OUTCOME OF ASSISTED REPRODUCTIVE TECHNOLOGY IN WOMEN WITH POOR OVARIAN RESPONSE UNDERGOING INFERTILITY TREATMENT IN THE REPRODUCTIVE MEDICINE UNIT OF GROOTE SCHUUR HOSPITAL: A FIVE-YEAR REVIEW

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This study is submitted to the University of Cape Town in partial fulfilment of the requirements for the degree Master of Philosophy in Reproductive Medicine

DECLARATION

I, Charles M. Senaya, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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DECLARATION BY SUPERVISOR

I supervised the research presented in this dissertation by Dr. Charles Senaya. I am satisfied it is his original work undertaken during his subspecialist training in Reproductive Medicine.

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ABSTRACT

Background: Poor response of the ovaries to gonadotropin stimulation is associated with poor outcome following in vitro fertilization. The historical lack of a standard definition for poor ovarian response has resulted in a wide variation in prevalence and outcome measures. More recently, the Bologna criteria has emerged as the standard for identification of poor ovarian responders. There is paucity of literature on poor ovarian response in the African setting. This study was conducted to document the prevalence and the outcome of in vitro fertilization among poor ovarian responders in women undergoing assisted reproduction technology in the public sector of Western Cape Province of South Africa.

Method: Retrospective review of data of women who underwent assisted reproduction technology between January 2011 and December 2015 was conducted. The Bologna criteria was used to identify women for inclusion into the study. For the analysis of prevalence and treatment outcomes, only a woman's first cycle at the Groote Schuur Hospital was included, however the occurrence of further cycles was recorded.

Main results: A total of 40 women met the criteria for poor ovarian response in this study. The prevalence of poor ovarian response was 3.6%. The mean age among the study population was 37.8years (25 – 42yrs). Cycle cancellation rate due to poor ovarian response was 15.0% and the average number of eggs retrieved was 1.8. Twenty-four (60%) women had at least one embryo transferred. The clinical pregnancy and live birth rates were 10.0% and 5.0% respectively, per cycle initiated. Half of those with failed IVF due to poor ovarian response withdrew from the program.

Conclusion: The prevalence of poor ovarian response among women who underwent assisted reproduction at Groote Schuur Hospital was 3.6% which is low compared to 9-24% reported in other studies. The clinical pregnancy and live birth rates were low. Half of the women did not continue with treatment after their first failed IVF cycle.

ABBREVIATIONS

AFC- Antral Follicle Count

AMH -Antiműllerian Hormone

ART -Assisted Reproductive Technology

BMI- Body Mass Index

ESHRE-European Society for Human Reproduction and Embryology

FSH - Follicle Stimulation Hormone

ICSI - Intracytoplasmic Sperm Injection

IVF - In vitro Fertilization

LH- luteinizing Hormone

ORT- Ovarian Reserve Test

POSEIDON-Patient Oriented Strategies Encompassing IndividualizeD Oocyte Number

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CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 BACKGROUND

The high fertility rate in Africa has created the erroneous impression that infertility is not a problem in Africa. On the contrary, there is high prevalence of infertility in Africa with one out of ten couples experiencing infertility at some point in their life(1). Moreover, the consequences of infertility in Africa are arguably more far reaching than those from other parts of the world. Dyer et al evaluated the psychological impact of infertility among women in urban South Africa and found a higher incidence of verbal and physical abuse as well as depression in infertile women when compared to fertile women(2). Additionally, these women experienced loss of social status, marital instability and poverty(3). There is therefore an immense pressure on infertile couples, particularly the women, to have children. In the majority of these cases, damage to the fallopian tubes (1, 4, 5) and male factor (4) were the reasons for the infertility. Assisted Reproductive Technology (ART) is therefore the only option to achieve pregnancy and their desire to have children.

Assisted reproductive technology (ART) involves the handling or manipulation of the human oocyte and sperm outside the human body followed by replacement of the resultant embryo back into the uterine cavity. Assisted Reproductive Technology (ART) has been defined as 'all interventions that include the in-vitro handling of both human oocytes and sperms, or of embryo, for the purposes of reproduction. This includes, but not limited to IVF (in-vitro fertilization), embryo transfer, ICSI (intracytoplasmic sperm injection), embryo biopsy, PGT (preimplantation genetic testing), assisted hatching, GIFT (gamete intrafallopian transfer), zygote intrafallopian transfer, gamete and embryo cryopreservation, semen, oocyte and embryo donation, and gestational carrier cycles' (6).

In-vitro fertilization comprises a sequence of procedures that involves the fertilization of the oocyte with the sperm outside of the human body and include conventional in-vitro fertilization (IVF), where both the oocyte, and the sperm are incubated in the same medium for sperms to move into and fertilize the oocyte as well as intra cytoplastic sperm injection (ICSI) in which case a single sperm is injected directly into the oocyte to initiate the process of fertilization(6). It is desirable to have an adequate number of oocytes for fertilization from which a good quality embryo can be selected to transfer into the uterus. In order to achieve multiple oocytes, the ovaries are stimulated with gonadotropin injections.

This process of using gonadotropins to stimulate multiple oocyte development from the ovaries is referred to as ovarian stimulation. The aim of the ovarian stimulation is to achieve the development of multiple follicles containing oocytes. The main reason for poor follicular recruitment and growth and consequently not retrieving an adequate number of oocytes during controlled ovarian stimulation is the inability of the ovaries to respond satisfactorily to the gonadotropin injections(7). The concept of poor ovarian response describes this phenomenon.

A poor ovarian response is the situation where only few eggs are produced when the ovaries are stimulated with the standard dose of gonadotropins (7). Garcia et al were the first to describe the poor ovarian responder. Since then several criteria have been used to define poor ovarian response(8). These criteria include number of dominant follicles, the number of oocytes retrieved, peak oestradiol levels, basal FSH (Follicle Stimulating Hormone), duration of stimulation, total amount or daily dose of FSH(9-11).These tests assess the ovarian reserve as a proxy to ovarian response.

The concept of ovarian reserve relates a woman's reproductive potential to the number and quality of the remaining oocytes in her ovaries (12). It gives an idea about the likely outcome of the ovarian response when stimulated with a gonadotropin. However, its use to predict the likelihood of a successful pregnancy is not reliable(13). The ovarian reserve screening tests commonly used in clinical practice include basal follicle stimulating hormone (FSH), antiműllerian hormone (AMH) levels and antral follicle count (AFC)(14, 15). The ovarian reserve tests used at the Groote Schuur Hospital were AMH and AFC. These two ovarian reserve tests were found to be the most reliable and correlate well with each other in predicting response to ovarian stimulation and defining poor ovarian response(16, 17). In addition to these tests, a woman's age is an important clinical factor that determines ovarian response and outcome of IVF(17, 18). This presupposes that where there is a high proportion of older women in a population wishing to undergo infertility treatment, a high prevalence of poor ovarian response would be expected.

The prevalence of poor ovarian response has been estimated to vary between 9 and 26% (19). The wide variation in the prevalence of poor ovarian response is the consequence of various authors using different definitions for poor ovarian response. In an attempt by the scientific community to standardize the definition of poor ovarian response in a reproducible manner, the European Society for Human Reproduction and Embryology (ESHRE) developed the Bologna criteria in 2011 (7).

The Bologna criteria comprise three components (i) advanced maternal age (≥40 years old) or any other risk factors of poor ovarian response, (ii) previous cycle cancellation due to poor ovarian response and (iii) abnormal ovarian reserve test. Any two out of the three criteria is used to make the diagnosis of poor ovarian response(7). There has been some criticism of the Bologna criteria as the different combinations of two out

of the three criteria creates different subgroups rather than one identifiable group of poor ovarian responders (20).

The pregnancy rate in women with poor ovarian response is generally lower compared to women with normal ovarian response(21, 22). Hence the majority of women with poor ovarian response may not achieve pregnancy in their first IVF cycle.

The management of women with poor ovarian response often presents a challenge to the fertility specialist because there is no clear evidence on how to improve outcome. Some authors found a beneficial effect of the use of adjuvant therapies such as growth hormones, androgens and Luteinizing hormone supplementation during ovarian stimulation(23-25). However these therapies have not been found in randomized controlled trials to be effective (26).

Once undergoing an IVF cycle, the possible options for women with poor ovarian response who wish to conceive include the following:

- Cancellation of the cycle and repeating the ovarian stimulation with a higher dosage of FSH with the hope of achieving an adequate response (21).
- Proceeding to follicle aspiration and using the limited number of oocytes available(21)
- ·. Repeat IVF cycle using donor Eggs (27)

There is also the option of curtailing the ART program and adopting a child, thus making the couple legal and social parents (28).

1.2 LITERATURE REVIEW

As part of this study, a literature review was conducted. The review focused on issues relating to the definition and prevalence of poor ovarian response, the identification of poor ovarian responders, gonadotropin dose for ovarian stimulation, cycle cancelation and the number of eggs retrieved. The literature on the outcomes of pregnancies in poor ovarian responders and the decisions that couple made after an IVF failure were also reviewed.

1.3 DEFINITION OF POOR OVARIAN RESPONSE

Some women produce few eggs when their ovaries are stimulated with the standard doses of gonadotropins during ovarian stimulation for IVF. These women are referred to as poor ovarian responders. The population of women who are poor ovarian responders are not a homogenous group but a subpopulation with various characteristics (7). It is therefore not an easy task to define or identify a poor ovarian responder.

The poor ovarian responder has been defined differently by different authors. In a notable systematic review, Polyzos and Devreoy identified 41 different definitions out of 47 studies conducted on poor ovarian responders. Furthermore, they found that not more than three trials used the same definition and the same authors used different definitions in different trials. (10).

Parameters that have been used in defining poor ovarian responders include; peak oestrogen levels, number of dominant follicles on day of hCG (human Chorionic Gonadotropin) administration, number of oocytes retrieved, Day 3 Follicle Stimulating Hormone, Antiműllerian Hormone, Antral Follicle Count, previously cancelled IVF cycle due to poor ovarian response, total or daily gonadotropin dose, duration of gonadotropin administration and age ≥ 40 (7).

To introduce some consistency in the definition and to be able to compare results and make reliable conclusions from various studies on poor ovarian response, the European Society for Human Reproduction and Embryology (ESHRE) came up with a working definition, the Bologna criteria, for defining poor ovarian responder.

In the Bologna criteria, at least two of the following three criteria are needed to define the poor ovarian responder:

I. Advanced maternal age (≥40 years) or any other risk factor of poor ovarian response
II. A previous ART cycle with poor ovarian response (cycle cancellation or aspiration with ≤3 oocytes following conventional stimulation)
III. An abnormal ovarian reserve test (AFC <5-7 follicles or AMH <0.5-1.1ng/ml) (7)

A woman with a history of two previous poor ovarian responses is also classified as a poor ovarian responder (7).

Notwithstanding this monumental attempt to standardize the definition of poor ovarian response, there have been some criticism of the Bologna criteria. One of the main criticisms of the Bologna criteria is the lack of clearly defined risk factors for poor ovarian responders as used in the definition (29). Some of the risk factors that have been suggested include 'previous ovarian cystectomy for endometrioma, short menstrual cycle, single ovary, chemotherapy, radiotherapy, chronic smoking, family history of premature menopause, chromosome derangement, fragile X mental retardation premutation and unexplained infertility. Most of these factors have not however been validated' (20). There is therefore a very high possibility of having various subgroups if these risk factors are used in identifying poor ovarian responders.

Papathanasious et al in their analysis of the different permutations of the three Bologna criteria derived four subgroups and up to eight subgroups if the combinations included the supplemental criteria of a history of two previous poor ovarian response. They opined that the different subgroups may have different outcomes (30).

Several authors have recognized that young women with poor ovarian response have a better prognosis than older poor ovarian responders in terms of pregnancy outcomes(31, 32). In view of this fact, a group of fertility experts, the POSEIDON group, have proposed a classification system that stratify poor ovarian responders based on their age (<35 and ≥35) and ovarian reserve test. Four groups were identified (Group I –IV). Poor ovarian responders less than 35 years and a normal ovarian reserve test (group I) have a better pregnancy outcome than older women 35 and older with abnormal ovarian reserve test (group IV) (33). This classification system may be more predictive of clinical outcome and more useful in counselling patients regarding the expected outcome of IVF cycles.

Despite the limitations of the Bologna criteria, it is the first realistic effort to harmonize the definition of poor ovarian responders and its use has been recommended (34).

1.4 OVARIAN RESERVE

The response of the ovaries to gonadotropin stimulation is always a retrospective assessment and therefore can only be judged after the ovaries have been stimulated. It would however be ideal to accurately predict poor ovarian responders before initiating IVF treatment cycles. The purpose of ovarian reserve testing is to identify patients who are at risk of poor response to ovarian stimulation with gonadotropins (35).

Several tests have been used in clinical practice to try to predict the likelihood of ovarian response to gonadotropin stimulation. Some of these screening tests such as the clomiphene challenge test, gonadotropin stimulation test, the exogenous follicle stimulation hormone ovarian reserve test, are laborious and are not reliable, hence are not routinely use in clinical practice. The ovarian reserve tests commonly used in clinical practice include basal Follicle Stimulation Hormone, (FSH), Antral Follicle Count (AFC) and Antiműllerian Hormone (AMH) (14).

An increase in serum levels of basal FSH occurs with ovarian aging and follicular depletion. There is no universally accepted cut-offs values for basal FSH to identify poor ovarian responders (36). Women with high basal serum FSH values of more than 25mIU/ml have been found to have a poorer ovarian response and pregnancy outcomes compared to those with serum FSH of 15mIU/ml (37). Though Follicle Stimulating Hormone (FSH) levels have been found to fluctuate inter and intra cycle with the consequent low reliability, the test is still commonly used in many fertility centres probably because it has been extensively studied and used for many years and that it is relatively easy to perform not requiring any significant sample preparations (35).

The number of follicles measured by transvaginal ultrasound in the early follicular phase is termed the antral follicle count. The AFC correlates with the pool of primordial follicles in the ovaries and the number of eggs retrieved after ovarian stimulation with gonadotropins. AFC is therefore a good indicator of ovarian reserve (14).

AFC is traditionally done with 2D ultrasound. The newer 3D ultrasound has some advantages including reduced shorter scanning time and storage capabilities with post procedure analysis (38). The 3D imaging for AFC however, does not seem to offer any significant advantage regarding information on

AFC (39). The use of real time 2D ultrasound is therefore adequate for measurement of AFC in clinical practice.

Notwithstanding the widespread use of AFC, some authors have raised concerns about the use of AFC as ovarian reserve assessment for ART. There is variation in the clinical definition as well as technical methodology used in counting the follicles, even though there have been some efforts at standardization of the measurement of antral follicles. Additionally, there is no evidence that the antral follicles seen on ultrasound are potentially healthy with competent oocytes(40). The main drawback in the use of the AFC to predict ovarian reserve is that it must be done during the early follicular phase of the menstrual cycle (41). AFC has been found to be comparable to antiműllerian hormone in predicting ovarian response to gonadotrophins(42).

Antiműllerian hormone (AMH) is a glycoprotein produced by the granulosa cells of small pre-antral and antral follicles in the ovaries (35). AMH is age dependant with highest values around menarche and virtually undetectable during the menopausal years. La Marca and colleagues clearly show a unique feature of AMH that its serum levels in not cycle dependent (43). The test can therefore be carried out on any day of the menstrual cycle. The main drawback of AMH is the lack of universal standardized assay and variability of results from different laboratories, hence an AMH value using a particular assay cannot be equated to another AMH result using another assay (35). The test for AMH also requires a specific storage condition and is laborious and time consuming. There is however some progress towards automation of AMH testing with the aim of performing the test within a short time (44). Though some reports indicated a large variability of AMH in the population as well as a significant intra and inter cycle variation (45, 46), AMH have been found to be an excellent predictor of ovarian response to ovarian stimulation and the potential for cycle cancellation. (47) However, its value for predicting pregnancy is not reliable. (48)

None of the ovarian reserve tests is hundred percent accurate in predicting ovarian reserve. However, AFC and AMH have been found to be most reliable for predicting ovarian response and are the two tests that are used in the Bologna criteria to define poor ovarian response (43, 49). Abdelazim et al found a positive correlation between pregnancy rates and the two ovarian reserve tests AMH and AFC. However, both AMH and AFC are generally not regarded as good predictors of pregnancy (50). In the prediction of ongoing pregnancy after IVF, Broer et al in their meta-analysis of individual patients data, found very small or no predictive effect. Their analysis indicates that FSH, AFC and AMH show AUC of 0.53, 050, and 0.55 respectively indicating no added predictive effect to patient characteristics (17).

1.5 PREVALENCE OF POOR OVARIAN RESPONSE

The reported prevalence of poor ovarian response is widely variable. Prevalence rates of between 9 and 26% have been reported(19). This wide variability is mainly due to lack of a standard definition as such various authors used various definitions for poor ovarian response. A more reliable prevalence could only be achieved with standardization of the definition of poor ovarian response. Recent studies show prevalence rates that seems to be higher than previous estimates. This apparent increasing prevalence of poor ovarian response is particularly evident with the introduction of the Bologna criteria. Devine et al, in the review of patients with diminished ovarian reserve in the Unites States Assisted Reproduction Technology (US ART) population, comparing 2004 and 2011 data, found that almost 70% of the patients that were allocated as poor responders on clinical basis, using the Bologna criteria, did not experience poor ovarian response after stimulation. This apparent increase in prevalence of poor ovarian response using the definition for the Bologna criteria seems to be due mainly to over-diagnosis on clinical grounds (22).

There have been conflicting reports on the influence of ethnicity and race on prevalence of poor ovarian response. Bhide et al found no independent association between AMH and ethnicity in unselected population of women undergoing ovarian stimulation for IVF (51). Lashen et al also found no difference in ovarian response to controlled ovarian stimulation between Asian women and white Caucasians (52). However Iglesias have documented diminish ovarian reserve in Indians compared to the Spanish women (53). In general, the prevalence of poor ovarian response does not seem to be influenced either by race or ethnicity.

1.6 GONADOTROPIN DOSE

In a natural cycle, a woman produces one dominant follicle containing an oocyte in her ovary per month. Gonadotropin medication can be administered to stimulate the ovaries to produce multiple dominant follicles, each follicle usually containing an oocyte. However, a minimum dose of gonadotropin is needed for recruitment and growth of these multiple follicles. The administration of insufficient dose of gonadotropin below the threshold needed for multiple follicular recruitment would therefore lead to poor ovarian response and the recruitment of few eggs(54). The dose of gonadotropin is therefore an important element during a controlled ovarian stimulation for IVF in a poor ovarian responder.

In women who had previously experienced poor ovarian response, using higher doses of gonadotropin than previously used may result in improved outcomes, however a ceiling effect is likely to exist. Hofmann et al used a high FSH dose of 450IU in women who had previously responded poorly to FSH dose of 300IU. This led to reduced cycle cancellation and increased pregnancy rate(55). On the contrary, some authors found detrimental effect of the high and increasing doses of FSH on pregnancy outcomes.(56, 57) Friedler et al, in their study of the effect of increasing doses of FSH, administered high dose (FSH 225IU -375IU), very high

dose (376- 450IU), or extremely high doses (451 -600IU) and found decreasing live birth rates with increasing FSH doses independent of age, BMI and previous cycle failure (56). This indicates that using very high doses of gonadotropin for ovarian stimulation may result in poor outcomes.

Kailasam et al recommended the inclusion of dosage of gonadotropin used for ovarian stimulation in the definition of poor ovarian response. His suggestion was based on the finding that if higher total dose of FSH >3000IU was used during ovarian stimulation and the oocyte yield is low, the pregnancy outcome is poor and the chances of retrieving higher number of eggs by increasing the gonadotropin dose in a subsequent cycle is low (58). This again shows the significance of gonadotropin dosage during ovarian stimulation in a poor ovarian responder.

The optimum dose of gonadotropin for ovarian stimulation is not easy to estimate. Several nomograms and algorithms exist to help physicians choose the starting dose of gonadotropins (59-61). However, clinicians usually use a trial and error approach to determine the initial gonadotropin dose.

In a more recent multicentre trial, the OPTIMIST trial, which aimed to evaluate the effect of individualized versus standard dosing of gonadotropins in predicted poor ovarian responders undergoing ART, increasing the dose of gonadotropins beyond the standard dose of 150 IU does not result in increased live births but was associated with increased cost (62).

In view of the conclusions of studies on gonadotropin dosage for controlled ovarian stimulation, using very high doses of gonadotropins with the aim of retrieving more oocytes and improving outcome of IVF in a poor responder is not recommended (63)

1.7 CYCLE CANCELLATION

The ground breaking event of the birth of the first baby through IVF resulted from the use of a single oocyte from a natural ovarian cycle (64). The discovery and introduction of ovarian stimulation with the resulting retrieval of several oocytes has increased pregnancy rates in ART (65). An adequate number of eggs is therefore an important determinant for improving the success in ART.

A major reason for cycle cancellation is failure of the ovaries to respond adequately to the gonadotropin stimulation resulting in no follicular development or the development of normal size but too few follicles (66).

Cycle cancellation could be classify into three based on when the cancellation occurs during the ART cycle. Cycles may be cancelled (i) during the ovarian stimulation due to poor ovarian response, (ii) after trigger but cancellation of embryo transfer if complications such as failure of fertilization (iii) cancellation of embryo transfer due to poor embryo quality or endometrial factors (67).

The use of mild ovarian stimulation protocols, to either reduce the cost of IVF treatment and the risk of ovarian hyperstimulation is also associated with increased risk of cycle cancellation (68). This protocol is however not considered a standard stimulation protocol and therefore not sufficient to define poor ovarian response (7).

A previous cycle cancellation due to poor ovarian response is associated with a higher risk of repeat cycle cancellation (69). It is however not definite that a previous cycle cancellation due to poor ovarian response would result in another cycle cancellation and in some cases the outcome may be favourable (70). On the other hand, it is almost definite that two consecutive previous cycle cancellations due to poor ovarian response will result in another poor ovarian response. This observation informed the decision to include two

previous cycle cancellations due to poor ovarian response as one of the definitions of poor ovarian response (7).

The decision to cancel cycles due to poor ovarian response must be taken with regards to the age of the woman since young poor ovarian responders have higher pregnancy rates from their few available eggs than the older women with poor ovarian response (33).

1.8 PREGNANCY OUTCOME IN POOR OVARIAN RESPONSE

In general, poor ovarian responders have a lower pregnancy rate compared to normal ovarian responders though female age and number of eggs retrieved may significantly influenced the outcome (21). It has been postulated that the poor responders have lower pregnancy rates as a result of fewer oocytes which lead to few good quality embryos for transfer (71). The availability of good quality embryos for transfer is therefore an important determinant of the outcome of IVF in poor ovarian responders.

Since the majority of women with poor ovarian response will not achieve pregnancy in the first IVF cycle, the low pregnancy rate must be discussed with the prospective couple early in the management of the poor ovarian responder. Various models have been developed to predict the outcome of IVF cycles. Of particular interest is the PROsPeR model which was designed specifically to predict the chances of live birth in the poor ovarian responder (72). The parameters used in formulating the PROsPeR model include age, number of oocytes retrieved in a previous cycle, AMH, AFC, type of infertility, cause of infertility, duration, previous number of pregnancies and previous number of ART. It was developed and validated using data gathered in a prospective study involving poor ovarian responders (73). The introduction of the PROsPeR model into clinical practice would help in counselling and managing expectation of patients with poor ovarian response.

In patients with poor ovarian response, younger women have better outcomes than women with advanced maternal age (21, 31). Despite a better prognosis in the younger poor ovarian responder, the pregnancy rate is lower than expected for a normal responder because of the few numbers of eggs and hence a few good quality embryos for transfer.

1.9 COUPLES' DECISIONS AFTER FIRST FAILED IVF

The physical stress associated with the process of IVF can be enormous. Frequent hospital visits during the period for monitoring of follicular growth, the multiple gonadotropin injections and the retrieval of oocytes under anaesthesia are all physically demanding. Some women may not wish to undergo such physically exhausting process after a failed IVF cycle especially if the prognosis is presumed to be poor (74, 75).

Assisted reproductive technology have been documented to be associated with psychological stress (74, 76). This is arguably more so in poor ovarian responders given the fact that the chances of pregnancy are slim. Interestingly, psychological interventions to reduce stress related to IVF treatment has not been shown to reduce drop-out rates, as such psychological counselling prior to initiation of first IVF cycle may not be necessary (77).

Financial stress is a common reason for discontinuation of treatment after a failed IVF especially in countries where IVF is funded out of pocket. This was evident in the study by Dyer and Vinoos who found that a quarter of couples who underwent IVF at a subsidized cost in the public health hospital in the Western Cape Province of South Africa could not recover financially four years after treatment for IVF procedure (78).

It is important to manage the expectations of couples undergoing IVF particularly the poor ovarian responders due to their low success rate. Informing patients about the chances of success in the first IVF cycle and also

discussing the cumulative live birth rates in a number of treatment cycles may encourage some women and reduce disappointment and drop-out rates after the first IVF cycle (79).

1.10 Summary of literature review

Critical search and analysis of the literature shows a lack of standard definition for poor ovarian response and a wide variation in the prevalence and pregnancy rates in poor ovarian responders. The Bologna criteria was instituted as the first attempt to harmonize the definition of poor ovarian responder albeit the criticism of poorly defined risks factors of poor ovarian response and lack of definite end points of ovarian reserve tests used in the criteria.

Compared with normal response, poor ovarian response is associated with higher risk of cycle cancellation, use of higher doses of FSH, retrieval of few eggs, few good quality embryos for transfer, poor IVF pregnancy rates as well as poor pregnancy outcomes.

1.11 PROBLEM STATEMENT AND RESEARCH QUESTIONS

There is evidence that poor ovarian response is associated with poor outcomes in IVF (21). The various choices that couples made after a failed IVF due to poor ovarian response have been documented (21, 27, 79).

The infertile couple as well as fertility specialists need information in counselling, planning and deciding on the management of the couple with poor ovarian response. However, there is paucity of literature on poor ovarian response in the African setting. Currently, the prevalence of poor ovarian response among women undergoing infertility treatment at the Reproductive Medicine Unit (RMU) of the Groote Schuur Hospital is not

known. Additionally, the outcomes of these cycles and the common choices that these couples made after a failed IVF cycle have not been documented.

This study therefore seeks to answer the following questions among women with poor ovarian response undergoing assisted reproductive technology (ART) at Groote Schuur Hospital,

- What is the prevalence of poor ovarian response in the study population?
- What is the outcome following autologous IVF among the study population?
- What choices do couples make after the first failed ART cycle?

1.12 STUDY AIM AND OBJECTIVES

AIM: To explore and document the frequency and treatment outcomes of autologous assisted reproductive technology in women with poor ovarian response undergoing infertility treatment at the Reproductive Medicine Unit of Groote Schuur Hospital.

1.12 Primary objectives

1. To determine the prevalence of poor ovarian response in women undergoing their first cycle of IVF/ICSI in the period of observation at the Reproductive Medicine Unit of Groote Schuur Hospital

2. To determine the outcome of initiated cycles in terms of cycle cancellation, number of oocytes retrieved, pregnancy rates (biochemical, clinical and live birth) among women with poor ovarian response undergoing ART at the Reproductive Medicine Unit of Groote Schuur Hospital

1.13 Secondary objectives

To determine the treatment choices following first IVF/ICSI failure in women with poor ovarian response undergoing ART at the Reproductive Medicine Unit of Groote Schuur Hospital

CHAPTER TWO

2.0 METHODS

This chapter describes the setting where the study was conducted, the study population, the process and procedure of ART at the Groote Schuur Hospital. It also details the method used in selecting the study subjects for this study as well as the data collection process and analysis.

2.1 The setting and study population

This study was conducted at the Groote Schuur Hospital, a level 3 referral centre in the public-academic health sector in the Western Cape Province of South Africa. The setting was the Reproductive Medicine Unit of the Groote Schuur Hospital, one of two Government and referral Hospitals which provide tertiary services for infertility treatment in the Western Cape Province. All infertility treatment options including ovulation induction, intrauterine insemination, in-vitro fertilization and ICSI are offered at the Unit. The Western Cape Government partially subsidises infertility treatment at the Groote Schuur Hospital. The hospital has a criteria that clients must meet to be eligible to enrol and benefit from the subsidy for the ART procedure.

The study population comprised women who were referred for infertility treatment and who had undergone IVF/ICSI at the Reproductive Medicine Unit within a five-year period between 1st January 2011 and 31 December 2015.

2.2 Type of study

The study was a retrospective descriptive study.

2.3 Inclusion criteria

1. The Bologna criteria was used in selecting women for inclusion in the study. Women meeting any two of the following three criteria were included in the study:

I. Advanced maternal age (≥40 years) or any other risk of poor ovarian reserve

II. A previous ART cycle with poor ovarian response (cycle cancellation due to poor ovarian response or aspiration of ≤3 oocytes) following conventional stimulation

III. An abnormal ovarian reserve test (AFC <7 follicles or AMH <1.1ng/ml)

2.4 Exclusion criteria

Women who were not stimulated according to a standard gonadotropin protocol

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2.5 Methodology

The names, folder numbers and the cycle information of all women who underwent a standard ovarian stimulation for IVF/ICSI and who had any one of the following characteristics:

- aged 40 or older,
- retrieval of ≤3 oocytes and
- cycle cancellation because of poor response

were retrieved from the existing electronic database of the Reproductive Medicine Unit of Groote Schuur Hospital.

The folders of these patients were then retrieved and reviewed for the ovarian stimulation protocol that was used and the results of any ovarian reserve tests. Women who fulfilled two of the three eligibility criteria were selected for inclusion in the study. The folders of women selected to be part of the study were further reviewed for the data pertaining to the other study objectives (Appendix 1). The check list was developed based on literature regarding poor ovarian response. The data were entered on a spreadsheet. Each subject was given a study number to ensure patient anonymity and for easy data verification and for retrieval of uncaptured data.

2.6 Data analysis

Relevant data for this study were collected using a spreadsheet. The data were cleaned and exported to STATA version 14.0 (https://www.stata.com/) for analysis.

Appropriate rates for background characteristics were presented. Measures of central tendencies, mean and standard deviation were calculated for BMI, duration of stimulation, total FSH dose and number of embryos

transferred. The mean was also computed for AMH, and AFC while percentages were computed for the number of cycles cancelled, clinical pregnancy and live birth rates and treatment options after failed IVF.

2.7 Stimulating protocol

The antagonist protocol was used for ovarian stimulation in all women undergoing assisted reproduction technology at the Groote Schuur hospital. All women were pretreated with combined oral contraceptives to enable batching of cycles.

Ovarian stimulation was done with one of the following three follicle stimulation hormone medications; Menopur, (Ferring Pharmaceuticals, Switzerland) Gonal F (Merck Seronto, Germany), or Pergoveris (Merck Seronto, Germany). A dose of between 150 and 300IU of follicle stimulating hormone was injected daily for 5 days. Ovarian response was assessed on day 6 of stimulation with transvaginal ultrasound and appropriate adjustments made to the FSH dose depending on the number of follicles and the size of the leading follicle. Serum levels of oestradiol, LH and progesterone were also checked. Daily doses of GnRH antagonist (Cetrotide, 0,25mg, Sherine, Switzerland) was started when the dominant follicular reached a size of 12mm or more. Follicular tracking with transvaginal ultrasound as well as serum oestradiol, LH and progesterone monitoring were done on alternate days from day 6 of stimulation till the day of ovulation trigger.

Ovulation trigger was done with human chorionic gonadotropin (hcg), (Ovitrelle, 10,000IU, Sherine, Switzerland) when at least 2 follicles were ≥18mm in size. In women with high risk of developing ovarian hyperstimulation, Lupron, 10-20ug, was used to trigger ovulation as an alternative to hCG. Each patient was given careful instructions regarding dosage, time of medication and method of administration. All medications were self-administered at home. Transvaginal ultrasound guided egg retrieval was done in theatre under general anesthesia 36 hours after ovulation trigger.

2.8 Fertilization, embryo transfer, luteal support and pregnancy assessment

All mature (metaphase II) oocytes retrieved were incubated with sperm about 3-5 hours after oocyte retrieval. In case of poor semen quality, ICSI was performed. Confirmation of fertilization by observing the presence of two pronuclei was done 16 to 18 hours after insemination.

The Gardner and Schoolman classification was used to grade the embryos. Embryo selection for transfer was done by one of the three embryologists. Blastocysts were transferred on day 5 while cleavage stage embryos were transferred on day 3 if there were few embryos or concerns that embryos may not survive to the blastocyst stage.

Embryo transfer was done, under ultrasound guidance, by one of the four sub-specialists or a fellow in Reproductive Medicine under the supervision of a sub-specialist consultant. It is the policy of the Groote Schuur Hospital that either one or a maximum of two embryos are transferred per patient per cycle.

Vaginal progesterone (Utrogestan, Merck Soronto, Milan, Italy) 200mg twice a day, was used for Luteal support starting on day of egg retrieval until pregnancy test. Pregnancy test with quantitative serum β-hCG was done at the Groote Schuur hospital 10 days after a day 5 embryo transfer and 12 days after a day 3 embryo transfer.

Clinical pregnancy was assessed by observation of a gestational sac with or without fetal pole or cardiac activity by transvaginal ultrasound six weeks after embryo transfer.

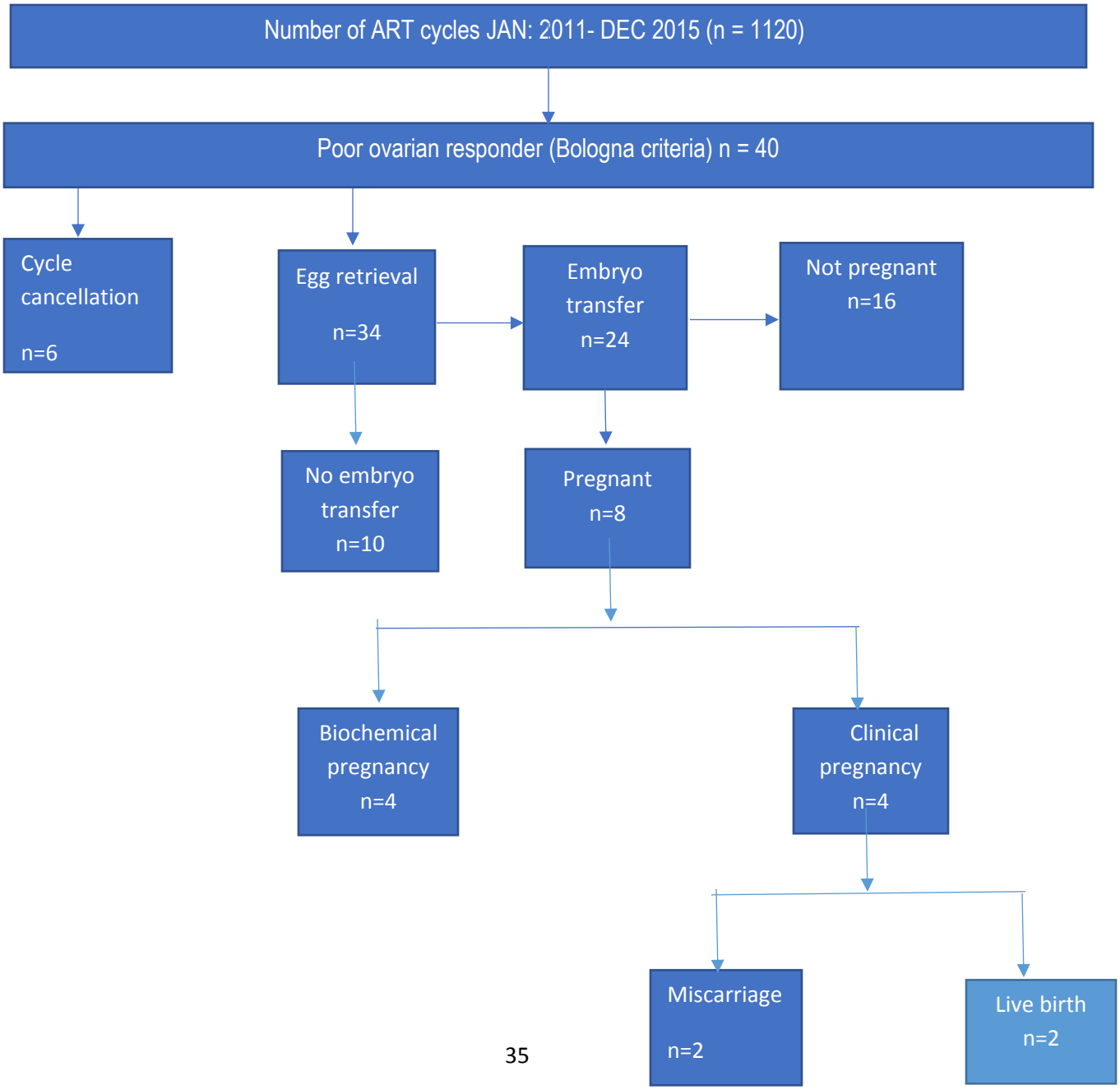
Women with clinical pregnancy were referred for antenatal care in a secondary level hospital. Pregnant women with high risk for pregnancy complications had tertiary level antenatal care at the Groote Schuur Hospital while women who desire antenatal care with a private obstetrician were appropriately referred.

CHAPTER THREE

3.0 RESULTS

During the study period, 1120 IVF cycles were done. Forty patients met the Bologna criteria for poor ovarian response. Fig 1 shows the flow chart for selection of patients who met the Bologna criteria and were included in the study. It also shows the outcome of initiated cycle.

Fig 1. **Flow chart of study**



3.1 BACKGROUND CHARACTERISTICS

Table 1 Shows the background characteristics of the patients. The youngest was 25 years while the oldest was 42years and the median age was 40.0years. More than half (52.5%) of the patients were 40 years or older. Of those with available data, majority (60%) have BMI above normal. No patient had BMI of more than 34kg/m2.

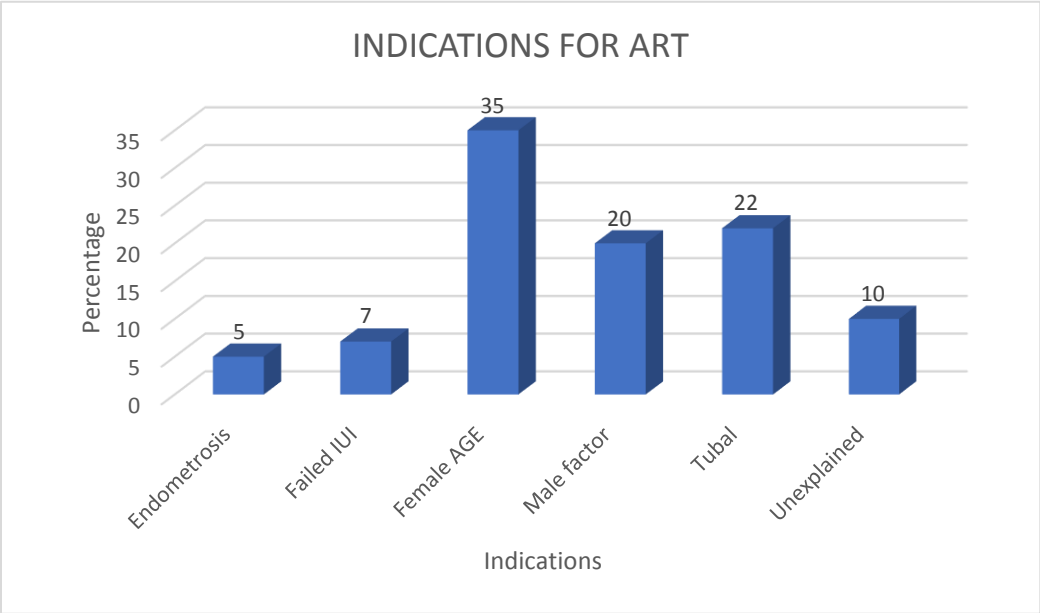
Table 1: Baseline characteristics of study sample (n=40)

Characteristics	**Distribution**
Age in years, median	40yrs
<40 years	19 (47.5%)
≥40 years	21 (52.5%)
Marital status, n (%)	
Married	38 (95%)
Co-habiting	2 (5%)
BMI in kg/m2: median	27kg/m2
BMI Range	(19-34)
BMI categories. (n=25)	
Underweight (BMI < 18.5kg/m2)	0
Normal weight (BMI: 18.5 -24.9kg/m2)	10 (40%)
Overweight (BM: 25-29.9kg/m2)	8 (32%)
Obese (BMI ≥30kg/m2)	7 (28%)

3. 2 INDICATIONS FOR ART

Fig 2 shows the distribution of indication for ART. The commonest indication for ART, among the poor ovarian responders, was advanced age of the female partner which accounted for 35.0% of the IVF cycles.

Fig 2 Indications for ART



3.3 OVARIAN RESERVE TEST

A total of thirty-three (82.5%) patients had an ovarian reserve test done. Twenty-seven (67.5%) of patients had AMH done. The median AMH was 0.37ng/ml.

Six (15%) of patients have available record for AFC. The median AFC was five.

3.4 DURATION OF STIMULATION AND CYCLE CANCELLATION

Table 2 shows the duration of stimulation, total amount of FSH used and the number of cycles cancelled. The median duration of stimulation was 9.0 days while the average total amount of FSH dose used in those who underwent egg retrieval was 2987.8 IU

Six (15.0%) cycles were cancelled prior to ovum pick up due to poor ovarian response. The average number of eggs retrieved was 1.8.

Table 2: Ovarian stimulation

Duration of stimulation, median	9.0 days
Total amount of FSH used, mean (±SD)	2987.8 (306.4) IU
Cycle cancellation, n (%)	6 (15.0%)

3.5 EMBRYO TRANSFER

Twenty-four patients (60%) underwent fresh transfer after retrieval. The Number of embryos transferred are shown in table 3

Table 3: Number of embryos transferred

Number of Embryos Transferred	N
Single embryo transfer	13
Double embryo transfer	11

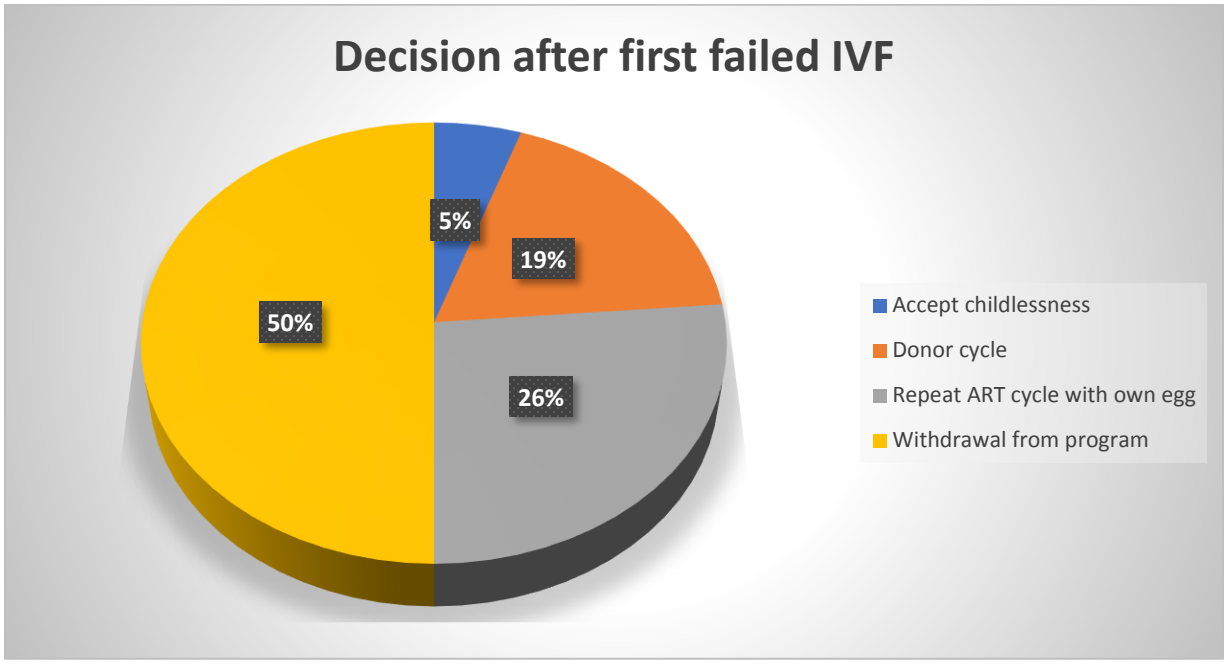
Table 4: OUTCOME PER INITIATED CYCLE

Pregnant, n=8 (20%)	
Biochemical pregnancy	4 (10.0%)
Clinical pregnancy	4 (10.0%)
Early pregnancy loses	2 (5.0%)
Term delivery	2 (5.0%)

3.7: DECISION AND TREATMENT OPTIONS AFTER FAILED IVF

Fig 3 shows the decision and treatment options adopted by women with poor ovarian response after their first failed IVF cycle. Half of the couples withdrew from the program

Fig 3: Decision after first failed IVF



CHAPTER FOUR

4.0 DISCUSSION

This chapter discusses the study findings with reference to previous studies on poor ovarian responders. Possible reasons were ascribed, where appropriate, for some of the discrepancy between the findings of this study and previous studies.

The results of this study show that the median age and BMI were 40years and 27.0kg/m2 respectively. Six cycles (15.0%) were cancelled prior to egg retrieval while the average number of eggs per aspiration was 1.8. Twenty-four women had at least one embryo transferred. Of the 40 initiated cycles, eight (20.0 %) resulted in a positive pregnancy test. Of these, four were clinical pregnancies (10.0%) resulting in two live births (5.0%) per cycle initiated. Among the women who did not achieve live birth, half withdrew from further ART cycle.

4.1 PREVALENCE OF POOR OVARIAN RESPONSE

The prevalence of poor ovarian response in this study was 3.6%. This is much lower than previous studies that estimated the prevalence of poor ovarian response to be between 9 and 24% (19). The low prevalence rate in this study may be due to the high number of cases where ovarian reserve tests were not available. Absence of ovarian reserve test could exclude two groups of participants that may have been included in the study: Firstly, women <40 years with ≤ three oocytes in whom ovarian reserve tests were not available; and, secondly women ≥40 years with > three oocytes in whom ovarian reserve tests were not available. Additionally, the definition of “risk factors for poor ovarian response” as one of the criteria for poor ovarian response in the Bologna criteria have not been clearly defined (29). Various authors used these poorly

defined risk factors to variable extent in their studies which may affect the prevalence rate (20). There was no use of any of these poorly defined risk factors for inclusion into the study. The exclusion of these patients who may have one or more of these risk factors which were not specifically captured in the ART database or the medical records may have contributed to the low prevalence.

Another factor that may have influenced the low prevalence is the criteria for inclusion into ART program at the Groote Schuur Hospital. The reproductive medicine unit has a policy to offer autologous ART up to 43 years because of the low probability of pregnancy in women >43years and the fact that treatment costs are in part funded through government resources. The exclusion of older women from autologous ART may contribute to the relatively low prevalence of poor ovarian responders found in this study.

4.2 AGE

Advanced female age with infertility is one of the indications for ART. The chronological age of a woman is an important parameter that is associated with ovarian ageing and poor ovarian response both of which influence success in ART(80-82). The median age of patients in this study was 40.0 years. The oldest patient was 42 years. Additionally, more than half of the women in the cohort were 40 years and older. The finding of large proportion of advanced female age in this study is similar to other studies where there is high proportion of advanced maternal age among poor ovarian responders defined using the Bologna criteria (83, 84). The skewed distribution of advanced maternal age among the poor ovarian responders in the study population buttress the point that poor ovarian response is associated with advancing female age

4.3 OVARIAN RESERVE TEST

The median for AFC in the study group was five. This is comparable to the average AFC found in other studies among poor ovarian responders (83). It was noted that only 15% of women had AFC documented, despite it being a reliable, non-invasive and accurate estimation of ovarian reserve test. Doing AFC alone has been found to be the most cost effective assessment for predicting the ovarian response in patients undergoing IVF (85).

Antral Follicle Count needs to be done within the early follicular phase of the menstrual cycle. Some of the patients may not be able to return within the time frame and therefore the AFC is forfeited. Compared to AFC, AMH as an ovarian reserve test can be done on any day of the menstrual cycle.

The mean AMH value in the study population was 0.37ng/ml suggesting that few eggs are likely to be retrieved with standard ovarian stimulation. AMH reduces with advancing age, reflecting diminishing ovarian response (86). More than half of the women in the study population were more than 40 years hence the median AMH is expected to be low.

The proportion of patients with available AMH results (67.5%) was not as high as expected given the high proportion of women with advanced maternal age in the study population. Some of the reason for not doing AMH in all patients prior to ART procedure may be four-fold. Firstly, while some fertility centres use AMH to disqualify women from undergoing IVF based purely on the chance of anticipated low response, other hospitals including the Groote Schuur hospital, do not use AMH in disqualifying women from inclusion in IVF programs because patients with very low AMH can still achieve pregnancy through IVF(87). It may therefore not be necessary to check AMH levels in all individuals before commencing ART. It is however a useful tool in counselling patients on the possible number of eggs that could be retrieved. Secondly, ovarian stimulation with gonadotropins is a dynamic test for ovarian response and none of the ovarian response

tests is full proof hence a strategy of entering the first cycle of IVF without any prior ovarian reserve test have been proposed (66). Some reproductive specialists do not routinely do AMH prior to ovarian stimulation but use the outcome of the stimulation to test the response of the ovaries to gonadotropin stimulation. Thirdly, AMH would give an indication of the number of eggs but does not predict the chances of pregnancy (88). Additionally, AMH is expensive and hence may not be cost effective to routinely do prior to ovarian stimulation.

4.4 GONADOTROPIN DOSE AND DURATION OF STIMULATION

The average total amount of gonadotropins used for ovarian stimulation of the women in the study was 2987.8 IU. This is low compared to other studies where a total FSH dose used in poor ovarian responders were much higher. Sandeen et at, Busnelli et al and Merviel et al, found an average total FSH dose of 4135IU, 3600IU, 4664IU respectively among poor ovarian responders stimulated for IVF (81, 89, 90). One of the factors that determines the total FSH dose is the duration of stimulation. An average number of days of stimulation in the study population was 9.5 days which was shorter than that found in other studies in Bologna poor responders (89).

One of the reasons for the short duration of stimulations may be asynchronous follicular growth during ovarian stimulation. This phenomenon is more common when antagonist protocol was used. If this occurs in poor ovarian responders, when 2 or 3 leading follicles are of adequate size, but the rest are too small to anticipate any mature oocyte, trigger is given, and the dominant follicles aspirated shortening the whole duration of stimulation. However, a comparison with the average duration of stimulation of normal responders at the Groote Schuur Hospital would give a clearer perspective if there is any significant difference in the duration of stimulation in the poor responder group.

4.5 CYCLE CANCELLATION

Central to the success of IVF procedure is the retrieval of an adequate number of oocytes. In cases of poor ovarian response where there are too few follicles, cycle cancellation is a recognized management option(69). The cycle cancelation rate in this study due to poor ovarian response was 15.0%. This finding shows a higher cycle cancellation rates compared to a study in Milan, Italy where the cycle cancellation rate among poor ovarian responders was 6% (89). The high proportion of women with advanced maternal age in the study population may have also contributed to the high cycle cancellation rate.

This cycle cancellation rate is however much lower than another study in Barcelona, Spain where the cycle cancellation rate was 54.2%. Their higher cancellation rate may be because their cohort of poor responders had a previous cycle cancellation due to poor response which make this cohort more likely to experience another poor ovarian response (69).

The women whose cycles were cancelled due to poor ovarian response may have to undergo another IVF cycle. This is likely to be associated with great anxiety as there is the likelihood of similar experience of poor response in the subsequent cycle.

4.6 NUMBER OF EGGS RETRIEVED, NUMBER OF EMBRYOS TRANFERED

The retrieval of an adequate number of eggs increases the chance of having a good embryo to transfer.

The mean number of eggs retrieved in this study was 1.8. This finding is similar to other studies where the average number of eggs retrieved in Bologna poor ovarian responders were few (83, 84).

The selection and transfer of a single good quality embryo is being advocated as the standard in ART. The aim of the single embryo transfer is to reduce multiple pregnancy and its associated complications while

making efficient use of all oocytes retrieved in one cycle(91, 92). In cases of elective single embryo transfer, there is usually several good quality embryos from which one embryo is selected. However, in the case of poor ovarian responders, there is usually very limited options due to the very few embryos available.

4.7 OUTCOME OF INITIATED CYCLES /PREGNANCY SUCCESS

A live birth is the desire of every patient undergoing fertility treatment. The live birth rate in the study population was 5.0% per initiated cycle. This is comparable to live birth rates of 4-7% found in Bologna poor responders in recent studies (22, 89, 93). While this low chance of live birth may be acceptable to some women with poor ovarian response undergoing ART, others may find it unacceptably low and may not wish to embark on this expensive and psychologically stressful process of ART. The Ethics Committee of the American Society of Reproductive Medicine opined that if the chance of live birth following IVF procedure is nonexistence or up to 1%, the procedure is said to be futile and is probably not worth performing. Expected outcomes of between 1% and 5% chance of success are said to be very poor and other appropriate options may be offered. In instances of futile or very poor prognosis, the decision to proceed with the procedure rests with the patient once the clinician has informed the patient of low odds of success (94).

The pregnancy rate in ART is greatly influenced by the quality and number of embryos. In situations where there are few embryos to select from, the pregnancy outcome is poor. Ovarian response and the number of available eggs also depend largely on the age of the woman. There was a high proportion of women with advanced age and there were few available embryos for transfer. These two factors may have contributed to the low pregnancy rate in the study population.

The age of a woman may significantly alter the outcome of ART in poor responders. It is important to note that the study population was not stratified by age. Stratification by age would have helped to target our counselling to the age specific rates which may relate more to patient's peculiar situation.

4.8 DECISION AFTER FIRST FAILED IVF CYCLE

Withdrawal from the ART program was the commonest choice (50.0%) for women in the study population. This rate was high compared to a study in Netherlands where 17% drop-out rate was found.(95) The co-payment method of financing ART at the Groote Schuur hospital may explain the high dropout rate as the financial recovery rate after IVF is very slow among most couples in the Western Cape Province of South Africa (78). These patients who withdrew or drop out from the program include those who deliberately decide not to undergo further treatment and patients who failed to return for follow-up and were not or could not be contacted. Some of these patients in the latter group may have gone to other fertility centres for further management.

Maternal age is one of the factors considered to be associated with dropout rates(79). The study population has a high proportion of advanced maternal age with more than half of the study subjects older than 40years. This may be another reason for the high dropout rate.

Male factor is a common indication for ART. Male factor infertility was the third most common indication for initiating ART in the study population. It forms 20% of the indications for the ART. It has been documented that males are more likely not to want to continue ART program after a failed IVF(96). The high proportion of male factor infertility in the study may have also contributed to the high discontinuation rate observed in the study.

Couples who have embryos frozen for future use are also more likely to continue the program than couples who do not have embryos frozen when their cycle failed (79). The glimpse of hope of pregnancy from the available embryos without the stress of going through another stimulation cycle is non-existent for these couples without frozen embryos. The absence of frozen embryos for future use by women in the study population might have contributed to the high withdrawal rate found in the study.

Five percent of women accepted childlessness after the first failed IVF and follow up counselling. This is usually a difficult decision for patients because of the social implications of childlessness in Africa (2).

4.9 LIMITATIONS

The retrospective nature of the study depends on adequacy of collected data. Some information relevant to this study may not be available in the electronic database or in the patients' folder. These missing data may have affected the findings of the study.

CHAPTER FIVE

5.0 CONCLUSIONS

In relation to the primary study objectives, the prevalence of poor ovarian response, (3.6%) in patients undergoing ART at Groote Schuur Hospital is low. The outcome of initiated cycle reveals that there was high cycle cancellation rate and few eggs were retrieved. The clinical pregnancy and live birth rates were low in this cohort of poor ovarian responders.

In relation to the secondary objectives, it was found that there was a high dropout rate after the first failed IVF among the poor ovarian responders. Although financial recovery after IVF has been documented to be very slow in patients undergoing ART at the Groote Schuur hospital, follow up studies on the reasons for the high dropout rate among the poor responders would be essential for planning a strategy to assist patients make other choices in fulfilling their desire to have children as well as counselling and support if they decide to accept childlessness.

The results of the study will be of value in providing potential patients with specific information regarding outcome of ART in poor ovarian responders. It would also aid counselling regarding expectations among poor ovarian responders in the Western Cape Province of South Africa.

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Appendix 1:

Data collection sheet

A. SOCIODERMOGRAPHIC CHARACTERISTICS

I. Age (years) a.< 40 b. ≥40

2. Employment status a. Employed b. Unemployed

3. Marital status a. Married b. Single c. Separated d. Divorced e. Cohabiting

4. BMI a. <18.5 b. 18.5-24.9 c.25-29.5 d. 30-34.9 e. >35

6. Duration of infertility

7. Indication for ART a. Tubal factor b. Male factor c. Endometriosis d. Unexplained e. Advanced maternal age

B. Ovarian Response Test

8. AMH: result

9. AFC: result:

C. Ovarian response

10. Cycle cancellation 1.yes 2. No

11. Number of oocytes retrieved.

12. Duration of Stimulation (In Days):

13. Total amount of FSH used:

D. Fertilization

14. Method of Fertilization: 1. IVF 2. ICSI

15. Number of embryos transferred

E. **Outcome**

16. Outcome:

a. Pregnant b. not pregnant

17. if pregnant

a. Biochemical pregnancy

b. Clinical pregnancy

c. Live birth

18. Treatment after first cycle I. Repeat ART cycle with self-cycle

II. Donor cycle

III withdrew from program

IV. accept childlessness

APPENDIX 2: ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6626
Email: [illegible]
Website www.health.uct.ac.za/fhs/research/humanethics/forms

18 October 2016

HREC REF: 743/2016

Dr H Patel
Obstetrics & Gynaecology
4-floor, OMB

Dear Dr Patel

PROJECT TITLE: OUTCOME OF ASSISTED REPRODUCTIVE TECHNOLOGY IN WOMEN WITH POOR OVARIAN RESPONSE UNDERGOING INFERTILITY TREATMENT IN THE REPRODUCTIVE MEDICINE UNIT OF GROOTE SCHUUR HOSPITAL: A FIVE YEAR REVIEW (MPhil-candidate Dr C Senaya)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th October 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Charles Senaya will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 743/2016