Demographic, Clinical and Cycle Characteristics of Study Participants

5.1.1 Demographic characteristics of study participants

In this study, most of the study participants were 35 years old and above and married. This indicates the study predominantly included women in their late reproductive years or approaching advanced maternal age. Most of the study participants being 35 years and older in the current study resonates with earlier studies among women with expected POR.[141,162] Nabaneeta *et al.* studied the demographic characteristics and clinical profile of 104 poor responders undergoing autologous IVF/ICSI-embryo transfer in India and reported that 60.57% were above 35 years of age.[164] The finding in the current study is not surprising considering that most of the study participants were made of women in POSEIDON group four whose classification aside from AMH and AFC their age of 35 years old and above based on the POSEIDON classification.[155] This age distribution may influence the treatment outcomes and response to OS, as advanced maternal age is associated with decreased ovarian reserve and diminished fertility.[88] Most of the study participants were married and this highlights the importance of considering both partners' perspectives and potential fertility issues when designing personalized treatment plans.[89]

In the current study, most of the study participants were employed. The high employment rate among the study participants suggests potential access to financial resources for treatments, although work-related commitments and stressors may affect treatment decisions and adherence.

With most of the study participants identifying as Christians, religious beliefs may shape attitudes towards fertility treatments and ethical considerations. Moreover, most (47.0%) of the study participants having tertiary education may suggest heightened awareness of fertility-related issues and treatment options, potentially impacting decision-making processes. Awareness of alcohol consumption (5%) underscores lifestyle factors that can affect fertility outcomes, highlighting the importance of lifestyle modifications. Understanding these characteristics is crucial for tailoring personalized treatment approaches, addressing potential barriers, and optimizing outcomes in autologous IVF/ICSI-embryo transfer programs.

5.1.2 Clinical characteristics of study participants

The clinical profile of the study participants provides insights into the characteristics of women seeking fertility treatment. In this current study, it was found that about two out of ten of the study participants had normal BMI, though over a third were overweight and 44.4% were obese. The median AFC was low at 5, and AMH levels were only 0.8 ng/mL, indicating diminished ovarian reserve. It was observed that less than a quarter (15.4%) of the study participants had previous IVF/ICSI, most commonly one prior cycle, and of those most of them experienced poor response to OS. For the poor responders, most produced fewer than 3 oocytes and pregnancy rates were low when the oocyte number was very low resonating the association between oocytes retrieved and OS outcomes in poor ovarian responders.[98]

The findings in this study also suggest that the study population faced challenges related to obesity, poor ovarian response, and low baseline fertility levels that could negatively impact treatment outcomes. Rittenberg *et al.* in a systematic review and meta-analysis involving 33 studies found that in 47,967 IVF/ICSI-embryo transfer cycles done, women who were obese or overweight had a reduced risk of achieving clinical pregnancy and live birth rate.[165] Similarly, among POR women in Egypt who underwent IVF/ICSI-embryo transfer, those who had normal weight achieved significantly higher biochemical and clinical pregnancy rates than those who were overweight or obese.[166]

Tailoring OS protocols and modifying lifestyle factors like weight could improve results. Comparing pregnancy rates and live births between groups with different clinical profiles may reveal which parameters most influence IVF/ICSI-embryo transfer success whilst further

research exploring individualized treatments targeting the clinical characteristics of poor responders and women with indicators for low ovarian reserve could improve outcomes. Enhancing outcomes for specific patient subgroups could help more women with infertility achieve successful pregnancy and delivery through IVF/ICSI-embryo transfer.

Again, in this study, most of the participants had primary infertility with a median fertility duration of six years. In Egypt, a study which was carried out among POR women also reported majority of them with primary infertility.[166] In this study, it was also found that the female factor was a major indication for autologous IVF/ICSI-embryo transfer followed by both male and female factors. This implies that the causes of infertility do not rest with females alone but some of the problems could also come from the males. This finding is in agreement with the findings of a study in China that reported female factors and both male and female factors as major indications for infertility.[141] However, in the African Network and Registry for ART report,[167] male factor was indicated as a major/primary indication for ART. The African Network and Registry for ART report covers all women undergoing ART[167] compared to this study's population of women classified as expected POR based on the POSEIDON criteria. This could explain the variations in the indications for ART in the two studies.

In this study, some (45.3%) of the study participants had a history of pelvic surgery and of those who had it, most of them were myomectomy. This finding in the current study is worrying considering that pelvic surgery or adhesion has been documented in the literature as a contributory factor to poor ovarian reserve which could affect OS outcomes among women undergoing autologous IVF/ICSI-embryo transfer.[168,169]

5.1.3 Cycle characteristics of study participants

The findings demonstrate a predominant utilization of a long agonist protocol for OS, with it being used in over two-thirds of the study participants. This finding in the study is suggestive that the fertility centres in Kumasi followed the recommended protocol for IVF/ICSI-embryo transfer which could be beneficial to achieving clinical pregnancy. The utilization of long agonist protocol for OS is well documented in the literature.[170,171] Additionally, highly purified FSH was used in more than half (51.3%) of the study participants who underwent OS indicating a

preference for this medication type by fertility specialists. Additionally, studies have not shown any benefit in the use of urinary FSH, hp-FSH and recombinant FSH over each other.[71,172]

The mean duration of stimulation was 11.2 days, suggesting variability in treatment duration among participants. The mean duration of OS observed in the current study is relatively higher than the 9 and 8 days reported among POSEIDON groups three and four women respectively in China.[141] This may be attributed to the long agonist protocol adopted by most fertility centres since the antagonist protocol has been documented to yield shorter stimulation durations among poor ovarian responders.[74] This finding is also at variance with Yu-Cheih *et al.* who studied the impact of stimulation duration in normal and poor responders using the GnRH antagonist protocol and found a shorter mean duration of stimulation despite higher live birth rates being recorded among poor responders in Taiwanese women.[74]

At trigger, the median estimated follicle count was 7, with considerable variability, indicating diverse ovarian responses to stimulation protocols. The variability in the duration of stimulation observed in fertility treatments underscores the personalized approach required to optimize outcomes for each patient. In OS, the goal is to stimulate the ovaries to produce multiple follicles containing eggs, which can then be retrieved for IVF or ICSI. However, the response to stimulation can vary significantly among individuals due to factors such as age, ovarian reserve, and underlying reproductive health conditions.[92,93] Some patients may require a longer duration of stimulation to achieve optimal follicular development, ensuring the maturation of a sufficient number of high-quality oocytes.[94] Poor ovarian responders and aged women are known to require a longer duration of stimulation.[20] This extended duration allows for more follicles to reach maturity, increasing the chances of successful egg retrieval and subsequent embryo development. On the other hand, some patients may respond more rapidly to stimulation, requiring a shorter duration to achieve the desired follicular growth.[74] Stimulation duration in IVF/ICSI-embryo transfer cycles among poor ovarian responders therefore appears to have a diverse impact on oocyte maturation, clinical pregnancy rates and live birth rates in both poor and normal responders.[74]

In the current study, over five out ten of embryos were graded as good on transfer day, reflecting overall embryo quality. It is important to also evaluate embryo quality among expected POR women as part of evaluating their treatment response.[10] In a cohort study, Yuan *et al*. examined

the quality of embryos and pregnancy outcomes for patients with low ovarian reserve. They found that in natural cycles, there were higher rates of available embryos, high-quality embryos, and oocyte utilization compared to their mildly stimulated counterparts. This, therefore suggests that natural cycles, when combined with appropriate oocyte retrieval timing, may be a better option for individuals with low ovarian reserve who are seeking IVF/ICSI-embryo transfer.[173]

A majority (80.0%) of the study participants underwent fresh embryo transfer, and the median total gonadotrophin dosage per cycle was 3900 IU. The high gonadotrophin dosage used in this study is consistent among women with expected POR.[141] [141] Sandro *et al.* in their multicenter and multinational prevalence study among low prognosis women classified by the POSEIDON criteria undergoing IVF/ICSI-embryo transfer recorded a total gonadotropin usage of 2,700 IU (1,100-5,100) among POSEIDON women as compared to 2,300 IU (1,050-4,465) in non-POSIEDON women.[148] Seven *et al.* also reported a variable range of total gonadotropin usage among POSEIDON group three (2,475IU [1000-53509]) and group four (2,700IU [1275-4575]) women in a retrospective cohort study where they assessed live birth rates of low prognosis women according to the POSEIDON criteria.[162] In a Korean study comparing IVF/ICSI-embryo transfer outcomes among the various POSEIDON groups, higher total gonadotropin usage per cycle was recorded for women with expected POR; POSEIDON group three (6300IU [2250-25,950]), and POSEIDON group four (5850IU [450-19,050]).[20] It has been reported in many studies that there was no difference in the amount of gonadotropin used in IVF/ICSI-embryo transfer for poor responders between 300-450 and 600U, even though most doctors normally start controlling OS for these patients by increasing the dosage.[75,174,71]

Notably, 23.6% and 34.6% underwent single and double embryo transfers, respectively, reflecting differing clinical practices and patient preferences. Many recommendations have been given to single embryo transfers to reduce multiple pregnancy rates.[175] The Ghanaian cultural dynamics are different from other populations which could influence the preference to transfer more than one embryo. Currently, in Ghana, no regulations are guiding the practice of ART, and though fertility specialists follow internationally accepted guidelines and protocols, they also adopt their local protocols, which can influence the number of embryos to transfer during IVF/ICSI-embryo.[176] This could explain the differences in the number of embryos transferred in

the current study. The observed variability in treatment protocols underscores the complex nature of fertility treatments, highlighting the necessity for personalized approaches tailored to individual patient characteristics and needs. Personalized approaches involve individualized treatment plans considering a patient's medical history, ovarian reserve, and treatment objectives.[177] Alternative protocols or adjunctive treatments may benefit patients with diminished ovarian reserve, while those with specific medical conditions may require tailored interventions. Personalized approaches extend beyond treatment protocols to include embryo selection, timing of embryo transfer, and supportive care.[91] By incorporating patient preferences, clinicians empower individuals to actively participate in their fertility journey, aligning treatment choices with their goals.

These findings provide valuable insights into the procedural intricacies and outcomes associated with OS among the studied population. Understanding these intricacies is crucial for refining treatment protocols, enhancing success rates, and safeguarding patient well-being in fertility interventions.

5.2 Proportion of Expected POR Among Women Who Underwent Autologous IVF/ICSI-Embryo Transfer.

In the current study, it was observed that three out of ten (31.6%) of the women who underwent autologous IVF/ICSI-embryo transfer were women with expected POR. This finding is similar to the 31.1% reported in a study in Turkey by Seven *et al.*[162] However, the proportion of women with expected POR in the current study is higher than the 20.2% reported in China by Abdullah *et al.*[141] in a retrospective study involving 461 women who underwent autologous IVF/ICSI-embryo transfer. The 19.6% prevalence of women with expected POR undergoing autologous IVF/ICSI-embryo transfer in three countries including Brazil, Turkey and Vietnam is lower than the rate (31.6%) observed in the current study.[148] In Italy, Levi-Setti *et al.* also reported 73.2% (Group 3 (11.7%) and Group 4 (61.5%) prevalence of expected POR among women who underwent 4828 autologous IVF/ICSI-embryo transfer cycles in an observational retrospective cohort trial.[178] The variations in the prevalence rates could be attributed to the differences in population characteristics, sampling approaches and clinical practices.

In general, among the expected POR, the current study observed women in the POSEIDON group four (75.2%) had the highest proportion of patients compared to those in group three (24.8%). This implies that most of the study participants had advanced age. Though not assessed in the current study, the advanced age of most of the study participants could have a negative effect on OS outcomes. The effects of advanced age of women undergoing autologous IVF/ICSI-embryo transfer have been well explained in the literature. While some studies have reported no significant effect of advanced age on OS outcomes,[179] others have reported a significant effect on its success.[7,98]

5.3 Cycle Cancellation Rates Among Study Participants

One of the objectives of the current study was to assess the cycle cancellation rates among the study participants. The capacity of the ovaries to react to gonadotrophin stimulation in addition to producing enough mature follicles to generate sufficient oocytes is significant for the success of IVF/ICSI-embryo transfer. However, not all IVF/ICSI-embryo transfer treatments result in pregnancy or childbirth because some women with expected POR are unable to produce enough mature follicles which could result in discontinuing the treatment.[180]

The current study observed a high (38.5%) cycle cancellation rate among the study participants. Of this, 18.8% of them cancelled their treatment before oocyte pick-up. This finding in the current study is not surprising considering that the study participants were mainly made up of women in the POSEIDON groups three and four who are known to have an increased risk of cycle cancellation. Generally, women in the POSEIDON groups three and four are known to have low ovarian reserve parameters.[156] Another possible reason for the high cancellation rate in the current study could also be attributed to previous poor response to OS by some of the study participants (66.7%) which could increase their likelihood of experiencing another POR and subsequently lead to cycle cancellation.

The 18.8% cycle cancellation rate before oocyte pick-up found in the present study is higher than the 11.5% reported among POR women in Japan.[135] Also, the 18.8% cancellation rate before oocyte pick-up observed in the current study is at variance with the 0.23% reported among women with expected POR using the POSEIDON classification in a multinational study involving Brazil, Vietnam and Turkey.[148] The variations in the study findings could be explained

by the difference in IVF/ICSI-embryo transfer technologies and the study population. The current study involved women with expected POR in POSEIDON groups three and four while the multinational study[148] consisted of both women with unexpected (groups 1 and 2) and expected (groups 3 and 4) POR using POSEIDON classification. The women in POSEIDON groups 1 and 2 are likely to have better outcomes to OS[20] resulting in a reduction in cancellation rate unlike those in POSEIDON groups 3 and 4 who are expected to respond poorly to OS.

5.4 Positive Pregnancy Test and Clinical Pregnancy Rates Among the Study Participants

The goal of autologous IVF/ICSI-embryo transfer treatment is to help women achieve clinical pregnancy and deliver a healthy baby. However, this study found that 24.8% of the study participants reached the first milestone of testing positive for pregnancy. Moreover, an even smaller percentage (21.4%) attained clinical pregnancy. The low rates may suggest issues with embryo quality that prevent implantation and fetal development. Additional factors that may have contributed to the outcomes include patients' general health, laboratory parameters and embryo transfer techniques. Further research is needed to clarify the specific barriers these women faced in trying to get pregnant through autologous IVF/ICSI-embryo transfer. Tailoring medical and laboratory procedures to each individual could help more women successfully progress from a positive pregnancy test to clinical pregnancy and subsequently bring home a baby.

The clinical pregnancy rate observed in the current study was low (21.4%). Based on the POSEIDON classification, the study population were mainly women in groups three and four. Women in the POSEIDON groups three and four are known to have low AFC and AMH and are likely to have fewer euploid embryos for transfer which could affect OS outcomes including achieving a clinical pregnancy.[148] Also, retrieving a significant number of oocytes in POSEIDON groups three and four women is challenging, which will raise the chance of having at least one euploid embryo.[181] POSEIDON groups three and four have low response rates due to low ovarian reserve, genetic variations in the FSH and LH receptors, and the potential presence of variant LH-β reducing their likelihood of achieving clinical pregnancy after OS.

The clinical pregnancy rate (21.4%) found in the current study is similar to the 21.5% reported among POSEIDON groups three (16.7%) and four (4.8%) by Lee *et al.*[20] in a study in Korea.

Also, the clinical pregnancy rate (21.4%) observed in the current study is higher than the 12.0% reported by Eftekhar *et al.*,[33] in Iran among POR women in POSEIDON groups three (4.5%) and four (7.5%). The 38.3% clinical pregnancy rate reported among POR women in POSEIDON groups three (21.6%) and four (16.7%) in India[84] was also higher than the 21.4% observed in the current study. Also, the clinical pregnancy rate found in the current study is relatively lower than the 31.6% among women with expected POR in POSEIDON groups three (21.3%) and four (10.3%) in a study in China by Abdullah *et al.* [7] The varying clinical pregnancy rates between the current study and previous studies[20,84] could be attributed to the difference in body mass index of the study participants, the number and quality of embryos as well as the number of oocytes retrieved. For instance, the current study had a mean body mass index of 29.7 (±5.4) compared to 25.7 (±4.8) for group three and 26.5 (±4.4) for group four in the Indian study which reported a clinical pregnancy rate of 38.3%.[84] Women undergoing OS may not achieve clinical pregnancy, particularly if there are limited embryos available for selection. On the day of embryo transfer, approximately 56.0% of the study participants had grade A embryos in the current study compared to the 33.9% reported among POSEIDON groups three (10.8%) and four (23.1%) women in the Iran study that found clinical pregnancy rate of 12.0%.[33]

5.5 Comparison of Outcomes of OS Among Women in Expected POR Groups Three and Four

Earlier studies have focused on the comparison of OS outcomes among POSEIDON groups (1 to 4) and reported varying results.[152,155,162] To the best of the author's knowledge, this is the first study to compare outcomes of OS in women with expected POR in POSEIDON groups three and four in Kumasi, Ghana. This study did not observe any significant difference in OS outcomes between the two groups of women classified as expected poor ovarian responders (i.e., women in POSEIDON groups three and four). The mean number of oocytes retrieved, the mean number of metaphase 11 oocytes, the mean number of embryos formed, the mean blastocytes number, cycle cancellation rates, positive pregnancy test rates and clinical pregnancy rates were similar in the two POSEIDON groups of expected POR women.

The clinical pregnancy rate was slightly higher in POSEIDON group four than in group three (21.6% vs 20.7%). This implies that none of the POSEIDON groups (three and four) had a better chance of achieving clinical pregnancy than the other. Women in both POSEIDON groups three

and four have fewer AFC and low AMH levels except that their ages are not the same. AFC and AMH levels play an important role in the success of OS outcomes so it is not surprising that clinical pregnancy rates between women in the two POSEIDON groups (three and four) did not differ significantly.

The number of matured oocytes (MII) and the number of grade A embryos formed are both important for achieving euploid blastocyst. In the current study, the mean number of matured oocytes, mean number of embryos formed and mean blastocyte number were similar in both POSEIDON groups three and four. This implies that expected POR women (POSEIDON groups three and four) did not differ significantly in regarding the number of matured oocytes, number of embryos formed and blastocyst. Women in POSEIDON groups three and four have low ovarian reserve which could affect the retrieval of matured oocytes. Seven *et al*. also observed a similar mean number of matured oocytes among women with expected POR in both POSEIDON groups three and four in Turkey.[162] Abdullah *et al.* in a retrospective study assessing cumulative live birth, perinatal and obstetric outcomes among the four POSEIDON groups in China reported a relatively higher mean number of oocytes retrieved in the POSEIDON group 3 (mean: 4.32 ± 1.20) than in group 4 (mean: 3.51 ± 2.54).[7] Abdullah *et al*. also reported a significant difference in the number of embryos obtained between the two groups of expected POR women.[7] Though findings from this study seem to be at variance with the study by Abdullah *et al.* this study was done in a sub-Saharan African country whose demographic characteristics are different from the Chinese population. Further research into the expected POR subgroup of POSEIDON women needs to be done among black people.

5.6 Strengths and Limitations of the Study

A strength of this study is that it is the first to compare OS outcomes among women with expected POR using the POSEIDON criteria in Ghana. Also, the multi-centre approach of this study enhances the generalizability of the study findings to women with expected POR who underwent autologous IVF/ICSI-embryo transfer in the six fertility centres in Kumasi, Ghana. Again, this study utilized a validated tool to classify the study participants into expected POR.

Despite the significant findings of the current study, some limitations are worth noting. This study utilized a non-probability sampling technique, which could lead to selection bias. The

choice of stimulation protocols was determined by the fertility consultants in the various fertility centres and therefore could also affect the outcomes of OS in the current study. Also, the current study did not assess ongoing pregnancy rates, live birth rates, or perinatal outcomes among women with expected POR undergoing autologous IVF/ICSI-embryo transfer. Another limitation of this study is the influence of combined oral contraception for cycle scheduling on ovarian response. The study participants were poor responders and using a combined oral contraception for pretreatment for cycle scheduling purposes may attenuate the ovarian response.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.0 Introduction

This chapter presented the important findings based on the specific objectives of the study. Also, some recommendations have been suggested to key stakeholders to inform potential strategies for ART management of women with expected POR in Ghana.

6.1 Conclusions

6.1.1 Proportion of expected POR among women who underwent Autologous IVF/ICSI-embryo transfer

The current study found that the proportion of expected POR among women who underwent autologous IVF/ICSI-embryo transfer in Kumasi was low.

6.1.2 Cycle cancellation rates among study participants

Again, the current study observed a high cycle cancellation rate among the women with expected POR who underwent autologous IVF/ICSI-embryo transfer in Kumasi. Of these, almost two out of ten of the study participants had their cycle cancelled before oocyte pick-up.

6.1.3 Positive pregnancy test and clinical pregnancy rates among the study participants

The current study demonstrated that the clinical pregnancy rate among women with expected POR who underwent autologous IVF/ICSI-embryo transfer in Kumasi was low (21.4%).

6.1.4 Comparison of outcomes of OS among women in expected POR groups three and four

Finally, the current study did not observe a significant difference in the outcome of OS (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) between women with expected POR groups three and four who underwent autologous IVF/ICSI-embryo transfer in Kumasi. Though no significant difference was observed

in OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) between women in the POSEIDON groups three and four, the current study provides reference data for future studies to build on in Ghana.

The null hypothesis for this objective was that OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among women in expected POR group 3 are the same as among women in expected POR group 4. Since, the current study observed similar OS outcomes (i.e., number of oocytes retrieved, number of metaphase 11 oocytes, number of embryos formed, number of blastocytes obtained, cycle cancellation rates, positive pregnancy test and clinical pregnancy rates) among women with expected POR groups 3 and 4, the author fails to reject the null hypothesis.

6.2 Recommendations

Policy, Guidelines and Clinical Practice

1. Based on the high rate of cycle cancellation among this population, it is recommended that fertility specialists provide women with expected POR who want to undergo autologous IVF/ICSI-embryo transfer adequate counselling that can inform their decision to commence treatment.
2. Due to the low clinical pregnancy rate among women with expected POR undergoing autologous IVF/ICSI-embryo transfer, it is recommended that their counselling should be focused more on their lower chances of conceiving. This could help them in deciding to either undergo autologous IVF/ICSI-embryo transfer or use donor oocytes.
3. It is recommended that the Ghana Health Service, the Society of Obstetricians and Gynecologists of Ghana, the Fertility Society of Ghana and other key stakeholders develop local guidelines and protocols to help in the management of women with expected POR as well as spearheading the passage of legislature to guide the practice of ART in Ghana.

Health Education and Promotion

4. The Ghana Health Service, the Fertility Society of Ghana, the Society of Obstetricians and Gynecologists of Ghana and other key stakeholders should promote education on the concept of POR which is commonly associated with ovarian ageing and this will create more fertility awareness-seeking behaviors among women.

Further Data and Research

5. It is recommended that future research employing a randomized control trial or a prospective cohort study on OS outcomes among expected POR women in Ghana and beyond be encouraged.
6. Further studies to access perinatal outcomes and cumulative live birth rates for women who are classified as expected POR in the Ghanaian population should be encouraged.

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APPENDIX ONE DATA COLLECTION INSTRUMENT

Study ID_____

Name of facility_____

Name of interviewer_____

SECTION A: Demographic Characteristics

1. Age _____ (years)
2. Marital status A. Single [ ] B. Married [ ] C. Divorced/Separated [ ] D. Co-habiting [ ] E. Others_____
3. Employment status**:** A. Employed [ ] B. Unemployed [ ]
4. Religious background**:** A. Christianity [ ] B. Islamic [ ] C. Traditional [ ] D. Others (specify) _____
5. Highest level of education: A. Basic [ ] B. Secondary D. Tertiary [ ] E. No formal education [ ]
6. Ethnic group: A. Akan [ ] B. Ga [ ] C. Ewe [ ] D. Guan [ ] E . Tribes of Northern Origin [ ] F. Others (specify) _____
7. Parity (All deliveries including stillbirths) A. 0 [ ] B. 1 [ ] C. 2 [ ] D. 3 [ ] E. ≥4 [ ]
8. Type of infertility: A. Primary [ ] B. Secondary [ ]
9. Duration of infertility (Years) _____
10. Indication for ART**:** A. Male factor [ ] B. Female factor [ ] C. Both male and female factor Endometriosis [ ] D. Unexplained
11. If female factor, is it _____ A. Tubal [ ] B. Ovulatory[ ] C. Uterine [ ] D. Endometriosis [ ] E. Unexplained [ ]
12. Do you smoke? Yes [ ] No [ ]
13. Do you drink alcohol? Yes [ ] No [ ]
14. Have you undergone any chemotherapy or radiotherapy for a health condition? A. Yes [ ] B. No [ ]
15. Have you undergone any pelvic surgery before? A. Yes [ ] B. No [ ]

15a. If yes in Ques 15, state type of surgery A. Caesarean section [ ] B. Myomectomy [ ] C. Ovarian cystectomy [ ] D. Salpingectomy [ ] E. Others (Specify) _____

16. Have you been diagnosed with endometriosis? A. Yes [ ] B. No [ ] C. Don't know [ ]
17. Do you have any chronic medical illness? A. Yes [ ] B. No [ ]
18. Are you on any long-term medication? A. Yes [ ] B. No [ ] 18a. If yes in question 18, what type of medication? A. Ante- hypertensive B. Anti-diabetic C. Anti-cancer medication D. Others (Specify) _____
19. Do you take herbal medications in any form (e.g. oral, vaginal, rectal, etc)? A. Yes [ ] B. No [ ]
20. Have you had previous IVF treatment? A. Yes [ ] B. No [ ]
    20a. If yes, how many attempts? _____
21. Have you had a poor response to controlled ovarian stimulation before? A. Yes [ ] B. No [ ]
    21a. If yes, how many oocytes were retrieved? A. ≤ 3 oocytes [ ] B. Between 4 -9 oocytes [ ] C. Between 10-15 oocytes [ ] D. > 15 oocytes [ ] E. don't know [ ]

SECTION B: CLINICAL DATA

22. Height (meters) [ ]
23. Weight (kg) [ ]
24. Antral Follicle count (AFC) [ ]
25. Antimullerian hormone (AMH)/ng/ml level [ ]

SECTION C: POSEIDON GROUP

26. Which POSEIDON group are you in?
    A.Group 1 (< 35 years with AMH ≥ 1.2 ng/mL, AFC ≥5 [ ]
    B. Group 2 (≥ 35 years with AMH ≥ 1.2 ng/mL, AFC ≥5 [ ]
    C. Group 3 (< 35 years with AMH < 1.2 ng/mL, AFC <5) [ ]
    D. Group 4 (≥ 35 years with AMH < 1.2 ng/mL, AFC <5) [ ]

SECTION D: OVARIAN STIMULATION

27. Ovarian stimulation (OS) protocol used. A. Long Agonist protocol [ ] B. Short Agonist/Flare protocol [ ] C. Antagonist protocol [ ] D. Others (state type) _____
28. Type of gonadotropin used for OS? A. uFSH [ ] B. hpFSH [ ] C. rFSH [ ] D. HMG [ ] E. Both FSH and HMG [ ] F. Others (Specify) _____
29. Starting dose of gonadotrophin (IU) _____
30. Total gonadotrophin (FSH/HMG) dosage used per cycle (IU) _____
31. Type of trigger used A. hCG [ ] B. GnRH Agonist [ ] C. Others (State)
32. Dosage of trigger used _____
33. Duration of simulation (Days)_____
34. Cycle cancellation before oocyte pick up? A. Yes [ ] B. No [ ]
35. Estimated follicle count at time of trigger _____

SECTION E: OUTCOME OF OVARIAN STIMULATION

36. Total oocytes retrieved_____
37. Total M11 oocytes retrieved _____
38. Method of fertilisation A. IVF [ ] B. ICSI [ ]
39. How many embryos were formed? _____
40. Blastocyst number _____
41. Morular number_____
42. 8-Cell number_____
43. 4-Cell number_____
44. Embryo grade on the day of transfer A. Grade A [ ] B. Grade B [ ] C. Grade C [ ]
45. Cycle cancellation before embryo transfer? A. Yes [ ] B. No [ ]
46. Was your cycle converted to egg- recipient cycle? A. Yes [ ] B. No [ ]
47. Were your embryos frozen? A. Yes [ ] B. No [ ]
48. How many embryos were transferred? _____
49. Fresh embryo transfer? A. Yes [ ] B. No [ ]
50. Frozen embryo transfer? A. Yes [ ] B. No [ ]
51. Day 5 embryo transfer ? A. Yes [ ] B. No [ ]

52. Day 3 embryo transfer? A. Yes [ ] B. No [ ]

SECTION F: PREGNANCY OUTCOME

53. Pregnancy test A. Positive [ ] B. Negative [ ]
54. Clinical pregnancy A. Yes [ ] B. No [ ]
55. Number of gestational sacs on transvaginal ultrasound _____
56. What option will you consider if you want to continue ART? A. I want to try another self-cycle [ ] B. I want to use donor oocyte [ ] C. Surrogacy [ ] d. Adoption [ ] E. others (Specify) _____

Appendix Two Participant information sheet

My name is Dr Mawuse Kanfra, I am a fellowship resident with the Ghana College of Physicians and Surgeons and I am conducting this study in all fertility hospitals in Kumasi, Ghana.

What is the study about? This study seeks to establish the proportion of women undergoing autologous IVF/ICSI in all the fertility hospitals in Kumasi who have been classified as expected poor ovarian responders (POR) according to their age and laboratory tests (antral follicle count and anti-mullerian hormone levels). The outcome of IVF/ICSI will be assessed in this group of women who access autologousIVF/ICSI in Kumasi. This is the pioneer study to assess the outcome of IVF/ICSI in these women in Ghana and will serve as reference data for future research. This study will provide baseline data to guide fertility specialists in counseling women with expected POR undergoing autologous IVF/ICSI in Ghana.

Why have I been approached? You have been approached because the study requires information from women who are undergoing autologous IVF/ICSI with the likelihood of poor ovarian response.

Do I have to take part? No. Participation is voluntary and it's completely up to you to decide whether or not you take part in the study.

What will I be asked to do if I take part? If you decide you would like to take part, you will be asked to suggest a date and time during your clinic visit that is convenient for you for a face-to-face interview with the researcher/research assistant using a structured questionnaire. This interview will last no more than 20 minutes.

How will my data be managed? The information you provide is confidential. The data collected for this study will be stored securely and only the researchers conducting this study will have access to this data. The data will be used as part of an academic dissertation and may later be published in academic journals. In all circumstances, data will be presented anonymously and cannot be traced back to any participant.

Voluntariness: Taking part in this study should be out of your own free will. You are not under obligation to and you can withdraw at any time if you wish to do so. After data has been collected, you can still indicate that you do not want to be part of the study within two weeks of

the interview, and your collected data will be removed if not yet analyzed together with data from other participants.

Refusal to participate? If you choose not to participate, this will not affect your treatment in this hospital/institution in any way. Agreeing to participate or refusing to participate will not influence nor affect the quality and standard of treatment you receive in the Hospital.

Withdrawal from the research: You may choose to withdraw from the research during the interview or within 2 weeks after the interview, without having to explain yourself. You may also choose not to answer any question you find uncomfortable or private.

Consequence of Withdrawal: There will be no consequence, loss of benefit, or care to you if you choose to withdraw from the study. Please note, however, that some of the information that may have been obtained from you without identifiers (name, etc.), before you chose to withdraw, may have been modified or used in analysis, reports, and publications. These cannot be removed anymore. However, I will make every effort to comply with your wishes and remove any information that can still be identified to you.

Costs/Compensation: There will be no financial compensation or cost to you for your participation in this study.

What will happen to the results? The results will be analyzed and reported in a dissertation/thesis. It may be submitted for publication in an academic or professional journal.

Are there any risks? There are no physical or medical risks anticipated with participating in this study. However, the researcher recognizes that discussions of ill health may trigger strong emotional responses and discomfort. If you experience any distress during the interviews or following participation, you are encouraged to inform the researcher/research assistant and you will be helped to deal with the stress. Additionally, you may also contact the resources provided at the end of this sheet.

Are there any benefits to taking part? There are no direct benefits envisaged for taking part in this study. However, the findings of the study may impact the quality of care for women with expected poor ovarian response seeking IVF treatment.

Where can I obtain further information about the study if I need it?

If you have any questions about the study, please contact:

Dr Mawuse Kanfra (Researcher)
Komfo Anokye Teaching Hospital
Tel: 0243309638
Email: mkanfra@yahoo.com

Dr Charles M. Senaya (Academic Supervisor)
Komfo Anokye Teaching Hospital
Tel: 0244368659/0208191555
Email: mcsenaya@yahoo.com

If you have any concerns about your rights and welfare as a study participant or the conduct of the study kindly contact:

Office of the Chairman
Committee on Human Research, Publications and Ethics
College of Health Sciences; School of Medicine and Dentistry
Kwame Nkrumah University of Science and Technology
Kumasi
Tel: 0322063248/0205453785
Email: chrpe.knust.kath@gmail.com/chrpe@knust.edu.gh

Thank you for taking the time to read this information sheet.

Appendix Three Consent Form

Before you consent to participate in the study, we ask that you read the participant information sheet and mark each box below with your initials if you agree. If you have any questions or queries before signing the consent form please speak to the researcher/research assistant.

Statement of the person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information about the study, including that on procedures, risks, and benefits, to enable the prospective participant to make an informed decision to or not to participate.

DATE: _____ NAME: _____

SIGNATURE_____

Statement of the person giving consent

1. I confirm that I have read the information sheet/ or have had it translated into a language I understand and fully understand what is expected of me within this study

2. I confirm that I have had the opportunity to ask any questions and to have them

3. I understand that my participation is voluntary and that I am free to withdraw up to 2 weeks after the interview without giving any reason, and without my medical care or legal rights being affected.

4. I understand that once my data has been incorporated into the global analysis it might not be possible for it to be withdrawn.

5. I understand that the information from my interview will be pooled with other participants' responses, anonymized, and may be published.

6. I understand that any information I give will remain strictly confidential and anonymous unless it is thought that there is a risk of harm to myself or others, in which case the principal investigator will need to share this information with her research s

7. I consent to take part in the above study.

8. I have received a copy of this information leaflet and consent form to keep for myself.

Name _____

Signature_____ Date _____

Appendix Four Ethical Approval

Kwame Nkrumah
University of Science
and Technology, Kumasi

College of Health Sciences
SCHOOL OF MEDICINE AND DENTISTRY

COMMITTEE ON HUMAN RESEARCH, PUBLICATION AND ETHICS

Our Ref: CHRPE/AP/769/23

23rd August, 2023

Dr. Mawuse Kanfra
Department of Obstetrics and Gynecology
Komfo Anokye Teaching Hospital
Post Office Box 1934
KUMASI.

Dear Sir,

LETTER OF APPROVAL

Protocol Title: ***"Outcome of Controlled Ovarian Stimulation in Women Classified as Expected Poor Ovarian Responders Undergoing Assisted Reproductive Technology in Kumasi."***

Proposed Site: ***Trust Care Specialist Hospital and Fertility Centre (TCSHFC), RUMA Fertility and Specialist Hospital (RFSH), Hallmark Medical and Fertility Hospital (HMFH), Aniniwaah Medical Centre, Adiebeba Hospital, and OAK Specialist Hospital.***

Sponsor: ***Self-Sponsored.***

Your submission to the Committee on Human Research, Publications, and Ethics on the above-named protocol refer.

The Committee reviewed the following documents:

- Notification letters from the Trust Care Specialist Hospital and Fertility Centre (TCSHFC), RUMA Fertility and Specialist Hospital (RFSH), Hallmark Medical and Fertility Hospital (HMFH), Aniniwaah Medical Centre, Adiebeba Hospital, and OAK Specialist Hospital (study sites) indicating approval for the conduct of the study at the Hospitals
- A Completed CHRPE Application Form.
  Participant Information Leaflet and Consent Form
- Research Protocol.
- Questionnaire.

The Committee has considered the ethical merit of your submission and approved the protocol. The approval is for a fixed period of one year, beginning **23rd August 2023** to **22nd August, 2024** renewable thereafter. The Committee may, however, suspend or withdraw ethical approval at any time if your study is found to contravene the approved protocol.

Data gathered for the study should be used for the approved purposes only. Permission should be sought from the Committee if any amendment to the protocol or use, other than submitted, is made of your research data.

The Committee should be notified of the actual start date of the project and would expect a report on your study, annually or at the close of the project, whichever one comes first. It should also be informed of any publication arising from the study.

Thank you for your application.

Yours faithfully,

Rev. Prof. John Appiah-Poku
Honorary Secretary
FOR: CHAIRMAN

Room 7, Block L, School of Medicine and Dentistry, KNUST, University Post Office, Kumasi, Ghana
Tel: +233 (0) 3220 63248 **Mobile:** +233 (0) 20 5453785 **Email:** chrpe.knust.kath@gmail.com/chrpe@knust.edu.gh

Appendix Five Approval from Study Sites

TRUSTCARE
SPECIALIST HOSPITAL & FERTILITY CENTRE
TRUST GOD FOR YOUR CARE

Bankers:
Ecobank
Harper Road Kumasi

P. O. BOX KS 14214,
Kumasi - Ashanti
TEL: 03200-34421 / 020-8181056
Email: trustcarehospital@yahoo.com
Web: www.trufert.com

Our Ref:_____ Your Ref:_____ Date: 25 MAY 2023

The Chairperson
Committee on human Research,
Publications and Ethics
School of Medicine and Dentistry
Kwame Nkrumah University of Science and Technology
Kumasi.

Dear Sir/Madam,

Permission to carry out Research at the Trustcare Specialist Hospital and Fertility Centre

Dr. Mawuse Kanfra, a Fellow- in- training at the Komfo Anokye Teaching Hospital, wish to carry out a study titled "Outcome of controlled Ovarian stimulation in women classified as expected poor ovarian responders undergoing assisted reproductive technology(ART) in Kumasi, Ghana".

This study if well conducted would yield results that will positively impact on the management of couples with infertility.

The Trustcare Specialist Hospital and Fertility Centre is happy to give permission for the facility to be used as a study site.

Thank you.

Yours faithfully

Mr. Paul Kofi Imbeah

RUMA FERTILITY & SPECIALIST HOSPITAL LTD.

Box YB 254,Kumasi.
AK-534-158, Denkyemuoso, Kumasi.
+233-54-199-1735 / 054267273
www.ruma.hospital
info@ruma.hospital

Our Ref: RUMA/06/020

Your Ref:.....

20th June, 2023

The Head of Directorate

Obstetrics and Gynecology

Komfo Anokye Teaching Hospital

P.O. Box 1934

Kumasi – Ghana

Dear Dr. Michael Yeboah,

RE: INTRODUCTORY LETTER

With reference to your letter dated 17th May 2023. We wish to inform you of our willingness to accept **Dr. Mawuse Kanfra** to conduct his study on the **"Outcome of controlled ovarian stimulation in women classified as expected poor ovarian responders undergoing assisted reproductive technology"** in our organization.

He is expected to abide by all rules and regulations governing the hospital. We shall also give him all the necessary assistance he may require in his area of study.

Thank You.

Yours faithfully,

DR. RUDOLPH KANTUM ADAGEBA

(CEO)

DR. RUDOLPH KANTUM ADAGEBA
(MD, FWACS, CERT-ART)
RUMA FERTILITY & SPECIALIST
HOSPITAL LIMITED
KUMASI-GHANA

Cc:

Dr. Mawuse Kanfra

ANINIWAH MEDICAL CENTRE
Location: Emena, Kumasi

Bankers:
Agric Development Bank, Kumasi
Ghana Commercial Bank, Kumasi
Stanbic Bank, Kumasi

P. O. BOX 5203, Kumasi-Ghana
Tel: +233 (0)244252895/ (0)553579456
Email: ameghanacare@gmail.com
Website: www:ameghana.com

Our Ref:..... Your Ref:.....Date:.....

23rd May, 2023.

The Chairman
Committee on Human Research Publications and Ethics
School of Medicine and Dentistry
Kwame Nkrumah University of Science and Technology
Kumasi.

Dear Sir/Madam,

LETTER OF APPROVAL: DR MAWUSE KANFRA

This is to confirm that approval has been given to the above doctor to conduct a study titled "**Outcome of controlled ovarian stimulation in women classified as expected poor ovarian responders undergoing assisted reproductive technology in Kumasi.**"

Thank you.

.....
Dr. Mike Addison.
Head of Obstetrics/Gynecology Unit
(0206300521)
niiaddison@hotmail.com

DR. MIKE ADDISON
ANINIWAH MEDICAL CENTRE
EMENA-KUMASI

AK Specialist HOSPITAL

Ref: OSH/27/05/2023/007

May 27, 2023

The Chairman
Committee on Human Research Publications and Ethics
School of Medicine and Dentistry
Kwame Nkrumah University of Science and Technology
Kumasi

Dear Sir/Madam,

LETTER OF APPROVAL: DR MAWUSE KANFRA.

This is to confirm that approval has been given to the above doctor to conduct a study titled **"Outcome of controlled ovarian stimulation in women classified as expected poor ovarian responders undergoing assisted reproductive technology in Kumasi."**

Yours faithfully,

OAK SPECIALIST HOSPITAL
P. O. BOX 420
KNUST. -KUMASI

Dr. Rex Djokoto
Obstetrician/Gynaecologist

Digital Address : AK-297-9012, Bek-Egg Hotel Road, Fankyenebra Santasi Kumasi, Ghana.
P.O.Box : 420 KNUST Kumasi, Ghana.
Tel : +233 32 - 200 - 6644
Email : info@oakspecialisthospital.com
www.oakspecialisthospital.com

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Hallmark Medicals
Quality Healthcare With A Difference
P. O. Box UP 1973
Location: Plot 38 D Block D, New Ahinsan Estate, Kumasi **Digital Address:** AK-245-6868
Tel: 0509861101 / 0591925258 **Email:** hallmarkmedicals@gmail.com

Our Ref: ..... **Our Ref:** ..... **Our Ref:** .....

31/05/2023

The Head,

Directorate of Obstetrics and Gynecology,
Komfo Akokye Teaching Hospital,

Kumasi.

Dear Sir,

APPROVAL FOR DATA COLLECTION FROM HALLMARK MEDICALS FOR DR MAWUSE KANFRA

I acknowledge receipt of your request for Dr Mawuse Kanfra to collect data from Hallmark Medicals as part of his research titled **'Outcome of controlled ovarian stimulation in women classified as expected poor responders undergoing assisted reproductive technology in Kumasi .'**

We are honoured that Dr Mawuse Kanfra chose Hallmark Medicals as the one of the centres to collect his data. I write to confirm that approval has been given by the Hospital Management to the request.

Thanks, Sir, for your kind consideration.

Yours Faithfully,

DR FRANCIS JOJO DAMALIE

31/05/2023

DR FRANCIS JOJO DAMALIE
FWACS, FCOG, FIGSMTI, ED
FERTILITY CONSULTANT
HALLMARK MEDICALS
KUMASI

Adiebeba Hospital™

29th May, 2023.

The Chairman
Committee On Human Research Publication And Ethics
School Of Medicine And Dentistry
Kwame Nkrumah University Of Science And Technology
Kumasi.

Dear Sir/Madam,

LETTER OF APPROVAL: DR MAWUSE KANFRA

Adiebeba Specialist hospital is pleased to inform you that approval has been given for the above doctor to carry out a research project on "**Outcome of controlled ovarian stimulation in women classified as expected poor ovarian responders undergoing assisted reproductive treatment in Kumasi"**, within our facility.

Thank you.

Yours Faithfully

DESLEIGH OPOKU-AGYEMANG
ADMINISTRATOR

+233 50 66 77 999 +233 544 11 11 66
N° 4 Melcom Road, Ahodwo Roundabout, Kumasi, Ghana
adiebebahosp@gmail.com
P.O. Box 1529 Kumasi, Ghana