Master of Sciences (Obstetrics and Gynaecology)

A Prospective Observational Study comparing the effect of a new One-Stop Fertility Clinic versus the Conventional NHS Fertility Pathway on NHS Costs and Patients' Quality of Life, and a study on UK and International ART treatment and the relationship with High Multiple Pregnancies and associated costs.

By

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Dedication:

To my parents, Dr. James Ignatius Batwala and Mrs. Ida Nanteza Batwala who have both made me the person I am and who have sacrificed so much for me, I am so truly grateful to both of you.

To my sisters Barbara, Rebecca, Suzanne, Dorcas, Akusa, Fiona and Pauline, who have always had love, faith, patience and always supported me in all that I do.

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Declaration:

I declare that while studying for the degree of Master of Science (MSc) by Research at University of Oxford, I have not registered for any other award at another University. Furthermore, the work undertaken for this degree is my original work and the conclusions were my own after reviewing the data collected and occasional discussions with experts in particular related fields. Where the work of others is referenced, it is acknowledged and referenced in this manuscript.

Contents

Abstract:

Background: NHS-funded ART cycles are gradually being reduced or completely stopped by several Clinical Commissioning Groups (CCGs) aiming to make savings of between £300,000-£800,000 per year. This has led to a decrease in NHS treatment available which may lead to an increasing number of UK residents seeking treatment overseas. Overseas ART treatment may be associated with higher rate of multiple pregnancies, associated with higher morbidity to patients and cost to the NHS. I proposed a study to assess if a One-stop fertility pathway could reduce investigation duration and lead to cost savings that could be used to maintain funding for ART cycles and improve the patients' Quality of Life (QoL). I also reviewed the High Multiple Pregnancies (HMP) at the John Radcliffe (JR) Hospital in Oxford to assess the impact from ART performed in the UK and overseas.

Methods: A prospective observational study comparing duration, costs and QoL of 191 participants going through the Conventional pathway and 28 participants going through a One-Stop pathway. And a retrospective observational review of 43 (HMP) at the JR over 7 years.

Results: One-stop pathway reduced the average duration by 426.9 days p=0.016 and cost by £435.1 p=<0.001, which could mean total savings £670,415.28 a year per CCG. One-stop participants had a lower average QoL score compared to the Conventional participants, 64.3 (16) vs 72.1 (14.0) p=0.018. Female participants QoL was lower than male, with a FertiQoL score of 67.9 (15.6) vs 75.6(13.2) p = <0.001 and approaching levels of clinical depression. A review of 43 HMPs at the JR between 2010 and 2017 showed that on average HMPs cost £68,222 per pregnancy and £366,695 per year and 53% of the HMPs were conceived by ART.

Conclusions: One-Stop Fertility clinics decrease the duration and cost of fertility investigation, saving as much as £670,415.28 per year for a CCG. These savings could be "ring-fenced" to fund NHS ART cycles which may reduce HMPs in the UK. The study recommends the establishment of a UK National Database for HMP and offering early psychological support especially to female patients, whose QoL approaching levels observed in clinical depression.

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Common Abbreviations Used:

ART- Assisted Reproductive Technology.

AMH- Anti-Mullerian Hormone.

CCG- Clinical Commissioning Groups.

CF Screen- Cystic Fibrosis Screen.

CTRG- Clinical Trials and Research Governance.

eSET- Elective Single Embryo Transfer.

ET- Embryo Transfer.

E2- Oestradiol.

FBC- Full Blood Count.

FET- Frozen Embryo Transfer.

FSH- Follicle Stimulating Hormone.

GP- General Practitioner.

Hep B & C- Hepatitis B and C.

HFEA- Human Fertilisation and Embryology Authority.

HIV- Human Immunodeficiency Virus.

HMP- High Multiple Pregnancy.

HRA- Health Research Authority.

HSG- Hystero-Salpingo-Gram.

HyCoSy- Hysterosalpingo-Contrast-Sonography.

ICSI- Intra-Cytoplasmic Sperm Injection.

IFR-Independent Funding Request.

IVF- In-Vitro Fertilisation.

Lap & Dye- Laparoscopy and Dye Test.

LFT's- Liver Function test.

LH- Luteinising Hormone.

NC- Natural Conception.

NHS- National Health Service.

NICE- National Institute for Health and Care Excellence.

OI- Ovulation Induction.

ONS- Office for National Statistics.

PC- Primary Care.

PCO- Polycystic Ovaries.

PCOS- Polycystic Ovarian Syndrome.

PIL- Patient Information Leaflet.

PPROM- Preterm Prelabour Rupture of Membranes.

P4- Progesterone.

SC- Secondary Care.

SERM- Selective Oestrogen Receptor Modulator.

SIS- Saline Infusion Sonogram.

TC- Tertiary Care.

TCI- Total Cost of Investigation.

TCPC- Total Cost in Primary Care.

TCSC-Total Cost in Secondary Care.

TDCC- Total Duration in Clinical Care.

TFT- Thyroid Function Test.

TSH- Thyroid Stimulating Hormone.

TTC- Time Trying to Conceive.

TV-scan- Trans Vaginal Ultrasound Scan.

U&E's- Urea and Electrolytes.

UK- United Kingdom.

1. Chapter 1: Introduction and Background

1.1. Introduction

Infertility, which is defined as failure to conceive after 12 months of active unprotected intercourse, affects 1 in 7 couples in the UK. The National Institute for Health and Care Excellence (NICE) recommends couples having difficulty conceiving should be seen together as both are affected by the decisions surrounding investigation and treatment(1). After 2 years of trying to conceive, NICE recommends up to 3 full cycles of In vitro Fertilisation (IVF) with or without ICSI in women up to 40 years and 1 cycle in women 40 to 42 years old(1, 2).

NICE is an executive non-departmental public body of the Department of Health in England that publishes guideline in health technologies, clinical practice, health promotion and social care services and serves both England and Wales NHS. NICE was set up in England in 1999 and it has gone on to acquire a high reputation internationally as a role model for development of high-quality clinical guidelines.

ART services are provided in tertiary care clinics in the National Health Service (NHS) as well as private providers, with treatment funded by the NHS for patients who satisfy their local Clinical Commissioning Groups (CCG) criteria(3). ART funding decisions are made mainly locally by CCGs depending on the needs of the local population. However, across the UK, the number of NHS funded ART cycles are being reduced, or even no longer offered by some CCGs, aiming to make financial savings of between £300,000 to £800,000 per calendar year per CCG(4). These cuts have differed from one region to another across the UK, with some patients able to receive all 3 of the NICE recommended IVF cycles for fertility treatment, while others may receive reduced or no funding, leading to the development of the so-called "Post-code lottery" of ART funding(5). For example, in 2018 in Scotland, 60% of treatment was NHS-funded, compared to 45% in Northern Ireland, 41% in Wales and 35% in England(3). These cuts to funding have led to a decrease in ART treatment available for infertility patients and yet the World Health Organisation (WHO) acknowledge infertility as a disease that can negatively affect patients Quality of Life (QoL) (6-9).

Given that cost saving is the primary motivation for cuts in access to ART, I proposed a study to assess if alternative savings could be made in the Primary Care (PC) and Secondary Care (SC) investigative pathway instead of reductions to ART provisions in tertiary care. I proposed

that the introduction of a "One-Stop Fertility Clinic" would be more "Time" and "Cost" efficient, compared to the current service, which I have referred to in this study as the "Conventional Pathway" and lead to financial and time savings. If savings were demonstrated then arguments could be made for this funding to be "ring-fenced" and used to maintain or possibly increase the current funding available for ART cycles. I further proposed that the reduction in duration that patients spend in PC and SC before starting their ART treatment in Tertiary Care (TC) may lead to a better patient experience and satisfaction from the service and lead to an improvement in their Quality of Life (QoL). ART in this study refers to treatment with In Vitro Fertilisation (IVF) with or without Intracytoplasmic sperm injection (ICSI) and does not include intra-uterine insemination (IUI).

The HFEA's "Fertility Trends 2018" has noted that an increasing number of UK residents are seeking treatment overseas for a variety of reasons including cheaper treatment when they do not qualify or when they have used up their NHS funded ART treatment entitlement (3). The same publication notes that foreign ART clinics may not be as firmly regulated as UK clinics especially as regards to the number of embryos transferred in a cycle to reduce the risk of multiple pregnancy. I therefore proposed, as a secondary aim of this study, to look at the impact of ART treatments received by UK residents overseas, on the High Multiple Pregnancy (HMP) rates and the financial and clinical implications of these types of pregnancies at the John Radcliffe Hospital in Oxford.

1.2. Pattern of natural conception for Heterosexual couples in the UK and NICE recommendation for investigation and treatment.

NICE advise that people concerned about fertility should be informed that over 80% of couples in the general population will conceive within 1 year if the woman is under 40 years and they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year, with a cumulative pregnancy rate of 90%(1).

NICE also recommend that a woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse in the absence of any known cause of infertility, should be offered further clinical assessment and investigation with her partner(1).

1.3. Categories of Causes of Infertility in the UK:

According to NICE, it is estimated that infertility affects 1 in 7 heterosexual couples in the UK. NICE also noted that since the original NICE guideline on fertility published in 2004, there has been a small increase in the prevalence of fertility problems, and a greater proportion of people now seeking help for such problems, thus adding pressure on fertility services(1).

Below are the main causes of infertility in the UK with percentage figures indicating approximate prevalence. Some of these causes may co-exist in couples:

- unexplained infertility (no identified male or female cause) (25%)
- ovulatory disorders (25%)
- tubal damage (20%)
- factors in the male causing infertility (30%)
- uterine or peritoneal disorders (10%).

In about 40% of cases, disorders are found in both the man and the woman. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also play a role(1).

1.4. NICE recommendation for treatment of Fertility with ART.

NICE recommends that women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), should be offered 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, the current full cycle should be completed but further full cycles should not be offered (1, 2).

In women aged between 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), NICE recommends that they should be offered 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled

1: They have never previously had IVF treatment

2: There is no evidence of low ovarian reserve
3: there has been a discussion of the additional implications of IVF and pregnancy at this age (1).

NICE goes on to state that where investigations show there is no chance of pregnancy with expectant management and where IVF is the only effective treatment, women should be referred directly to a specialist team for IVF treatment. (1, 2, 10, 11).

ART refers to all treatments and procedures that involve the in vitro handling of human oocytes or sperm (gametes) or embryos with the intention of achieving a pregnancy, including In-Vitro Fertilisation (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI) (12). Artificial Insemination using either partner or donor sperm are not included in this definition for the purposes of this study.

For couples where there is no chance of getting pregnant with expectant management, such as bilateral blocked fallopian tubes, ART is the only effective treatment and they should be referred expediently and offered IVF treatment without delay. (13, 14).

The number of ART procedures in the United Kingdom (UK) has increased rapidly from approximately 6,000 in 1991 to over 65,000 in 2015. There are many factors that account for this increase, including increased awareness of services, patients' willingness to seek advice, increased affordability and increased access to ART services (13).

The NHS funding for ART treatment is controlled and decided by the local Clinical Commissioning Groups (CCGs). CCGs are clinically-led NHS bodies which are composed of all of the GP groups in the geographical area as well as at least one registered nurse and a doctor who is a secondary care specialist. (14). CCGs typically look after a local population of approximately 200,000-300,000 people and are responsible for assessing local needs, deciding priorities and strategies and purchasing services on behalf of the local population they represent from local, regional and national hospitals, clinics and other healthcare bodies. There are approximately 210 CCGs in England and they are responsible for managing approximately 2/3 of the total NHS England budget. The total NHS England annual budget was approximately £75.6 billion in 2018/19(15).

A survey in 2013 by the Fertility Fairness (FF) lobbying group on IVF provision in England found that only 24% of CCGs were offering the 3 IVF cycles to eligible women as recommended in the NICE guidelines(16). This figure had further decreased to 12% of CCGs in 2017 that were offering the 3 IVF cycles recommended by NICE (16). This decrease may be as a result of budgetary pressures on CCGs due to limited increase in their budgets (0.1% in 2017) and a population that is increasing in number and morbidity related to increasing age. The exact reason CCGs are reducing or stopping ART funding is beyond the scope of this study(3, 14, 17).

Below are some examples of qualifying criteria, or in some cases excluding criteria, for couples to receive funding in their local CCGs including but not limited to:

1: Some CCGs will only fund ART of women under the age of 35 years. Other CCGs will others fund up to 42 years old as per NICE guidelines.
2: Female participants will need to have a BMI of less than 30.
3: Patients will need to be non-smokers, or have demonstrated they stopped smoking for a minimum 6 months with evidence such as carbon-monoxide breath test or attendance to "quit smoking" classes.
4: Patients would have had to have been Trying to Conceive for a minimum of 2 years.
5: Female patients should have a good ovarian reserve demonstrated with a serum FSH of less than 10.0 IU/L or AMH of more than 6.0 pmol/L.
6: Some CCGs would only fund 1 ART cycle, other CCGs would fund up to 3 ART cycles.
7: Some CCGs included Frozen Embryo Transfer (FET) of embryos created in a fresh ART cycle in the definition of a funded cycle, other CCGs did not.
8: Patients would have to prove they have been in a stable relationship for at least 3 years.
9: Patients should have been living at the same address for at least 3 years.
10: Neither partner should have had children whether genetically related or adopted.
11: Neither partner should have been sterilised in the past.

Couples who do not meet their local CCG criteria can either fund their own treatment privately, or can appeal against a declined application using a Specialised Services Individual Funding Request (IFR). IFRs are usually requested if there are exceptional circumstances for example an administrative delay in submitting their application before going over the criteria age for funding(18). However, the IFR approval rate for fertility treatment is extremely low. NHS

England funds Fertility Preservation for Oncology patients and the Ministry of Defence funds members of the Armed Forces. The criteria for the Armed Forces is very similar to that recommended by NICE (18).

The changes in NHS funding for ART treatment is not uniform across the UK. Even within England there is little uniformity in CCG criteria. Scotland, for example, had an increase in NHS funded cycles, as a proportion of all ART cycles, from 51% in 2013 to 60% in 2018. Northern Ireland has also seen an increase in NHS funded cycles as have a few CCGs in England(3, 13). Funding for ART cycles is set nationally in Wales, Northern Ireland and Scotland while in England, this is set by local CCGs (HFEA Fertility treatment 2018: trends and figures)(3). The whole of England has seen an overall decrease in funding of approximately from 41% in 2013 to 35% in 2018. As England accounts for 84% of the UK's 66 million population, the overall picture for the whole of the UK has been a decrease in NHS funding for ART and as a result approximately 2000 fewer patients had their first round of round of ART funded by the NHS (3, 17).

According to the HFEA, most CCGs either offer fewer cycles than recommended or have reduced the upper-limit age of female partners that are eligible for treatment. In some CCGs both of these limitations apply and, in some cases, CCGs have ceased funding ART completely(13, 19). In 2013, 1% of CCGs offered no NHS-funded ART cycles. In 2017, this figure had increased to 3% with a further 7% of CCGs consulting to reduce or stop funding completely. A typical NHS funded ART cycle costs about £3,500. NHS Croydon CCG in London stopped all funding for IVF in March 2017 in order to save approximately £800,000 a year, despite a local consultation where 77% of people opposed this step. (4)

The HFEA has noted that it is conceivable that reduced NHS funded ART cycles has led to more fertility patients seeking treatment overseas, as this is often less costly than treatment in the UK(20). However, the HFEA through its "Fertility Trends" publication has suggested that several overseas clinics are less regulated compared to UK clinics and may be contributing to a higher proportion of multiple pregnancies (twins or higher multiples). They therefore argue that if monetary savings are realized, they could be ring-fenced to maintain or even increase current NHS ART funding(3).

Approximately 15% of all IVF cycles in the UK are funded by the NHS. There are 106 licensed specialist clinics of which 22% are NHS, 34% are fully private, 15% are research units and

29% are joint NHS-private partnerships. CCGs normally give their patients the freedom to choose a clinic that they prefer and is convenient for them to access(21).

Most of the reductions in fertility services by the CCGs are targeted at NHS funded ART treatments offered in Tertiary Care in Specialist Fertility Clinics. Reduction in funding have not focused on primary and secondary services such as consultations, diagnostic investigations such as blood tests, pelvic ultrasound scans, hysteroscopies and laparoscopies or some treatments and interventions such as ovulation induction (OI), laparoscopy and diathermy for endometriosis and ovarian drilling for Polycystic Ovarian Syndrome (PCOS)(19).

However, some Fertility Specialists and Consultants, such as the Chief Investigator (CI) of this study, Associate Professor Tim Child, and myself as the author of this thesis, have noted from their personal experience and observation that there may be some financial and temporal inefficiencies in the investigative pathway in the primary and secondary NHS care. These may include unnecessary or repeated investigations and follow-up consultations leading to delays in making a diagnosis and starting effective treatment. I hypothesize that if these inefficiencies were addressed and the investigative pathway improved, this could lead to savings to the NHS. The delays in finding a diagnosis and starting effective treatment could also have a negative impact on the Quality of Life (QoL) of these patients.

1.5. Random sampling to assess viability of proposed study

Prior to designing this study, I undertook an unpublished review of 20 randomly selected patient NHS medical files at Oxford Fertility. I found that on average, couples had spent 2-5 years having investigations in primary and secondary care and could have been referred earlier for tertiary care and management with ART. This delay may be associated with increased expenses to the NHS as the review revealed several baseline investigations that were in my medical opinion unnecessarily duplicated, such as early follicular hormone levels, mid-luteal progesterone and semen analysis without a clear clinical benefit. There were also often additional follow-up appointments that were made without clear clinical indication. This information was not retained as it was obtained prior to ethical approval however it helped me formalise and plan the structure of the study and plan my study and the ethics application.

1.6. Genesis of Study Design

I therefore proposed and designed, this study, to assess if there is an association between Duration in the Conventional pathway (the time patients go through from first presentation from their GPs through primary and secondary care until they start their ART treatment) and the Cost to the NHS and the QoL of both female and male participants. I designed this to run from May 2016- May 2018.

I also designed a retrospective review of the High Multiple Pregnancies (HMP) at the John Radcliffe Hospital, to assess whether there was a possible link between decreased NHS funding for ART and HMPs from the 2010-2017 period.

1.7. NICE Guideline on investigation and treatment of fertility problems (CG156)

The NICE Guideline for the Assessment and Treatment of Fertility Problems (CG156) was published in February 2013. It lists the investigations that are needed for patients experiencing difficulty trying to conceive. The guideline states that if couples have been trying to conceive for more than 2 years, ART presents them with the most efficient means of achieving pregnancy. (1, 2, 22)

1.8. Conventional Pathway Definition

For the purposes of this study, I defined the "Conventional" Pathway as the current investigate pathway patients follow in the Oxfordshire CCG and other participating CCGs after presenting with infertility to their GP. There isn't a nationally agreed pathway as the investigations sometimes depend on the skills of staff available, agreement with the local NHS fertility clinic and funding by the local CCG. However, from the participating local NHS fertility clinics that agreed to participate, they generally follow the following pathway when investigating and referring patients presenting with infertility illustrated in Table 1.

1.8.1. Primary Care Management

Couples would normally seek the advice of their GP after trying to conceive for 12 months. The GP would then give them some life-style advice if applicable such as increasing frequency of intercourse, losing weight, quitting smoking and then arrange for preliminary investigations

such as test of ovarian reserve (early follicular hormone profile), test for ovulation (mid-luteal progesterone, Rubella immunity screening, Sexual Transmitted Infection screening (chlamydia) on the female partner and a semen analysis on the male partner. The GP would then review the couple with their results and if the couple have still not conceived or abnormal results found, arrange for referral and review in Secondary care.

1.8.2. Secondary Care Management

The couple would be reviewed by a Fertility Specialist or Gynaecologist with a specialist interest in Fertility. Their results from Primary care would be reviewed and a treatment plan or further specialist investigations arranged. These could include, a test for tubal patency such as a Hysterosalpingogram (HSG), Hysterosalpingo-contrast-sonography (HyCoSy) scan, Laparoscopy and Dye Test, Pelvic scan, specialist blood tests for azoospermia or premature ovarian failure. There would then be a follow-up review with the Fertility Specialist and a treatment plan arranged or further tests. The pathway that patients usually follow is illustrated in Figure 1.

1.8.3. Referral for Assisted Reproductive Treatment

NICE recommends that a woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse in the absence of any known cause of infertility, should be offered further clinical assessment and investigation with her partner (1). NICE also recommends that, after a couple have been trying to conceive unsuccessfully for 24 months, or where investigations have shown there is no chance of pregnancy with expectant management and IVF is the only effective treatment, they should then proceed for ART treatment. This could therefore indicate that a couple may expect to spend 12 months in the investigative pathway before they are offered or referred for ART treatment if they are not pregnant after 24 months of actively trying to conceive (1).

1.8.4. One-stop Fertility Clinics

I therefore designed this study to investigate whether introducing the “One-Stop Fertility Clinic” that I designed and initiated (see chapter 2 for details), can reduce the duration patients spend in the investigative pathway and the cost of investigating the patients to the NHS. I also

set out to assess whether the One-stop Fertility Clinic, by reducing the duration of the investigative pathway, would also lead to an improvement in the QoL of patients.

1.8.5. Quality of Life (QoL) of Participants

In addition, the study was designed to assess the Quality of Life (QoL) of patients going through fertility treatment in order to determine whether a One-stop fertility clinic improves the QoL of patients going through this shorter pathway. WHO defines Quality of Life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns(23).

Fertility is an emotive issue that affects QoL of couples involved. Infertility investigations and treatment can cause anxiety to individuals experiencing it. The World Health Organisation (WHO) recognises that every human being has a right to the enjoyment of the highest attainable standard of physical and mental health and infertility can negate the realisation of these essential human rights(8). Aarts et al. (2011) showed the link between QoL and distress due to infertility (24). Karabulut et al. (2013) stated that QoL in couples was negatively affected by prolonged duration of infertility. (24, 25)

Previous studies have shown that couples and individuals who are going through fertility investigations and treatment experience high levels of anxiety, psychological and psychiatric pathology, even when there is no history of previous psychiatric illness prior to the diagnosis of infertility(26). Pedro et al. (2013) showed that the Quality of Healthcare can affect a patient's compliance with their treatment, dropout of treatment and return of a couple or individual for further fertility treatment if a cycle is unsuccessful(27).

In this study, I assessed and analysed the relationship between the duration of investigation and Quality of Life (QoL) of participants in the Conventional Pathway as well as any differences in QoL between the female and male participants in the study to see if there were any gender-specific trends or clear differences between the male and female participants. I was interested in seeing if fertility affected the QoL of different genders in different ways.

1.8.6. FertiQoL, a disease specific tool for Measurement of Quality of Life (QoL).

There are many generic objective assessment tools for measuring QoL development such as the QALYs, WHOQOL BREF, WHOQOL 100 and EUROHIS QOL which quantify QoL based on an individual's responses. These are usually questionnaires that the participants fill in and the responses are usually graded numerically or pictorially. These questionnaires are cross-cultural generic instruments (23, 28). These tools are not disease specific however, they allow for comparisons of QoL between different diseases, conditions and settings.

However, for the purpose of this study, I selected a disease specific QoL tool called FertiQoL. FertiQoL is an Internationally Validated Quality of Life Questionnaire used specifically to measure the QoL of participants going through either fertility investigation, treatment or both.

FertiQoL was designed in June 2011 following an initiative by the European Society of Human Reproduction and Embryology (ESHRE), the American Society of Reproductive Medicine (ASRM), University of Cardiff in Wales and McGill University in Canada, to specifically assess QoL of patients going through Fertility Investigation and Treatment(29, 30).

Some other studies have chosen to use both FertiQoL and one of the other traditional QoL measurement Tools such as WHO-BREF and SF-36(31). However, FertiQoL has been found to be more sensitive, reliable, valid and acceptable tool to use in relation to fertility studies. I also felt requesting participants to fill in 2 questionnaires may decrease recruitment in the time available as potential recruits might have found it time consuming filling in 2 questionnaires compared to 1 and also more complicated to analyse with the resources and time limitations available to complete the MSc.

FertiQoL has been in use for over 9 years and has been used in over 100 peer-reviewed publications in last 5 years. It is a sensitive, reliable and valid fertility problems and is evolving into the gold standard for measurement of QoL in Fertility studies and also allows for ease of comparisons between fertility studies, which would be more difficult if different generic scoring tools were used (25, 27, 32). Furthermore, FertiQoL measures more precisely the true impact of infertility on QoL and no other non-fertility related stressful events that patients may be encountering(24, 32).

1.8.7. High Multiple Pregnancies (HMP). An unforeseen consequence of ART funding cuts

The rise in multiple pregnancies in the UK and in most developed countries has been directly related to the increase in fertility and ART treatment available(33). This study will also look at the effect ART, both done in the UK and overseas, has on the number of High Multiple Pregnancies (HMP), maternal and neonatal morbidity and costs at the John Radcliffe, Oxford University NHS Hospital Trust between the 2010-2017 period. It will look at whether there is a causal relationship between the decrease in ART funding in the UK leading to more patients seeking ART treatment overseas, and whether this is leading to a rise in HMP numbers and make a case for "ring-fencing" any potential savings from one-stop fertility clinics to maintain or even increase the number of NHS-funded ART cycles.

1.9.Hypotheses for study:

Therefore, the hypotheses my study set out to investigate are: -

1. The longer the duration that a patient (female or male) spends in the investigative pathway of infertility, the higher the cost to the NHS, and the lower their QoL.
2. The introduction of a One-stop fertility clinic will decrease the duration and cost of the investigative pathway and improve the QoL of patients.
3. The increase in HMP at the John Radcliffe Hospital is linked to ART cycles that were performed overseas.

2. Chapter 2: Methodology

2.1. Primary Objective

1: To assess the effect that "duration", measured in days, that a couple spend having primary and secondary fertility investigations on the NHS has on "cost" to the NHS.

2: To assess the effect that "duration", measured in days, that a couple spend having primary and secondary fertility investigations on the NHS has on "Quality of Life" (QoL) of the participants.

3: To assess the effect that a One-stop Fertility Clinic has on "duration", "cost" and "Quality of Life (QoL)" of participants having primary and secondary fertility investigations performed in the NHS compared to the traditional "Conventional" pathway.

2.1.1. Design

In order to answer these questions, I designed a Prospective Descriptive Study using cross-sectional analysis.

2.1.1.1. Obtaining Study Ethical Approval

I obtained Ethical Approval from the NHS Health and Research Authority (HRA), South East Coast- Surrey Research Ethics Committee in April 2016. I carried out this study between May 2016 and May 2018. I also applied for and obtained site approval from the Research and Development (R&D) Departments of NHS Hospitals from whom participants would be recruited from and provided both face-to-face training for local recruiters as well as over the phone training.

I adhered to the ethical standards set by the Declaration of Helsinki as well as guidelines of the University of Oxford. Written informed consent was obtained from each patient to participate in this study by either myself, or by study group members I had trained on the study protocol including a senior Research Nurse, Consultant Gynaecologists, Fertility Specialist Doctors, Clinical Research Fellows and Fertility Nurses at the recruitment sites.

2.1.1.2. Study Participant Recruitment

I only approached couples in a heterosexual relationship for recruitment into this study, neither of whom had ever had a child before, nor had previous ART treatment (private or NHS funded), and had met the criteria for NHS-funded ART treatment from the local CCG. I made the decision on recruitment criteria, after discussion with the CI, in order to make the study population as homogenous as possible. The reasoning for this was that this study set out to not only assess cost to the NHS but also QoL of the patients. Several external factors may affect QoL such as social status, personal finances, previous successful or unsuccessful ART treatment or previous children.

Study Population

Inclusion Criteria:

1: Heterosexual couples.
2: Couple eligible to receive NHS funding for ART from their local CCG.
3: The Female partner must give consent to study recruitment.
4: The Male partner consent to recruitment was optional.

Exclusion Criteria:
1: Neither partner had a biological child.
2: Neither partner had an adopted child.
3: Neither partner had undergone previous IVF/ICSI treatment whether NHS or privately funded.

2.1.1.3. Setting

Recruitment into the study was initially to all heterosexual couples who qualified for NHS-funded IVF/ICSI cycles at Oxford Fertility.

Oxford Fertility is a private Tertiary ART centre that holds several CCG contracts to provide ART services for NHS funded patients. Oxford Fertility was also the site for the secondary care NHS fertility clinic for the Oxford University Hospitals NHS Trust as well as the study's One-stop clinic.

The referring hospitals/fertility clinics, depending on the funding CCG, have differing qualifying criteria for couples to receive funding and also differing limits to the number of ART cycles funded and whether FETs are funded or not. The criteria and limits included but not limited to:

1: Age (some CCGs fund couples where the female partner's age is up to a maximum 34 years inclusive, for example Oxfordshire CCG, while other CCG's fund up-to the age of 42 years e.g., Gloucestershire CCG).
2: Female participants must have a BMI of less than 30.
3: Participants have to be non-smokers or have stopped smoking for a minimum 6 months.
4: Participants must have been Trying to Conceive for a minimum of 2 years.
5: Some CCGs funded 1 ART cycle; other CCGs funded up to 3 ART cycles.
6: Some CCGs included Frozen Embryo Transfer (FET) of embryos created in a fresh ART cycle in the definition of a funded cycle, other CCGs did not.

2.1.1.4. Referring Hospitals of Participants:

The participants recruited into this study were receiving their ART treatment at Oxford Fertility Unit. However, they were referred for their ART treatment from their local CCG via their local NHS fertility clinic in their regional hospital. Fourteen hospitals in total referred the patients in this study. The breakdown of participants from the hospitals that referred them is listed in the table below in Table 2.

Initially the study only recruited participants who were referred to Oxford Fertility for their ART treatment from May 2016. However, there was an initial low recruitment rate identified between October 2017 and April 2018. In addition, there were unexpected organisational changes at Oxford University Hospitals NHS Trust when the NHS Fertility Clinic was relocated back to the John Radcliffe Hospital where the study group no longer had access to this patient cohort for recruitment. Therefore, a decision was taken to also recruit participants from Create Fertility at St Paul's in London and to extend the study to April 2019. Create Fertility, is a private Tertiary ART centre that also holds several CCG contracts to provide ART services to different NHS Hospitals. The participants also had to satisfy the study criteria above.

I informed the Study Sponsor, University of Oxford, of these changes and the Clinical Trials Research and Governance forms were amended and I also informed the local Health Research Authority (South East Coast- Surrey Research Ethics Committee) by submitting a notification of non-substantial minor amendments which was approved in January 2017. A total of six regional hospitals referred the participants who were recruited into this study at Create Fertility. The hospitals that contributed to these participants are included in Table 2.

2.1.2. Methodology

Recruitment:

1: All Heterosexual couple who were about to start their 1st NHS funded IVF cycle at either of the two recruitment centres were approached and given information about the study and asked to consider participation. Potential participants were approached by myself, Medical Doctors (Consultant Gynaecologists, Fertility Specialist Doctors), Senior Research Nurse or Fertility Nurses in the recruitment centres who had been briefed and trained by myself on the recruitment protocols and criteria of the study and the Senior Research Nurse. If participants agreed to join the study, they were given a study recruitment pack to take home with them which contained:

1: A patient information leaflet (PIL).
2: A Study consent form.
3: A FertiQoL Questionnaire.
4: A pre-stamped return envelope.

The FertiQoL questionnaire was used to calculate their QoL. FertiQoL is an Internationally Validated Quality of Life Questionnaire used to assess participants QoL. FertiQoL was designed in June 2011 following an initiative by the European Society of Human Reproduction and Embryology (ESHRE), the American Society of Reproductive Medicine (ASRM), University of Cardiff in Wales and McGill University in Canada, to specifically assess QoL of participants going through Fertility Investigation and Treatment. FertiQoL has since then become very popular in Fertility studies and publications when evaluating. QoL and has risen to become the Gold-Standard for QoL studies in fertility (29, 30). A copy of the FertiQoL questionnaire used to measure QoL is referenced in Appendix 1 and the scoring system used to calculate the QoL score in Appendix 2.

2.1.3. One-stop Fertility Clinic Set-up:

I designed and set up a One-stop Fertility Clinic at Oxford Fertility. Some of the GP's who referred patients to the Oxford Fertility NHS secondary care clinic were approached to refer patients to the One-stop Fertility clinic that was run once a week from 2016 until 2018. The One-stop clinic saw between 3-4 couples a week during the study. I saw most of the patients who went through the One-stop clinic and offered recruitment into the study for those eligible to join the study.

I also trained medical doctors, nurses and associated staff how to perform HyCoSy scans and manage patients in the 1 stop pathway. I also co-ordinated with laboratory staff (andrology section) at Oxford Fertility to perform semen analysis on the male partner when they attended their appointment. The results of the semen analysis were checked by the clinician or Nurse performing the HyCoSy scan and familiar with the study protocol before the female partner had her HyCoSy scan. After the HyCoSy scan, the couple would then proceed for their Consultation with a Fertility Specialist and planning of their future management and treatment.

If the male partner had a sub-optimal semen analysis or his Total Motile Sperm Count (TMSC) was less than 2 million, which was the Fertility Clinic's criteria for HyCoSy (unless couples or female patients were considering using Donor sperm), a HyCoSy scan was not performed and the couple proceeded on for their Consultation with a Fertility Specialist.

HyCoSy scan was also not performed if the female partner had a past history of chlamydia infection or history of a sexually transmitted disease, evidence of pelvic pathology such as endometriosis, fibroids, previous ectopic pregnancy or extensive pelvic surgery. In this situation, the couple would proceed on for their consultation with a Fertility Specialist who may consider them for a diagnostic laparoscopy or a more appropriate investigation and management plan.

2.1.4. Referral Pathway for One-stop Participants:

The Administrative NHS Staff at Oxford Fertility had been briefed and trained on the pathway of the One-stop clinic. They called General Practitioners (GPs) in the local Oxford area who

would normally refer patients in the conventional pathway to explain the new pathway. The GP's then referred patients who met the study criteria. Prior to referral they carried out only the follicular (Day 2 to Day 5 of menstrual cycle) baseline hormone investigations and other investigations already agreed with Oxford Fertility for referral of fertility patients. The additional required tests were: FSH, LH, TSH, testosterone, prolactin and chlamydia screen on the female patients as well as a cervical smear (if due) and rubella status. The referrals to the One-stop clinic would be checked for suitability according to the study protocol by the administrative staff. If any concerns were identified, I would be asked to review the referral in my capacity as the study PI. Participants who were not suitable for the One-stop pathway were then allowed to proceed in the traditional Conventional pathway.

The One-stop clinic was run once a week on a Tuesday morning session from 8:30am to 1:00pm in the afternoon every fortnight during the study period. This was due to availability of staff, andrology slots for semen analysis, scan rooms and consultations rooms to run the One-stop clinic. Between 3-4 couples a day were seen at the clinic for the duration of the study and not all were eligible for recruitment as some did not meet criteria for ART treatment as set by their local CCG which was mainly patients who had been trying to conceive for less than 2 years.

The male partner of the couple was asked to arrive 45 minutes earlier to have the semen analysis (SA) done. The results of the semen analysis were then available prior to the female partner having a HyCoSy scan and only if the SA demonstrated suitable sperm parameters. The HyCoSy scan lasted 30 minutes and was followed by a 30-minute consultation with a Fertility Specialist discussing the results and formulating a management plan. The planned total clinic appointment time was 1 hour 45 minutes.

2.2. Flowchart comparing traditional conventional pathway vs One-stop fertility pathway.

Figure 1 demonstrates the typical pathway followed by patients attending Oxford Fertility-through the traditional Conventional referral route along-side the One-stop fertility pathway that I designed.

Figure 1: Flowchart Comparing Conventional and One-stop Fertility Investigative Pathway:

2.3. Data Collection:

Once participants returned their consent form and FertiQoL questionnaire, the participants QoL score could be calculated from the responses on the FertiQoL questionnaire. The consent form allowed the study group permission to access the patient's NHS medical records. From the NHS records, the following information was be obtained:

1: The types and number of investigations performed.
2: The number and types of consultation or follow-up appointments in Primary and Secondary Care.
3: The duration they spent in the investigative pathway. I separated the duration divided into the different stages in the pathway from when patients starting actively trying to conceive, primary care, secondary care and total duration in the clinical pathway as defined below:

2.4. Definitions of different stages of Duration in Investigative Pathway

1: **TTC**- (Time Trying to Conceive)- Time from when couples self-reported when they actively started trying to conceive to when they began ART treatment.

2: **PC**- (Primary Care)- Time from when a couple saw their GP to when they were referred for secondary care NHS Fertility Clinic

3: **SC**- (Secondary Care)- Time from when a couple were referred to their secondary care NHS fertility Clinic to when they were referred for NHS funded ART treatment.

4: **TDCC**- Total Duration in Clinical Care- The sum of the duration in PC and SC.

2.5. Calculation of Cost of Fertility Investigation to the NHS

This was calculated based on detailed information collected from the patient's NHS medical notes. This included the details of number of GP appointments, NHS Fertility appointments, the investigations carried out including blood tests, scans, imaging and procedures such as

laparoscopies and hysteroscopies. This information was entered into a Microsoft Excel spreadsheet.

The NHS National Schedule of Reference costs for the year 2017-18(34), which gives average costs of consultations, investigations and procedures across the NHS for NHS Trust and Foundation Trusts was used to calculate the cost to the NHS used to estimate the Cost to the NHS of investigating the participants.

The tariffs for the relevant clinical activities were used to allocate a price per item/investigation/consultation. These different tariffs were then multiplied by the frequency a patient had them. This was obtained from their medical records, and added to give a total cost of investigation for each participant. The relevant tariffs used are listed in Table 3 in results chapter 3.

The National Schedule of Reference Costs takes the costs of all the most common investigations, appointments, surgical procedures and in-patient hospital stays in NHS Trusts across the country and calculates the average cost they all charge, however, there are variations across the regions.

The costs to the NHS were divided and categorised depending on which part along the clinical pathway they were spent as stated below:

1: **TCPC**- Total Cost in Primary Care (Cost to the NHS in Primary Care of Investigations from when a participant first present to their GP to when they are referred to Secondary Care in an NHS Fertility Clinic).

2: **TCSC**- Total Cost in Secondary Care (Cost to the NHS in Secondary Care of Investigations from when a participant is first seen in an NHS fertility clinic to when they are referred for ART treatment).

3: **TCI**- Total Cost of Investigation (Total combined cost to the NHS of Investigations for a participant in both Primary and Secondary care before starting ART treatment).

2.6.Data Verification

The data was first checked for completeness and missing values. Data explorations were performed by running frequency checks and descriptive statistics. Where appropriate the data

are presented graphically for a visual impression of the distribution of the data using histograms.

All the data entry and determining that the participant met the study criteria was checked by two members of the study group separately, these included:

1: Myself, the PI and author of this thesis, a Consultant Obstetrician and Gynaecologist.

2: A Senior Research Nurse appointed specifically for this study.

3: A Data Entry Management Assistant, recruited, appointed and trained specifically for this study

Where there was disagreement on the data or that the participant met the study criteria, the study group members would review the particular participants medical notes together for clarification and correction. If there was persistent disagreement, the particular case was discussed with the CI and a final decision reached.

2.7. Statistical Data Analysis

All statistical analysis was performed in STATA version 13 (StataCorp, College Station, Texas)**.** All statistical significance was assessed at the 5% level of significance (P value < 0.05). Significance of correlation between variables was assessed with Spearman's correlation. Mann Whitney Test was used to calculate the significance between groups.

2.8. Secondary Objective

1: To review the High Multiple Pregnancies (HMP) and deliveries at the John Radcliffe Hospital (a Tertiary NHS Fetal-Maternal Unit) in Oxford between 2010 and 2017 and assess the contribution of ART performed in the UK and overseas to this number.

2.To investigate the possible link between HMPs to decreased NHS funding for ART cycles.

2.8.1. Introduction

ART has long been associated with an increase in multiple pregnancies and cost to the NHS. A multiple pregnancy is defined as a pregnancy with more than one embryo developing at the same time. This would refer to twins, triplets or higher order multiples (35, 36). For the

purposes of this study, we reviewed the number of High Multiple Pregnancies (HMP) at the John Radcliffe Hospital (A Tertiary Referral Hospital) in Oxford to see what the influence, if any, ART treatment from overseas and within the UK was having on its numbers. For the purpose of this. study, High Multiple Pregnancies (HMP) was defined as being those pregnancies with triplets or higher order at their viability scan at between 7-13weeks gestation.

2.9. Settings and Population: Materials and Methods

2.9.1. Study Design

This is a retrospective observational study. I designed a customized spread sheet to collect data collected on all high multiple births at the John Radcliffe Hospital between September 2010 and December 2017. Data collected included;

2.9.2. Maternal Data Collected

1 Type of conception

2: If ART involved, whether autologous oocytes (eggs) or donor eggs used.

3: Number of antenatal appointments.

4: Number ultrasound scan.

5: Numbers and types of blood tests.

6: Number and length of antenatal inpatient admissions.

7: Antenatal complications.

8: Antenatal treatments received or interventions performed.

9: Maternal Age at Delivery

10: Type of Delivery

11: Maternal Postnatal complications

12: Length of Postnatal Hospital stay.

2.9.3. Embryo and Neonatal Data Collected

1: Chorionicity and amnionicity.

2: Foetal complications and interventions during the pregnancy

3: Gestation at Delivery.

4: Weight at Delivery.

5: Neonatal complications at Delivery.

6: Length of post-delivery hospital stay.

7: Neonatal complications.

This information was also used to estimate the cost of care for these HMP to the NHS.

2.9.4. Study Population

All patients identified as having an HMP and had all or part of their antenatal care at the John Radcliffe (JR) Hospital in Oxford during the study period of September 2010 to December 2017. HMP were confirmed on ultrasound scan during the pregnancy with 3 or more foetuses at their viability scan performed between 7 and 13weeks gestation.

2.9.5. Data Collection

Patients were identified from the electronic patient record system of the John Radcliffe (JR) Hospital in Oxford, Obstetric Department sub-division of Feto-Maternal Medicines' data management software called "View Point". This software keeps record of all high-risk pregnancies managed at the JR Hospital. The records were analysed from September 2010, the earliest the date the system started keeping records until December 2017 when the study stopped collecting data.

Other information on the antenatal care, delivery, postnatal care and neonatal outcomes from these pregnancies such as complications, in-hospital admissions, mode of deliveries and post-natal complications were retrieved with a combination of review of the hospital's Electronic Patient Record (EPR) and the patient's and neonate's physical medical records. All the

information was anonymized and recorded into a password protected Microsoft Excel spreadsheet for analysis.

2.9.6. Data Verification

All the data entered was proof checked by 2 medical doctors (Obstetricians) separately. The first being the PI and author of this article, a Consultant Obstetrician and Gynaecologist. The second, a Clinical Fellow Medical Doctor (Registrar level) Obstetrician, working in the Nuffield Department of Women's and Reproductive Health.

Where, there was disagreement on the data, the particular participant's medical notes were reviewed together for clarification and correction. If there was still disagreement, the particular case was discussed with the CI and a final decision reached.

2.9.7. Data analysis

The data collected was organized in tablet and graphs, generated from Microsoft Excel, to identify trends in the high multiple pregnancy rates.

3. Chapter 3: Results, Tables, Graphs and Discussion on the Effect of Duration on Cost of Investigation to the NHS and Quality of Life (QoL) of Participants in the Conventional Fertility Pathway.

3.1. Hypothesis for effect of Duration of Investigation on Cost to the NHS and Quality of Life of participants in the Conventional Pathway.

In this study, I proposed that the longer the duration a female or male participant takes in the conventional fertility pathway before they start their ART treatment, the higher the cost and expenditure to the NHS and the lower their QoL.

Below I discuss the results of the participants in the Conventional pathway.

Table 1. below lists the most common investigations and appointments that are carried out in Primary and Secondary care in the conventional pathway from when a couple first presents to their GP, gets referred to a fertility clinic in secondary care and are referred for ART if indicated and they satisfy their local CCG funding criteria.

Table 1: Table of Investigations and Appointments in the Conventional Pathway

A:	**Investigations in Primary Care (PC) at General Practitioner level.**
1:	First GP appointment. Couples that have been trying to conceive for at least 12 months can start investigations.
2:	A Semen analysis on male partner.
3:	A test of ovarian reserve (FSH, LH and E2) or (AMH) or both.
4:	A test of ovulation (Mid-luteal progesterone).

5:	Testosterone, prolactin, TSH (These are suggested by NICE if patients are symptomatic, however many GPs performed them as routine).
6:	Rubella serology.
7:	Chlamydia screening.
8:	Advise on coitus frequency, weight loss if BMI over 30 and smoking cessation if applicable.
9:	Follow-up appointment with GP for review of results.
B	**Investigations and Appointments in Secondary Care (SC) At the local NHS fertility clinic:**
1:	Initial Fertility Consultation with a Fertility Specialist.
2:	Test for tubal patency (HSG, HyCoSy or Laparoscopy & Dye test).
3:	Pelvic ultrasound scan.
4:	Specialist investigations, procedures and treatment if necessary, for example in PCOS, azoospermia, fibroids and endometriosis in patients.
5:	Follow-up appointment with Fertility Specialist for review of results.

3.1.1. Participant Demographics

There were 191 participants who went through the conventional pathway in this study and met the qualifying criteria. Table 2. below lists the hospitals the participants had their secondary care before they were referred for ART at the recruitment centres in this study (Oxford Fertility and Create Fertility (London)).

Table 2: Table of Number of Participants in Conventional Pathway and Referring Hospitals.

Oxford Fertility (Oxford)	
Referring Hospital:	**Number of participants:**

Churchill Hospital, Oxford University Hospitals (OUH) NHS Foundation Trust	4
John Radcliffe Hospital, OUH Foundation Trust, Oxford	71
Basingstoke and North Hampshire Hospital NHS Foundation	4
Cheltenham Hospital, Gloucestershire Hospitals Foundation Trust-	2
Frimley Park, Frimley Health NHS Foundation Trust	2
Great Western Hospitals NHS Foundation Trust, Swindon	4
Heatherwood Hospital, Frimley Health NHS Foundation	8
Milton Keynes University Hospital NHS Foundation Trust	2
Princess Anne Hospital, University Hospital Southampton NHS Foundation	2
Royal Berkshire Hospital NHS Foundation Trust- Reading	6
St Mary's, Isle of Wight NHS Trust	2
Stoke Mandeville Hospital, Buckinghamshire Healthcare NHS Trust	12
Wexham Park Hospital, Frimley Health NHS Foundation Trust-	12
Wycombe Hospital, Buckinghamshire Healthcare NHS Trust	9
Total Participants Oxford Fertility	**140**
Create Fertility (St Paul's London)	**Number of Participants**
Lister Hospital, East and North Hertfordshire NHS Trust	2
Peterborough City Hospital- North Anglia Foundation Trust	2
Princess Alexandra Hospital NHS Trust- Harrow	16
Royal Surrey County Hospital NHS Foundation Trust, Guildford	2
Southend University Hospital NHS Foundation Trust	10
St George's University Hospitals NHS Foundation Trust- London	19
Total Participants Create Fertility	**51**

3.2.Calculation of Cost to the NHS:

To calculate the cost to the NHS of each participant in this study, I used the participants medical records to list all encounters (appointments) they had in PC and SC and all the fertility related investigations they had and the frequency of these encounters and

investigations. These were entered into a bespoke Microsoft Excel sheet created by myself. The cost of each encounter and investigation was tallied for each participant to give a cost to the NHS. The costs of each encounter and investigation were calculated using the National Schedule of Reference Costs Year 2017-2018-NHS Trust and NHS foundation trusts which lists the average costs to the NHS across the UK. The costs used in this study are listed in Table 3 below.

Table 3: Table of Reference Cost Collection: National Schedule of Reference Costs Year 2017-2018- NHS trust and NHS foundation trusts.

Procedure	**NHS National Schedule Reference Cost**
General Practitioner (GP)Appointment	£166
Gynaecology Out-Patient Appointment	£133
Full Blood Count (FBC)	£6
Urea & Electrolytes (U&E)	£4
Thyroid Function Test (TFT)	£4
Follicle Stimulating Hormone (FSH)	£4
Luteinising Hormone (LH)	£4
Oestradiol (E2)	£4
Testosterone	£4
Progesterone (P4)	£4
Anti-Mullerian Hormone	£10
Prolactin	£4
Semen Analysis (SA)	£12
Cystic Fibrosis Screen	£36
Y-chromosome deletion screen	£36
Karyotype	£36
Rubella screen	£9
HIV, Hepatitis B & C serology	£22
Chlamydia screen	£11
Trans-vaginal Gynaecology Ultra Sound Scan (US)	£151
Hysterosalpingogram-Gram (HSG) X-ray	£289

Hysterosalpingo-Contrast-Sonography (HyCoSy) ultra-sound scan.	£323
Laparoscopy & Dye Procedure	£1819
Diagnostic Laparoscopy	£1516
Hysteroscopy	£960

[1]

Blood tests include £3 phlebotomy charge

3.3. Demographics of participants in Conventional Pathway:

Of the 191 participants, 128 (67%) were married and 63 (33%) were co-habiting. There were 97 female participants with an average age of 33.6 (4.9) and Average BMI of 25 (3.6). There were 94 male participants with an average age of 35.1 (5.5) and average BMI of 26.4 (3.7). A summary of the participants demographics is shown in Table 4 below.

Table 4 also lists the average durations participants spent in the pathways, the cost to the NHS and the participants Quality of Life scores. These results were also sub-categorised by the gender of the participants and the QoL was further sub-analysed into Core, Emotional, Mind/body, Relational and Social sub-categories of QoL for further analysis all depicted in Table 4 below.

Table 4: Table of Demographics of Participants in Convention Pathway, Durations of Investigations, Cost of Investigations, Quality of Life (QoL) of Participants and Correlations

Participant Demographics:	
Total Participants:	191
Married	128
Co-habiting	63

[1] The National Tariff does not have direct costs for every single procedure performed by the NHS, for example Laparoscopy & Dye Procedure is not directly referenced, but the tariff used is for intermediate, Laparoscopic or endoscopic, upper genital tract procedures with CC scores 0-1. There was therefore some subjective selection of the tariff that best described the gynaecology procedure.

Age	33.6(4.9)		
BMI	25.0(3.6)		
Female Participants:	97		
Female average age	32.2(3.8)		
Female average BMI	25.0(3.6)		
Male Participants:	94		
Male average age	35.1(5.5)		
Male average BMI	26.4(3.7)		
Cause of Infertility Reported:			
Tubal Factor	8		
Male Factor	37		
Ovulatory Disorder	17		
Uterine Factor	6		
Unexplained	113		
PGD	8		
Cancer Preservation	2		
Duration of Investigation:	Days (SD)		
TTC	1297.5(687.5)		
PC	403.5(737.8)		
SC	307.8(459.5)		
TDCC	634.0(931.4)		
Cost of Investigation:			
All Participants	£	Spearman Correlation rho	P value
TCPC	402.9 (295.6)	0.217	0.005
TCSC	577.0(354.9)	0.362	<0.001
TCI	979.9(476.6)	0.343	<0.001
Female	£		
TCPC	418.0(293.5)	0.436	<0.001
TCSC	663.0(391.3)	0.397	<0.001
TCI	1081.1(516.5)	0.359	<0.001
Male	£		P value
TCPC	387.3(298.5)	0.275	0.033
TCSC	488.2(289.2)	0.332	0.069
TCI	875.5(408.6)	0.309	0.004
FertiQoL Scores (QoL)			

All Participants	QoL	Spearman Correlation to Duration TDCC	P value
Core	71.7(14.9)	0.022	0.761
Emotional	64.8(22.2)	-0.010	0.886
Mind/body	70.8(18.1)	-0.059	0.416
Relational	79.5(14.6)	-0.010	0.094
Social	73.2(18.1)	0.030	0.676
Female			
Core	68.6(14.0)	0.019	0.848
Emotional	58.1(22.7)	-0.031	0.760
Mind/body	65.4(18.1)	-0.070	0.492
Relational	80.6(13.8)	0.167	0.101
Social	70.3(19.3)	0.051	0.618
Male			
Core	75.6(13.2)	0.008	0.939
Emotional	71.4(19.5)	0.009	0.929
Mind/body	76.4(16.5)	0.049	0.638
Relational	78.4(15.4)	0.020	0.846
Social	76.2(16.3)	0.006	0.953

3.4. Summary of results of Conventional Pathway:

3.4.1. Duration Trying to Conceive.

I found participants in the conventional pathway spent on average 1297.5 (687.5) days from when they started trying to conceive before starting their ART treatment (TTC). This duration of almost 3.5 years, which most participants spent before starting their ART treatment points to either a lapse in public health awareness or patients were finding barriers in accessing help in achieving pregnancy or delays in the investigative pathway. This delay can lead to a decrease in the success rate of ART and possible increase in the cost to the NHS of subsequent treatment and management.

3.4.2. Duration of Investigation in Clinical Care

Once in clinical care, participants spent an average of 403.5 (737.8) days in PC with investigations and treatment being undertaken by their GP and 307.8 (459.5) in SC with investigations and treatment being undertaken by Fertility Specialists respectively. Participants in the conventional pathway spent a Total Duration in Clinical Care (TDCC) of 634.0 (931.4) days before starting ART treatment. They spent an average TTC of 1297.5 (687.5) days, just

about 3.5 years trying to conceive from when they first saw their GP to the start ART treatment. If we subtract the average duration they spent in clinical care, TDCC (634.0) from the TTC (1297.5), patients were spending an average of 663.5 days (1.8years) before they first presented to their GP with difficulty trying to conceive.

3.4.3. Female and Male Durations in Pathways

There was no difference in duration between the female and male durations, 1296.53 (71.03) vs 1298.51 (73.15) p = 0.984 indicating it was not statistically significant. This study only recruited heterosexual couples, for a participant to move from one stage in the investigative pathway to the next was co-dependent on the partner having their investigations completed. The male investigative duration was slightly higher than that of the female participants, this was because there were 3 more females recruited into the study compared to males and the 3 extra female participants had a duration of investigation below the overall groups mean.

3.4.4. Cost of Investigation to NHS in Conventional Pathway

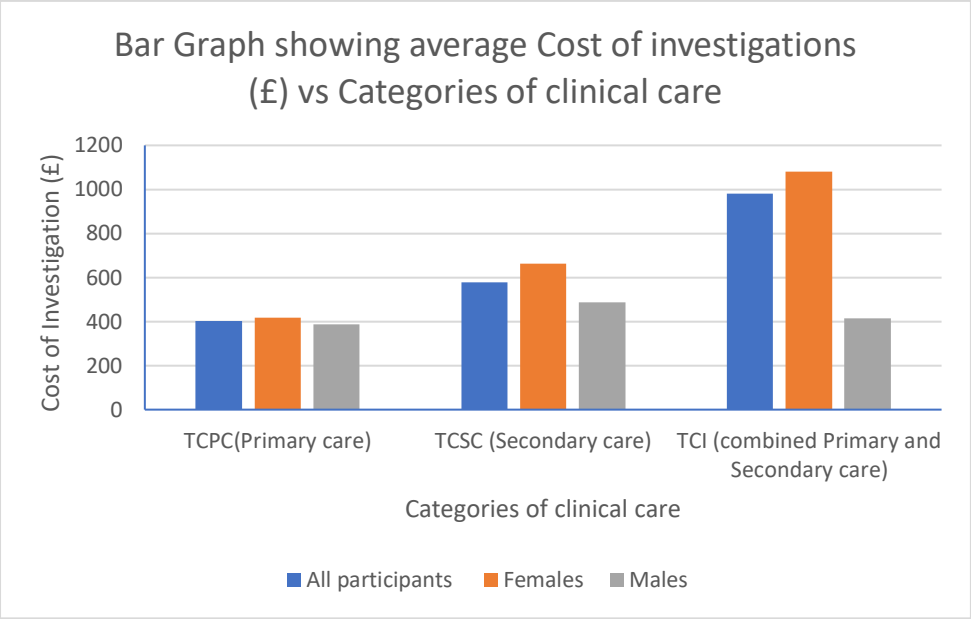
The Average Total Cost of investigations in Primary Care (TCPC) of participants was £402.9 (295.6) and average Total Cost in Secondary Care (TCSC) was £577.0 (354.9) with an average Total Cost of Investigations (TCI) of £979.9 (476.6). The correlation between duration and expenditure was found not to be statistically significant in primary care (TCPC) with a p value of 0.474. This this could be a reflection that the investigations performed on the 2 genders were not significantly different in cost.

Participants spent a shorter duration in SC compared to PC but the NHS spent more money during the SC period. This is explained by the type of investigations carried out in SC compared to PC. Investigations in SC tend to be more specialised, invasive and expensive, for example laparoscopy, hysteroscopy, HSG and HyCoSy. Even the blood tests performed in SC are more specialised, complicated and costly for example karyotype for chromosomal analysis, cystic fibrosis screen, Y-chromosome deletions. However, the shorter duration does point towards are more streamlined and efficient approach in secondary care where despite the investigations being more complex and invasive, they are carried out in a shorter time-span compared to PC.

3.4.5. Differences between Female and Male Participants Costs to the NHS

Female participants had a higher cost of investigation with a mean TCPC, TCSC, TCI of £387.3(298.5), £663.0(391.3), £1,081.1(516.5) respectively compared to Male participants with a mean expenditure of £418.0(293.5), £488.2(289.2) and £875.5(408.6) shown in table 7. These findings were statistically significant with p values of 0.027, <0.001 and 0.002 respectively. This is also graphically illustrated in Figure 2 below, a bar graph comparing the average cost of investigation of all participants, female, male in the sub-categories of primary care (TCPC), secondary care (TCSC) and overall cost in the pathway (TCI).

Figure 2: Comparison of Cost of Investigation of Couples, Females and Males participants in conventional pathway



One of the reasons female cost of investigations was higher than male cost of investigations was there were more specialised and invasive investigations carried out exclusively and more frequently on females compared to male participants. These included laparoscopies, hysteroscopies, pelvic ultrasound scans and HyCoSy scans or HSG X-rays for tubal patency where indicated compared to male participants who had less costly and less invasive secondary investigations such as karyotype, cystic fibrosis (CF) screen, Y-chromosome deletion and male genital tract ultrasound scans. Also, the frequency of Male Factor Infertility (MFI) requiring further investigation was 19.7% in this study meaning only 19.7% of males required more than a standard semen analysis, this was performed in primary care.

3.4.6. Correlation of Duration in Investigation to Cost of Investigation

The average Total Cost of Investigation (TCI) was £979.9 (SD 476.6) and the mean TDCC was 634.0 days (SD931.4) days. On correlation analysis I found that the longer participants spent in the investigative process the greater the cost to the NHS. This was shown with a Spearman's correlation of 0.343 and p value of <0.001 showing it was a statistically significant finding. (Table 4). The Regression coefficient was 0.11, which suggests each day a participant spent in the Conventional investigative pathway care cost the NHS £0.11. This is shown in Table 4a below.

The mean duration of investigating a in PC and SC was 403.5 (SD 737.8) days and 307.8 (SD 459.5) days with cost of TCPC and TCSC of £387.3(298.5) and £488.2 (289.2) respectively. The Spearman's Rho correlation was 0.217 and 0.362 with. p value of 0.005 and <0.001 respectively, both statistically significant. The regression co-efficient for primary care was 0.09 and for secondary care was 0.38 suggesting each day in primary and secondary care cost the NHS approximately £0.09 and £0.38 respectively. This is shown in Table 4a below.

Table 4a: Table of Correlation of Duration to Cost of Investigation in the Conventional Pathway.

All Participants	£	Rank Correlation rho	P value	Regression Coefficient	95% Confidence Interval
TCPC	402.9 (295.6)	0.217	0.005	0.09	0.01-0.19
TCSC	577.0(354.9)	0.362	<0.001	0.38	0.24-0.53
TCI	979.9(476.6)	0.343	<0.001	0.11	0.06-0.16
Female	£				
TCPC	418.0(293.5)	0.436	<0.001	0.11	0.05-0.28
TCSC	663.0(391.3)	0.397	<0.001	0.49	0.27-0.70
TCI	1081.1(516.5)	0.359	<0.001	0.13	0.06-0.21
Male	£		P value		
TCPC	387.3(298.5)	0.275	0.033	0.09	0.03-0.21
TCSC	488.2(289.2)	0.332	0.069	0.28	0.11-0.46
TCI	875.5(408.6)	0.309	0.004	0.08	0.03-0.14

1: Correlation analysis was done using non-parametric Spearman correlation. Findings were considered statistically significant if p value was <0.05.

3.4.7. QoL of Participants in Conventional Pathway:

The mean participants Core QoL score was 71.7 (14.9) on a scale of 0 to 100 as shown in Table 4. This was further sub-divided into Emotional, Mind/body, Relational, and social and their averages were 64.8 (22.2), 79.5 (14.6), 70.8 (18.1) and 73.2 (18.1) respectively. The Spearman's correlation was small for Core and Social at 0.022 and 0.030 and neither was statistically significant with a p value of 0.761 and 0.676. The correlation was negative for Emotional, Mind/body and Relational at -0.010, -0.059 and -0.010 but again this was not statistically significant with p values of 0.886, 0.416 and 0.094. This is illustrated in Table 4a above.

3.4.8. Female QoL in Conventional Pathway

The female participants Core QoL score was 68.6 (14.0) on a scale of 0 to 100 as shown in Table 4. This was further sub-divided into Emotional, Mind/body, Relational, and social and their averages were 58.1 (22.7), 65.4 (18.1), 80.6 (13.8) and 70.3 (19.3) respectively. The Spearman's correlation was small for Core, Relational and Social at 0.019, 0.167 and 0.051 and were not statistically significant with a p value of 0.848, 0.101 and 0.618. The correlation was negative for Emotional and Mind/body at -0.031 and -0.492 but again this was not statistically significant with p values of 0.760 and 0.492 respectively.

3.4.9. Male QoL in Conventional Pathway:

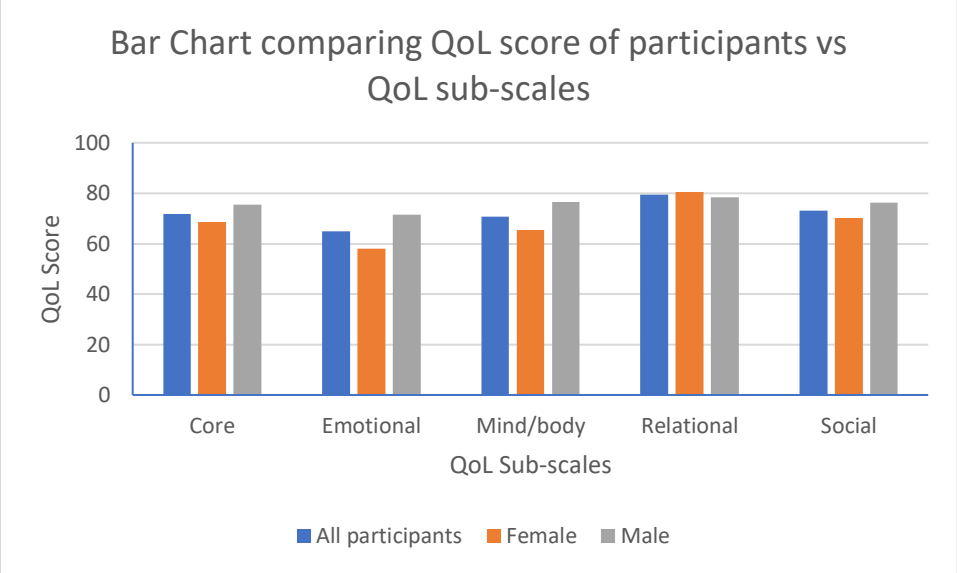
The Male participants Core QoL score was 75.6 (13.2) on a scale of 0 to 100 as shown in Table 4. This was further sub-divided into Emotional, Mind/body, Relational, and social and their averages were 71.4 (19.5), 76.4 (16.5), 78.4 (15.4) and 76.2 (19.3) respectively. The Spearman's correlation was small for Core, Emotional, Mind/body, Relational and Social at 0.008, 0.009, 0.049, 0.020 and 0.006 and were not statistically significant with p values of 0.939, 0.929, 0.638, 0.846 and 0.953.

3.4.10. Comparison of QoL of Female vs Male participants in the Conventional pathway:

Female QoL was lower than Male QoL for Core, Emotional and Mind/body with scores of 68.6 (14.0) 58.1 (22.7), 65.4 (18.1) compared to 75.6 (13.2), 71.4 (19.5), 76.4 (16.5) and this was strongly statistically significant with p values of <0.001, <0.001 and <0.001 respectively. Female QoL score for social sub-scale was also lower than males with 70.3 (19.3) compared to 76.3(16.3) but this was not statistically significant with a p value of 0.023.

The only sub-group that female QoL was higher than male QoL was Relational with the female score of 80.6(13.8) vs male with 78.4(15.4), however this was not statistically significant with a p value of 0.300. This is also illustrated in the bar chart in Figure 3 below.

Figure 3: Comparison of QoL of Couples, Females and Males Participants:



3.5. Discussion of results of Conventional pathway

Dhillon et al (2016) found that the age of a woman when she presents for ART is the single biggest prognostic factor in the success of an ART cycle (37). It would therefore follow that the older a woman is when she presents for treatment, the less likely her ART will be successful. The lower the success rate of ART treatment, the higher the likelihood of increased cost to the NHS for fertility treatment due to the potential need for more fresh NHS funded ART cycles, or the need for Frozen Embryo Transfers (FETs), if extra embryos were frozen in the initial treatment. It is therefore an advantage to the NHS for couples to spend as short a

time as necessary in PC and SC before starting ART treatment. However, the longer a couple stay in the NHS pathway, the more likely they are to conceive naturally and save the NHS money by avoiding the need for IVF. Gathering data on number of couples who conceived during the investigative pathway was beyond the scope of this study however such data would give more information and should be considered in the planning of future studies.

In this chapter, I analysed the duration participants spent during the investigative process and whether this duration had an influence on cost to the NHS and Quality of Life (QoL) of the participants.

Although participants spent longer in PC 403.5 (SD 737.8) days compared to SC 307.8 (SD 459.5) days, their cost in SC was higher and the cost per extra day spent in SC was also higher with a regression coefficient of 0.09 and 0.38 which meant the cost in primary care and secondary care were increasing by £0.09 vs £0.38 per day respectively shown in Table 4a.

The increase cost per day in secondary care was also associated with more invasive and expensive investigations which are done in secondary care that require more preparative time and could not be done in primary care such as hysteroscopies, laparoscopies, HyCoSy, HSG, chromosome analysis, male and female genital tract scans, cystic fibrosis screens and similar investigations.

3.5.1. Female versus Male Cost of Investigations.

Female participants had a higher cost of investigation with a mean TCPC, TCSC, TCI of £387.3(298.5), £663.0(391.3), £1,081.1(516.5) respectively compared to Male participants with a mean expenditure of £418.0(293.5), £488.2(289.2) and £875.5(408.6) also respectively. These findings were statistically significant with p values of 0.027, <0.001 and 0.002 respectively. This is also graphically illustrated in bar chart in Figure 2.

I also found that the higher expenditure for both the sexes was in SC compared to PC. This is shown in Table 4a. The higher expenditure in SC is expected as secondary care is associated with more expensive specialised investigations compared to PC where most investigations are blood-based or interventions involve lifestyle changes.

In addition, I found the Regression co-efficient for Female participants for PC and SC was 0.11 and 0.49 compared to Male participants which was 0.09 and 0.28, showing the NHS spent more money per day on female participants compared to male participants.

The difference in costs between the two genders to the NHS was mainly down to the increased number of baseline investigations required for female compared to male participants as listed below.

Common Female Investigations in Primary Care:

1: FSH,
2: LH,
3: Prolactin,
4: Testosterone,
5: TSH,
6: Mid-luteal progesterone,
7: Rubella serology

Compared to the most common baseline investigations for a male participant which was a

Common Male Investigations in Primary Care:

1: Semen analysis only.

Extra Cost to NHS due to prolonged stay of participants in the Investigative Pathway:

NICE recommend patients should start investigations for infertility after 12 months of trying to conceive. NICE also recommends that couples should be referred for ART if they have been trying to conceive for 24 months in total. In theory participants should spend an average of 12 months (365 days) between first seeking advice from their GP and starting ART if appropriate. However, in this study I found participants are spending an average TDCC of 634 days from presentation in primary care to start of ART, meaning 269 extra days spent in clinical care. If I extrapolate the mean cost per extra day in clinical investigative care of £0.11, this assumes £29.59 extra money was spent on participants in this study due to the prolonged stay in the investigative process. This would work at as £5,651.69 extra money was spent by the NHS on all 191 participants in this study.

From a Freedom of Information (FOI) request from Oxfordshire CCG, in the 2016 – 2017 Oxford Fertility NHS clinic patient data, the Oxford Fertility Unit saw 746 new couple referrals a year (1,492 individuals). An extra expense of £29.59 per individual due to prolonged duration in the investigative pathway could potentially mean an extra expense to the NHS of £44,148.28 during their investigation period before they start ART.

3.6. Causes of prolonged duration in Referring for ART

To investigate the causes of prolonged duration in the conventional pathway, which may lead to the delay in referral for ART for participants, I reviewed the NHS records of the participants. The delays could be broadly divided into "Administrative" and "Clinical" causes which I have discussed below.

3.7. A: Administrative

3.7.1. GP and NHS Waiting Lists:

Some couples had difficulty accessing a GP or NHS Fertility clinic appointment due to no suitable appointments available. Some Fertility Clinics had waiting lists of 3 to 6 months before an appointment was available. They were a few incidences where patients would cancel a scheduled appointment due to their own work or personal commitments. There were also appointment cancellations as the GP or NHS doctor became unavailable.

3.7.2. Patient Choice

Some participants had their investigations done in a timely manner for primary and secondary care and would have a timely referral to the next stage of care. However, some of these participants chose not to proceed with further treatment at that point for non-clinical reasons. The reasons varied from personal choice, the stress of the investigative process, professional/work commitments, family issues such as bereavement and wanting to take a personal break before proceeding to what they perceive as a more intrusive stage of investigation and treatment.

3.8. B: Clinical

3.8.1. Initiation of Life Style Changes

I found that there were clinically justifiable delays in referring along the pathway. These included, but were not limited to, lifestyle changes initiated in primary and secondary care such as advice on frequency and timing of intercourse, and weight loss for female participants with BMIs over 30 and smoking cessation for at least 6 months. Some of these measures also meant a participant could not progress to the next step in the investigation pathway until they met CCG funding criteria such as weight loss or smoking cessation of at least 6 months.

3.8.2. Initiation of non-ART treatment in PC and SC:

Primary and Secondary Care did not only offer investigative measures but treatments as well such as ovulation induction with Selective Oestrogen Receptor Modulators (SERM's) with medications such as clomiphene citrate for anovulatory women with polycystic ovarian syndrome (PCOS). These interventions are cheaper, safer and less invasive than ART and have a success rate of almost 50% over 6 months in carefully selected couples.

In addition, I also found surgical interventions were performed in secondary care, such as laparoscopy for endometriosis and ovarian drilling for PCOS and hysteroscopy for endometrial pathology and were clinically justified. However, less than 20 out of the 191 participants had surgical interventions so its contribution to the delays were minimal.

3.8.3. Repetition of Investigations an unlikely consequence of delay in referral

A factor that seemed to increase the cost of the patients was a repetition of investigations. This seemed more common in primary care where if a patient was not seen over a long duration for example 8-16 months, when they returned for a follow-up appointment, the investigations that were initially done at the 1st appointment despite being normal, would be repeated again. This could be a case of "Clinician Anxiety" in wanting to show empathy to a couple by offering an investigation or measure to show "something is being done". There were many cases where no justifiable need to repeat the investigations could be identified.

3.8.4. Investigations Done as routine with no clinical Indication:

From reviewing the participants records, I found some GP's and NHS fertility clinics carried out investigations as routine which were meant only to be performed when clinically indicated. Examples of these were TSH, Testosterone, SHBG, Prolactin. These investigations, according NICE guideline are indicated for women with anovulation and irregular periods when there is a suspicion of PCOS and ruling out other possible causes such as thyroid disease, adrenal disease or pituitary tumours. These investigations were performed on women with regular periods with elevated mid-luteal phase serum progesterone, suggestive of ovulation. Performing these investigations added cost to the NHS and inconvenience to participants who had to arrange to attend to have investigations done, possibly having to take time off work and also anxiety of waiting for these results. Follow-up Consultations would also have to be arranged to discuss the results.

3.9. Discussion of Effect of Duration on Quality of Life (QoL) in the Conventional Pathway.

In this study, I assessed and analysed the relationship between the duration of investigation and Quality of Life (QoL) of participants in the Conventional Pathway as well as any differences in QoL between the female and male participants in the study to see if there were any gender-specific trends or clear differences between the male and female participants. I was interested in seeing if fertility affected the QoL of different genders in different ways.

3.10. FertiQoL: Description of the tool.

The FertiQoL Questionnaire used in this study is a fertility-specific questionnaire designed to purposely assess QoL of participants going through Fertility Investigation and Treatment (29, 30).

The FertiQoL Questionnaire has 36 questions which grades QOL based on their responses on a scale of 0 to 4. The first 24 questions assess the investigative phase of infertility. The final 12 questions assess patients QoL based on the environment during treatment at an ART centre(25). For the purpose of this study, participants were only required to fill in the first 24 questions which assess the investigative process of treatment. An example of a FertiQoL questionnaire is shown in Appendix 1.

It allows for the objective assessment of influences such as general health, self-perceptions, emotions, partnership, family and social relationships, work life and future life plans in participants from the investigative and treatment process. FertiQoL consists of 36 items (questions) that yield six subscales and three total scores.

For the purpose of this study, participants were asked to fill in the 24 questions which allow for calculation of the "Core" FertiQoL score. These 24 responses then allow us to measure;

1: The Emotional subscale score shows the impact of negative emotions (e.g., jealousy & resentment, sadness, depression) on quality of life.

2: The Mind-Body subscale score shows the impact of fertility problems on physical health (e.g., fatigue, pain), cognitions (e.g., concentration) and behaviour (e.g., disrupted daily activities, delayed life plans).

3: The Relational subscale score shows the impact of fertility problems on the marriage or partnership (e.g., sexuality, communication, commitment).

4: The Social subscale score shows the extent to which social interactions have been affected by fertility problems (e.g., social inclusion, expectations, stigma, and support).

Each Sub-scale is scored 0-100. The Core FertiQoL total is then calculated as an average on the 4 sub-scales above. The higher the score from 0 to 100, the better the QoL. A manual tool used to calculate the QoL based on participants responses is shown in Appendix 2. There is also an online version calculation tool used to calculate the QoL.

For the purpose of this study, I entered the responses to the questionnaire into a Microsoft Excel sheet and used a formula supplied by the FertiQoL website to calculate the Total core scores and sub-scores. Appendix 2 shows the FertiQoL scoring system of the FertiQoL questionnaire and how to calculate the Total and subscale totals based on the participants responses.

3.11. QoL of Participants

One of the objectives of the study was to assess whether there was a correlation between the duration needed to perform investigations in PC and SC and the participants QoL.

The mean participants Core QoL score was 71.7 (14.9) on a scale of 0 to 100 as shown in table 4. A study by Koert et al (2019) of 16,315 participants in 23 countries across the world in clinical settings found average FertiQoL Core scores to be between 60 and 75 showing this study's participants average QoL compared favourably with that of other patients going through fertility investigation and treatment in a clinical setting (38).

A previous Dutch Study by Aarts JW et al (2011) comparing FertiQoL scores and patients Hospital Anxiety and Depression Scale (HADS) have found participants exhibited clinical anxiety with a FertiQoL score of less than 58.8 and clinical depression with a FertiQoL score of less than 51.9 (24). So overall in this study, participants had a relatively good and normal QoL.

3.12. Comparison of Female vs Male QoL in Conventional Pathway:

The Core female participants QoL was lower than the male participants Core QoL with a mean FertiQoL score of 67.9 (SD 15.6) compared to 75.6(SD 13.2). This was statistically significant with Mann Whitney p value of <0.001. Analysis of the other QoL sub-scales revealed lower scores in female participants for emotional (impact on emotions such as jealousy, resentment, sadness and depression), mind/body (impact on physical and mental health, attention, concentration impact on work and life plans) and social (social interactions e.g. social inclusion, expectations, stigma and support) with averages of 58.1(22.7), 65.4 (18.1), 70.3(19.3) respectively compared to male participants with averages of 71.7(19.5), 76.4(16.5), 76.2(16.3) respectively (Table 7) and were statistically significant with p values of. <0.001, <0.001 and 0.037.

The only sub-scale which female participants scored higher than male participants was Relational (aspects to sexuality and commitment to partner) with a score of 80.6(13.6) compared to male participants with an average score of 78.4(15.4). This was also the highest scoring sub-scale score for both genders and perhaps indicating that the couples felt strongly supportive of each other in their personal relationship. However, this finding was not statistically significant with a p value of 0.426.

Most significantly, female participants average Emotional QoL score was 58.1 (22.7) indicating clinical anxiety and reflecting the stress the investigative process was having on

them. This could point to females having fertility investigation and treatment requiring more professional emotional support. This is recommended by NICE before, during and after ART treatment, however reviewing medical notes revealed most clinics only proactively offer counselling once patients start ART treatment.

3.13. Possible Causes of lower Female QoL compared to Male participants in Conventional Pathway:

1: Number of investigations performed on Female compared to Male Participants:

Female participants generally had more investigations compared to male participants. In a routine investigative pathway for unexplained infertility (the most commonly recorded cause of infertility amongst participants in this study), female participants could expect to have 8 separate blood test investigations, some of which require correct timing during the menstrual cycle for example early follicular FSH and LH for ovarian reserve and mid-luteal progesterone for ovulation, a virology screen and 1 pelvic imaging test for tubal patency, while male participants would have a semen analysis and a virology screen. Having the tests and the proceeding anticipation before receiving the results could have led to heightened anxiety and negatively affect the QoL.

2: Societal Pressures on female participants and sense of identity:

Society has historically and culturally placed expectations on women as "home-makers" and this may place more pressure on themselves compared to their male partner when they are having difficulty getting pregnant. This is seen in the significantly lower QoL score of emotional, mind/body and social subscales compared to male participants which is also a reflection of how female participants view themselves in their environment, community and profession.

3.14. Proposed Strategies to address Gender in-balance of QoL:

1: Counselling Services:

These findings do indicate that female QoL is affected more than males. Sub-analysis of the different categories average QoL for females indicate more women participants going through

infertility treatment may demonstrate clinical anxiety. This would suggest counselling services should be tailored to provide more support to females from early in the investigative process as they would appear to be more affected that male participants by this process.

2: Performing only clinical indicated Investigations:

In addition, performing less tests on female participants may also improve their QoL, for example not performing mid-luteal progesterone in women with regular periods between 26-35days or considering substituting an Anti-Mullerian Hormone (AMH) blood test for the timed early follicular FSH/LH. Other alternatives a HyCoSy with AFC to replace AMH/FSH/LH and HSG or Laparoscopy and Dye test for women with regular periods and uncomplicated medical history. This would put less pressure and appointments on female participants and perhaps improve their QoL.

3.15. Correlation of Duration of Investigations and QoL

I performed a Spearman's Correlation between Total Duration in Clinical Care (TDCC) 634.0 (SD 931.4) days and the Core FertiQoL score of 71.7 (SD 14.9) was 0.022 and it was not statistically significant relationship between the duration and the QoL scores of the participants with a p value was 0.761.

I found similar findings, shown in Table 4, across the other QoL subscales of Emotional, Mind/body, Relational and Social with Spearman's rho values of -0.010, -0.059, -0.010 and 0.030 and p values of 0.760, 0.492, 0.101 and 0.618 respectively showing no statistically significant relationship with even negative correlations in the first 3. Sub-scales. Sub-analysis by gender also found no relationship between duration of investigation and QoL with p values of 0.848 and 0.939 for female and male participants respectively.

This was an unexpected finding as I had hypothesized that participants having a shorter duration of the Investigative process would have a higher and better QoL as had been found in previous studies(25). The possible reasons for this unexpected finding may include:

3.15.1. 1: Life Style Interventions

Life style interventions initiated during the primary and secondary care by clinicians such as advice to weight loss for raised participants with a raised BMI, smoking cessation and increase intercourse frequency may have had a beneficial effect on the QoL. As participants progress through their pathway, they feel positively about the advice they have been given and this makes them feel better that help is at hand.

3.15.2. 2: Support from community

As the participants progress through their journey, they encounter support either directly or indirectly from family, friends, co-workers, clinical staff, magazines and social media. They read more about their condition and possible interventions and successes and they feel that help is at hand.

3.15.3. 3: Clinical Interventions:

Clinical interventions such as treatment of ovulatory disorders with SERM's, laparoscopic ovarian drilling for PCOS or even information from the clinician to explain the cause of infertility may also have had a beneficial effect on the QoL despite an increase in the duration of investigation.

3.15.4. 4: The Kübler-Ross Change Curve® model of Grief

Infertility leads to anxiety and stress on patients affected by it. Isla P et al (2008) compared the process patients deal with disease as similar to when they are dealing grief and their response and coping with new diagnosis of disease with time similar to how they would cope with grief and go through the same stages of grief described in the Kübler-Ross Change Curve® stages of grief(39).

The Five Stages of Loss® in this model have been defined as Denial, Anger, Negotiation, Depression and Acceptance. As patients go through the stages of grief with time, there is an initial rise in moral (comparable to QoL) in the first 2 stages (Denial and Anger), followed by the lowest point in moral with Negotiation and Depression and finally an improvement in moral with Acceptance and adaption to the new clinical reality. This has also been described and illustrated in the Kübler-Ross Change Curve® depicted in Appendix 3 in Appendix.

Not all people affected by infertility would follow this exact pattern when dealing with the grief of infertility. However, most models have shown the lowest moral and QoL is experienced at stage 3 and 4 of Denial and Depression. With time comes the acceptance stage which is accompanied by improvement of morale and QoL. It could be the study is depicting this progression through the stages and measurements of higher QoL with longer duration is reflecting participants who have come to accept their clinical circumstances and their morale and QoL has improved with the onset of referral for ART and the optimism that their treatment may be successful and a way out of their distress.

3.16. Limitations of Study and Recommendations for future work:

This study only included couples who satisfied their local CCG criteria for NHS funding for ART. However, to get a broader picture of NHS expenditure and Quality of Life of all fertility patients, it may have been useful to design a study that gathered information on patients who became pregnant while waiting for ART treatment as these spontaneous pregnancies saved the NHS money and are an advantage for delaying the start of ART treatment. Future studies should also include couples who did not satisfy their CCGs funding criteria and what options they follow when ART is offered as their best option of achieving pregnancy. It would also important to investigate how patients who do not meet funding criteria are managed in the NHS and also investigate the options they may consider or choose regarding their fertility treatment and how they may choose to fund them. It would also have been important to keep a record of all patients who were eligible for and approached for the study and the number who agreed to participate for planning of future studies.

It would important to find out how the QoL of patients who do not satisfy local funding criteria compares to those patients who did meet the funding criteria. The funding criteria varies across the UK ranging from some CCGs offering no ART treatment to others offering all the cycles advised by NICE with the majority of CCGs offering in between these two options. For future work, I would consider planning a study which investigated the QoL of patients assessed the influence of their local CCG ART funding criteria.

My study did not find a correlation between Duration and QoL which has been seen in previous studies from other countries. This could be due to the size of the study sample in my study or a reflection of the quality of care in the recruitment centres that made the patients experience

better and QoL improve. The study design may also be at fault as patients were recruited at the time when they were about to start their NHS funded ART treatment. The start of the treatment may mark a highpoint in their long fertility journey causing a "temporary" elation in their QoL.

These possible short-comings in my study design may be addressed by designing a larger multi-centre study and assessing the QoL of the same participants at several different points of the fertility pathway, i.e., measuring the QoL when they first see their GP, when they are referred to secondary care and finally when they are referred for ART. This would allow investigators to assess a more dynamic view of how QoL changes during the pathway and how it is influenced by duration in the care of fertility patients.

3.17. Conclusion

In this study, participants were found to have spent on average 1297 days, almost 3.6 years, before presenting to their GP for help in getting pregnant. This points to a lapse in public health awareness. More emphasis should be put into public health awareness and education on patients seeking help after 12 months of trying to conceive.

Participants spent 403 days in PC and 307 days in SC with investigations and treatment being undertaken with a mean TDCC of 634 days before starting ART treatment. They also had an average TTC of 1297.5 days, just about 3.5 years, trying to conceive. This was almost 1.5 years more than what NICE recommend for the duration a couple should spend trying to conceive before starting ART treatment.

The mean duration in clinical care (PC and SC combined) was 634 days, an average delay of 269 days spent in clinical care over the anticipated duration of 365 days (12 months) in clinical care that would be anticipated if NICE guidelines are followed of starting ART after 24 months of from actively trying to conceive. This delay was associated with an increased daily cost of £0.11 or £29.59 per patient and this is statistically significant and points to rising costs to the NHS from the delays in referral. The delays were however found to have both administrative, social and clinical causes.

The duration of investigation in this study did not have a correlation with the QoL of participants. Participants in this study had a relatively normal QoL with a mean FertiQoL score of 71.7 which was well above the level for clinical anxiety and depression of 58.8 and 51.9

respectively. However, there was a difference between the female and male QoL with means of 67.9 and 75.6 respectively which were statistically significant showing females had a lower QoL compared to their partners when going through fertility investigations.

Sub-analysis showed that females had an emotional FertiQoL score of 58.1 which would indicate they had clinical anxiety. NICE recommend offering psychological support for couples before, during and after ART treatment, however the participants medical records indicate this was mainly offered once they started ART treatment. This study demonstrates a need to offer couples, especially females professional psychological support early in the investigative pathway.

4. Chapter 4: Results, Tables and Graphs of comparison of Participants in the Conventional versus One-stop fertility Pathway.

4.1. Hypothesis for Effect the a One-stop Clinic Pathway will have on the Duration of Investigation, Cost of Investigation to NHS and Quality of Life of participants compared to the Conventional Pathway.

In this study I proposed that the introduction of a One-stop fertility pathway will decrease the duration of the investigation to the start of ART leading to a decrease in cost to the NHS and an improvement in the QoL.

In the previous chapter, I found and showed that the longer the duration participants were having investigations led to higher expenditure and cost to the NHS. I also found that QoL of participants were normal and comparable to other fertility patients. I did find on sub-analysis of QoL of that female participants emotional sub-scale score levels were decreased and at a level comparable to patients with clinical anxiety.

I therefore proposed that a One-stop fertility clinic pathway model may be more efficient by reducing the number of Consultation appointments and avoiding repetition of investigations or avoiding investigations not clinically indicated and therefore reduce the duration participants spent in PC and SC, thereby reducing the cost to the NHS and lead to improvement of participants QoL.

I therefore designed and set up a One-stop fertility clinic to investigate whether a One-stop fertility clinic would:
1: Reduce the duration of investigation.
2: Reduce the cost of investigation to the NHS.
3: Lead to an improvement of the Quality of Life (QoL) of participants.

Below, I discuss results of the comparison of the traditional NHS “Conventional” pathway versus the newly designed One-stop pathway.

4.2. Results:

4.2.1. Demographics of One-stop Participants.

The demographics of the patients who went through the "Conventional" pathway have already been described in the previous chapter. The demographics and findings of the participants who went through the One-stop Pathway are shown in Table 5. There were 28 participants who went through the One-stop pathway, 18 (64%) were married and 10 (36%) were co-habiting. There were 14 (50%) female participants with an average age of 33.9 (4.6) and Average BMI of 24.5 (3.0). There were 14 (50%) male participants with an average age of 36.5 (5.1) and average BMI of 25.0 (3.1).

Comparisons of the Demographics of the Conventional vs One-stop for means of their Age were 33.6 (4.9) and 35.2 (4.9) and BMI 25.0 (3.6) and 24.5 (3.0) with p values of 0.150 and 0.535 using Mann-Whitney test, showed the demographics of both groups were very similar. Comparisons of demographics of the 2 groups is shown in Table 6 below.

Table 5: Table of Demographics of Participants in One-stop Pathway, Durations of Investigations, Cost of Investigations, Quality of Life (QoL) of Participants

Demographics:	
Total Participants No:	28
Married Couples	18
Co-habiting	10
Age	35.2(4.9)
BMI	24.5(3.0)
Female Participants No:	14
Female average age	33.9(4.6)
Female average BMI	24.5(3.0)
Male Participants No:	14
Male average age	36.5(5.1)
Male average BMI	25.0(3.1)
Cause of Infertility Reported:	
Tubal Factor	4
Male Factor	8
Ovulatory Disorder	8

Uterine Factor	0
Unexplained	8
PGD	0
Cancer Preservation	0
Duration of Investigation:	Days (SD)
TTC	1014.7(280.4)
PC	417.6(134.0)
SC	59.5(101.7)
TDCC	207.1(159.0)
Cost of Investigation:	
All Participants:	
PC	206.4(50.5)
SC	338.4(166.4)
TDCC	544.8(174.5)
Female	
TCPC	215.2(50.4)
TCSC	458.9(130.3)
TCI	674.1(117.8)
Male	
TCPC	197.6(50.9)
TCSC	217.9(96.2)
TCI	415.5(115.5)
FertiQoL Scores (QoL)	
All Participants	
Core	64.3(16.0)
Emotional	56.0(19.6)
Mind/body	58.6(22.4)
Relational	74.8(14.0)
Social	67.8(18.9)
Female	
Core	63.5(16.2)
Emotional	53.3(22.1)
Mind/body	58.8(23.8)
Relational	75.9(13.8)
Social	66.0(19.4)
Male	
Core	65.1(16.3)
Emotional	58.6(21.6)
Mind/body	58.4(21.7)
Relational	73.8(14.8)
Social	69.7(19.0)

Table 6: Comparison of Participants in Conventional vs One-stop Pathway

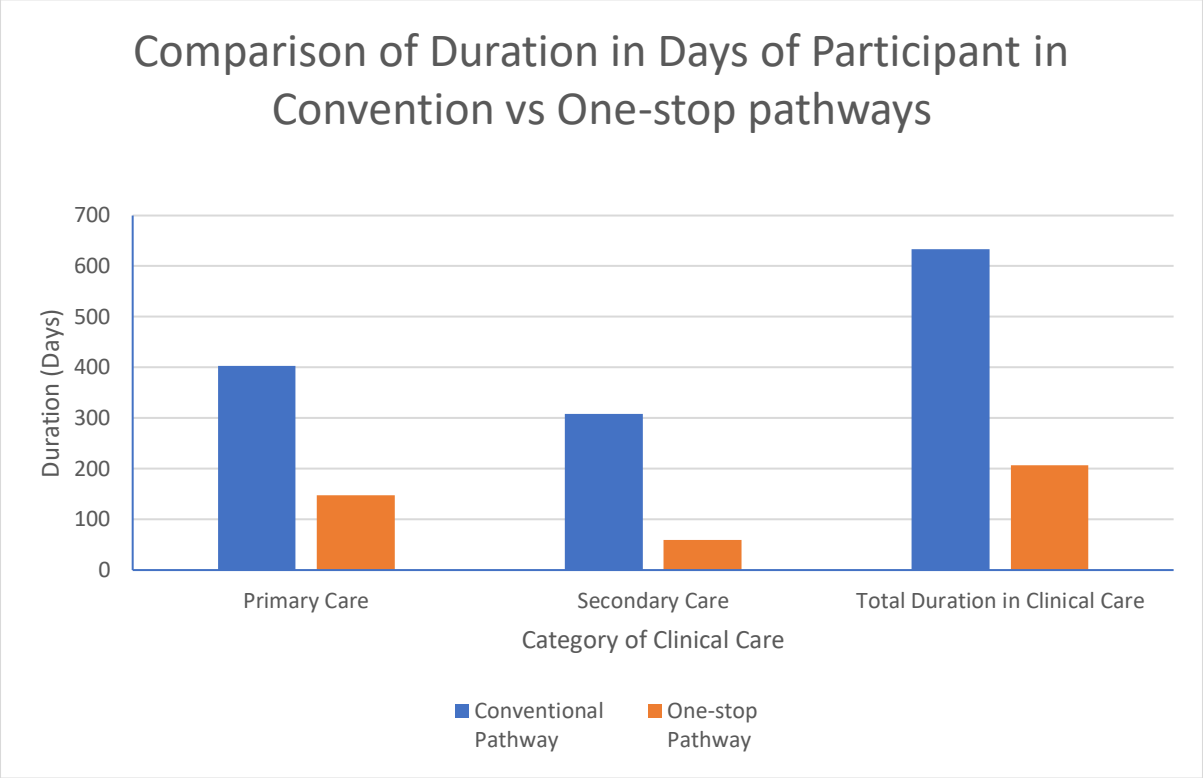
Demographics:	**Conventional Pathway. mean (SD) or n (%)**	**One-stop Pathway. mean (SD) or n (%)**	**Mann-Whitney U Test p value**
Total Participants No:	191	28	
Female	97	14	
Male	94	14	
Married	128	18	
Co-habiting	63	9	
Age	33.6(4.9)	35.2(4.9)	0.120
BMI	25.0(3.6)	24.5(3.0)	0.515
Female Participants No:	97	14	
Female average age	32.2(3.8)	33.9(4.6)	0.135
Female average BMI	25.0(3.6)	24.5(3.0)	0.515
Male Participants No:	94	14	
Male average age	35.1(5.5)	36.5(5.1)	0.38
Male average BMI	26.4(3.7)	25.0(3.1)	0.188
Duration:	Conventional (SD)	One-stop (SD)	P value
TTC	1297.5(687.5)	1014.7(280.4)	0.033
PC	403.5(737.8)	147.6(134.1)	0.069
SC	307.8(459.5)	59.5(101.7)	0.004
TDCC	634.0(931.4)	207.1(159.0)	0.016
Cost of Investigation:	£	£	
TCPC	402.9(295.6)	206.4(50.5)	<0.001
TCSC	577.0(354.9)	338.4(166.4)	<0.001
TCI	979.9(476.6)	544.8(174.5)	<0.001
Female Participants	£	£	
TCPC	418.0(293.5)	215.2(50.4)	0.011
TCSC	663.0(391.3)	458.9(130.3)	0.056
TCI	1081.1(516.5)	674.1(117.8)	0.004
Male Participants	£	£	
TCPC	387.3(298.5)	197.6(50.9)	0.020
TCSC	488.2(289.2)	217.9(96.2)	<0.001
TCI	875.5(408.6)	415.5(115.5)	<0.001

QoL:			
All Participants			
Core	71.7(14.9)	64.3(16.0)	0.008
Emotional	64.8(22.2)	56.0(19.6)	0.047
Mind/body	70.8(18.1)	58.6(22.4)	0.115
Relational	79.5(14.6)	74.8(14.0)	<0.001
Social	73.2(18.1)	67.8(18.9)	0.145
Female			
Core	68.6(14.0)	63.5(16.2)	0.215
Emotional	58.1(22.7)	53.3(22.1)	0.450
Mind/body	65.4(18.1)	58.8(23.8)	0.221
Relational	80.6(13.8)	75.9(13.8)	0.234
Social	70.3(19.3)	66.0(19.4)	0.439
Male			
Core	75.6(13.2)	65.1(16.3)	0.007
Emotional	71.4(19.5)	58.6(21.6)	0.023
Mind/body	76.4(16.5)	58.4(21.7)	<0.001
Relational	78.4(15.4)	73.8(14.8)	0.299
Social	76.2(16.3)	69.7(19.0)	0.172

4.2.2. Duration of Investigation (Conventional vs One-stop)

Duration of investigation in the Conventional compared to One-stop in PC, SC and Total Duration in Clinical Care (TDCC) was 403.5 (737.8), 307.8 (459.5) and 634.0 (931.4) compared to 147.6 (134.1), 59.5 (101.7) and 207.1 (159.0) respectively and shown in Table 6. I found that the One-stop clinic pathway reduced the duration of investigation for PC, SC and TDCC by 255.9, 248.3 and 426.9 days respectively. The reduction in duration for PC, SC and TDCC were statistically significant with P value of 0.069, 0.004 and 0.016 respectively. These findings are illustrated in Figure 4 below.

Figure 4: Comparison of Duration (Days) for Participants in Conventional vs One-stop Pathways



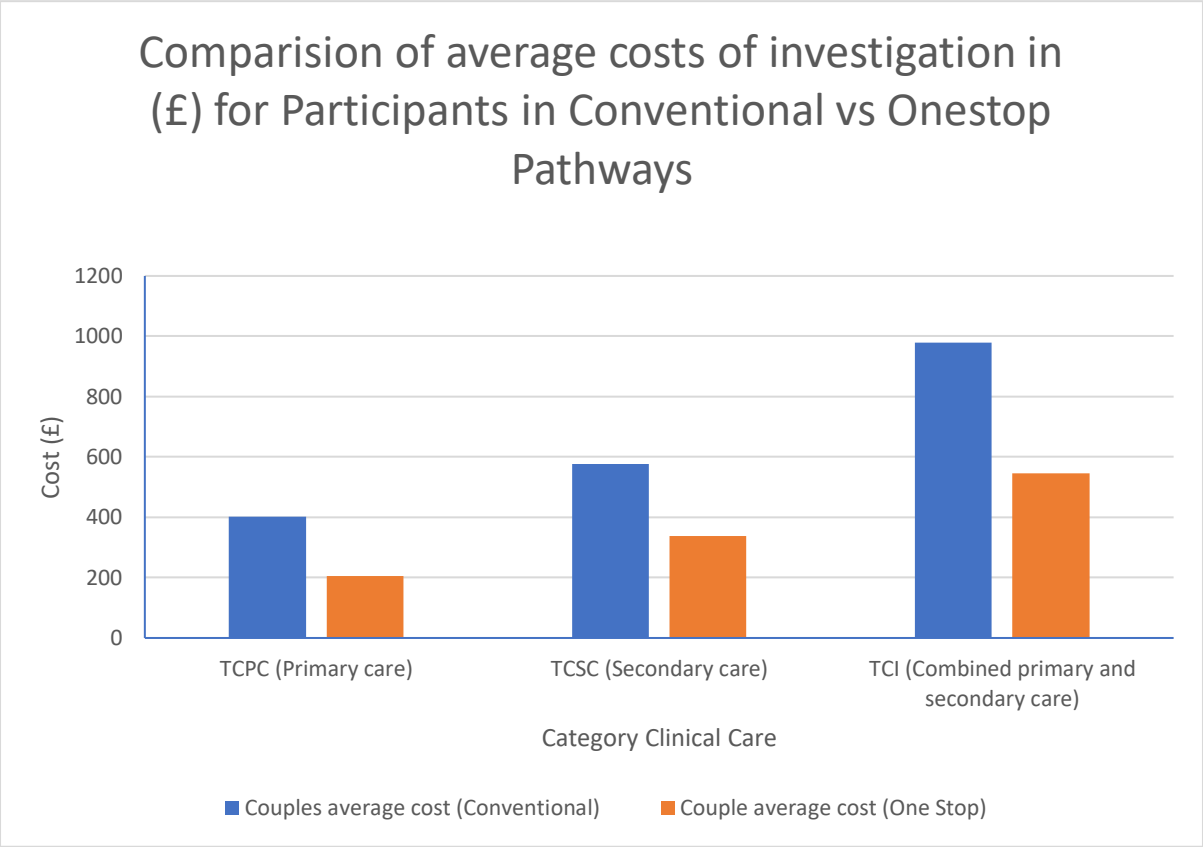
The reduction in duration of 426.9 days for Total Duration in Clinical Care (TDCC) in the One-stop pathway means that participants in the One-stop pathway on average started their ART treatment over a year earlier than participants the conventional pathway and this could have clinical implications. Van Loendersloot (2010) in a systematic review showed that female age at the start of ART is one of the best predictors of success(40). It could also mean some patients who are close to the age threshold for qualifying for NHS funded treatment, receiving that treatment or being excluded as they go above the age that CCGs offers funding for ART.

4.2.3. Cost of Investigation (Conventional vs One-stop)

The mean cost of Investigating participants in the One-stop pathway for Primary Care (TCPC), Secondary Care (TCSC) and Total Cost of Investigation (TCI) was £206.4(50.5), £338.4(166.4) and £544.8(174.5) compared to the Conventional Pathway which was

£402.9(295.6), £577.0(354.9) and £979.9(476.6) respectively. This demonstrated that the One-Stop pathway reduced costs in PC, SC and TDCC compared to the conventional pathway by £195.8, £238.6, and £435.1 respectively. This was also found to be clinically significant with p values of <0.001, <0.001 and <0.001 respectively. This is illustrated in Table 6 in the results chapter and graphically in Figure 5.

Figure 5: Comparison of costs (£) of Conventional vs One-stop Participants



There were more consultation appointments and investigations performed on participants in the conventional pathway compared to the One-stop pathway which would explain the differences in costs. However, on deeper analysis of the cost of Investigation, the most significant differences in the pathways were the mean number of consultations as shown in Table 8, in both primary and secondary care. In the Conventional Pathway the average number of GP Consultations was 2.24(SD 1.78) compared to the One-stop pathway 1.07(0.26) and this was statistically significant with a p value of <0.001. The Conventional pathway had on

average 1 more consultation in primary care. The cost of a GP appointment is £166, which makes for the bulk of the £195.8 difference in the pathway. This is shown in table 8.

In secondary care, the Conventional pathway had an average of NHS Consultations of 3.40(2.14) compare to the One-stop of 1.32(0.54), there were therefore almost 2 more NHS fertility Consultations in the Conventional Pathway compared to the One-stop pathway and this was statistically significant with a p value of <0.001. Each NHS Consultation cost £133, this would lead to a savings of £266 per participant and again makes the bulk of the £238.6 savings realised in the One-stop pathway.

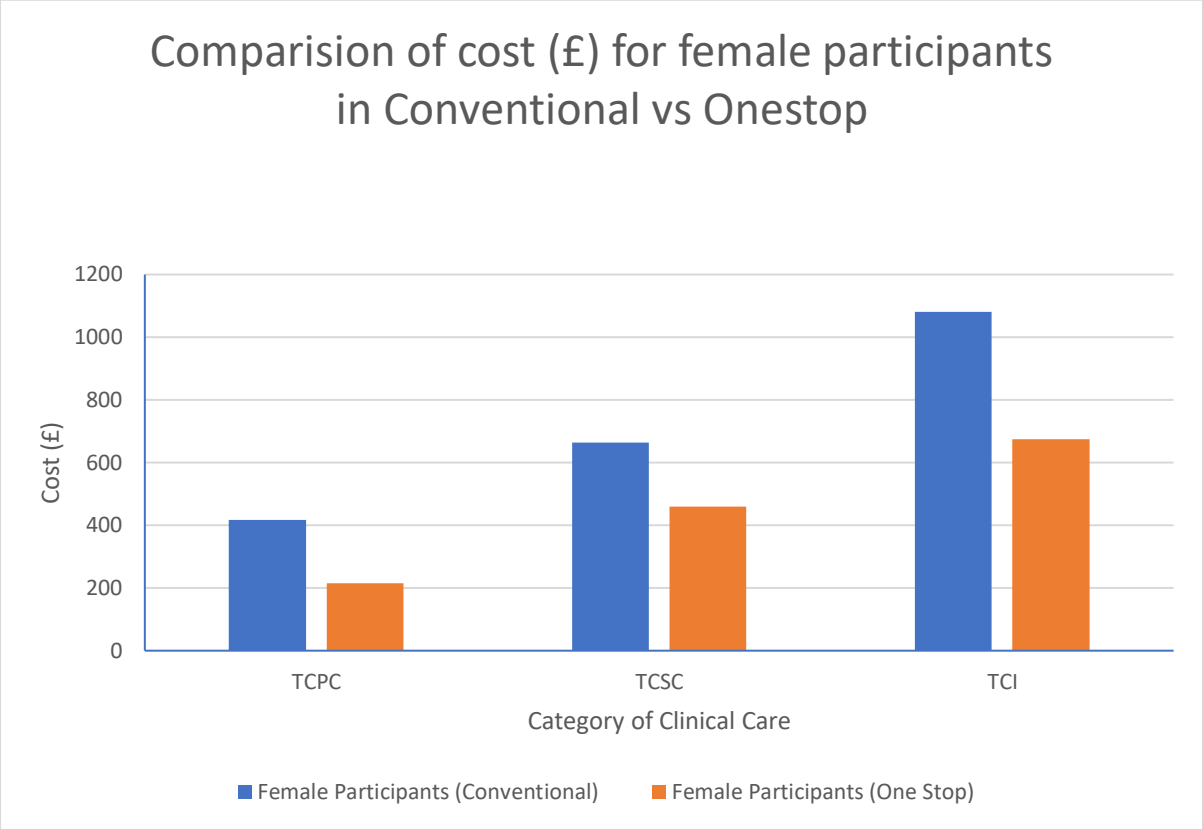
The other investigations could not fairly be compared due to differences in their standard investigative pathways. Some investigations like HyCoSy were only available at Oxford Fertility and Watford General Hospital where the One-stop clinics were run and had a higher frequency compared to Conventional pathway participants where it wasn't available at their local fertility clinics due to no staff being able to perform them at those hospitals. In addition, some hospitals did not offer HyCoSy or HSG at all and only offered a chlamydia screen and if positive, patients were offered a laparoscopy and Dye test. These findings were due to the skill sets of staff and availability of equipment at the different participating hospitals and the components of the pathway agreed with the local CCG.

4.2.4. Differences between Female and Male Participants cost of Investigation: (Conventional vs One-Stop)

4.2.4.1. Females Cost – Conventional vs One-stop

The costs of female participants in the Conventional pathway for TCPC, TCSC and TCI were £418.0(293.5), £663.0(391.3) and £1081.1(516.5) respectively compared to the One-stop pathway which were £215.2(50.4), £458.9(130.3) and £674.1(117.8) as shown in Table 6. This showed the One-stop pathway reduced costs for female participants in PC, SC and TDCC by £202.8, £204.1 and £344.0 with a p value of 0.011, 0.056 and 0.004 respectively and was statistically significant. This is also illustrated in Figure 6 below.

Figure 6: Comparison of costs (£) of Conventional vs One-stop Female participants.



TCI was the sum of the TCPC in primary care and the TCSC in secondary care and in the One-stop arm, had a reduced the cost of £344.0 with a p value of <0.001 which was statistically significant. These findings show that the One-stop pathway reduced the cost to the NHS for female participants.

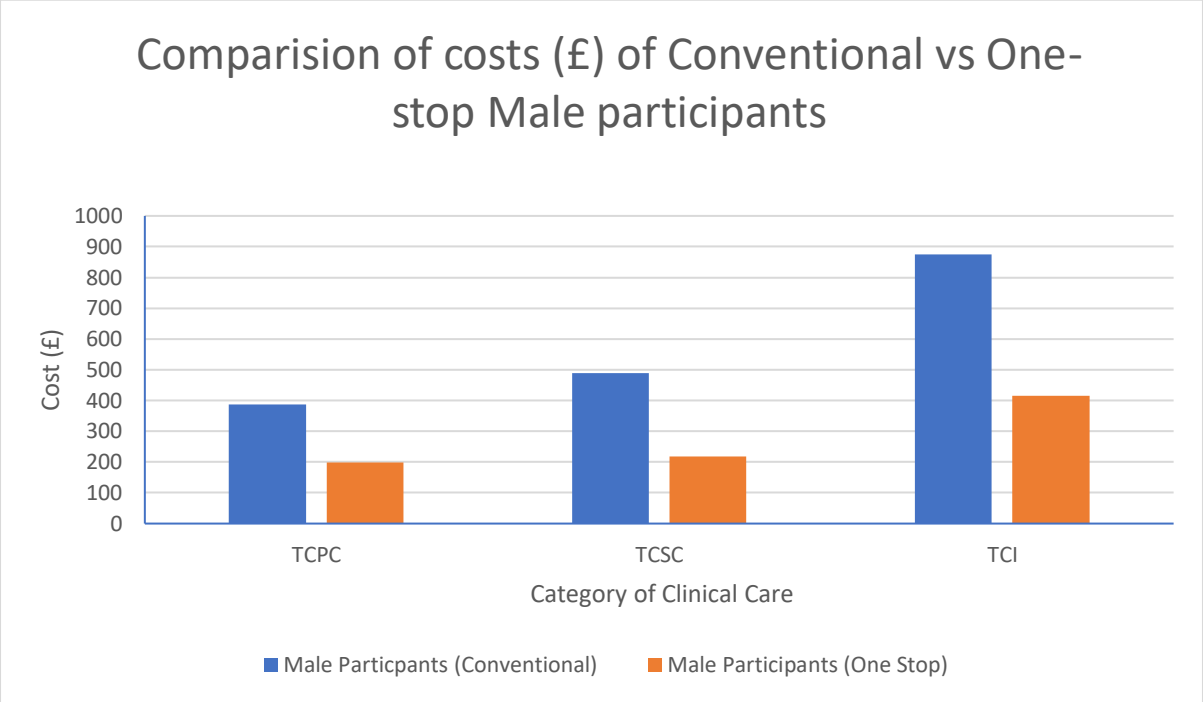
However, in secondary care, the TCSC was reduced by £204.1 but it was not statistically significant with a p value of 0.056 although this was very close to statistical significance of 0.05. On sub-analysis of the pathway, the most significant investigation that was repeated in primary and secondary care were the number of Consultations. Female participants in the Conventional pathway had 2.53 (1.67) Consultations in primary care compared to 1.02 (0.26) in the One-stop pathway, almost double the number of consultations and this was statistically significant with a p value of <0.001.

This pattern was repeated in secondary care with Conventional pathway participants having 3.52 (2.14) consultations compared to the One-stop pathway participants with 1.28 (0.46) consultations. The cost of the extra consultations in PC and SC accounted for the bulk of the difference in the costs of the 2 pathways. The cost of a GP appointment was £166 and the cost of an NHS fertility appointment was £133, which accounts for the bulk of the £195.8 difference in the two pathways of £202.8 in primary care and £204.1 in secondary care respectively.

4.2.4.2. Males Cost – Conventional vs One-stop

The costs of male participants in the Conventional pathway for TCPC, TCSC and TCI were £387.3(298.5), £488.2(289.2) and £875.5(408.6) respectively compared to the One-stop pathway which were £197.6(50.9), £217.9(96.2) and £415.5(115.5) as shown in Table 6. This showed the One-stop pathway reduced costs in PC, SC and TDCC by £189.7, £270.3 and £460.0 respectively with p values of 0.020, <0.001 and <0.001 respectively. This demonstrated that the One-stop pathway reduced the duration and costs for male participants across the whole of their clinical care during the investigative pathway. This is also illustrated in Figure 7.

Figure 7: Comparison of costs (£) of Conventional vs Pathway Male participants.



On sub-analysis of the pathway, the most significant investigation that was repeated in primary and secondary care were the number of Consultations. Male participants in the Conventional pathway had 2.53 (1.70) Consultations in primary care compared to 1.07 (0.26) in the One-stop pathway, almost double the number of consultations and this was statistically significant with a p value of <0.001.

This pattern was repeated in secondary care with Conventional pathway participants having 3.48 (2.04) consultations compared to the One-stop pathway participants with 1.35 (0.63) consultations and was statistically significant with a p value of <0.001. The cost of the extra consultations in PC and SC accounted for the bulk of the difference in the costs if the 2 pathways. The cost of a GP appointment is £166 and the cost of an NHS fertility appointment is £133, which makes for the bulk of the £195.8 difference in the two pathways of £189.7 and £270.3 respectively.

4.2.4.3. Female verses Male Participants

I also compared the cost of investigations of female participants with male participants in the One-stop pathway, this is shown in Table 7. Female participants investigations cost more than male participants at all stages of the pathway. For PC, SC and TDCC the costs for Female participants were £215.2(50.4), £458.9(130.3) and £674.1(117.8) respectively compared to male participants whose costs were £197.6(50.9), £217.9(96.2) and £415.5(115.5) with p values of 0.002, <0.001 and <0.001. These findings were statistically significant.

Table 7. Comparison of Female vs Male Participants in Conventional and One-stop Pathways

Cost of Investigation	**Female**	**Male**	**P value**
Conventional	£ (SD)	£ (SD)	
TCPC	387.3(298.5)	418.0(293.5)	0.027
TCSC	663.0(391.3)	488.2(289.2)	<0.001
TCI	1081.1(516.5)	875.5(408.6)	0.002
One-Stop			
TCPC	215.2(50.4)	197.6 (50.9)	0.002
TCSC	458.9(130.3)	217.9(96.2)	<0.001
TCI	674.1(117.8)	415.5(115.5)	<0.001

QoL:			
Conventional			
Core	67.9(15.6)	75.6(13.2)	<0.001
Emotional	58.1(22.7)	71.7(19.5)	<0.001
Mind/body	65.4(18.1)	76.4(16.5)	<0.001
Relational	80.6(13.8)	78.4(15.4)	0.426
Social	70.3(19.3)	76.2(16.3)	0.037
One-Stop			
Core	63.5(16.2)	65.1(16.3)	0.764
Emotional	53.3(17.9)	58.6(21.6)	0.406
Mind/body	58.8 (23.8)	58.4(21.7)	0.835
Relational	75.9 (13.7)	73.8(14.8	0.763
Social	66.0 (19.4)	69.7(19.4)	0.549

This was a similar finding to comparisons of female and male participants in the conventional pathway and a reflection that it is more expensive to investigate female patients as they require more tests and some of these tests are more expensive as they are more complicated and invasive. This is also illustrated in Table 8 below which shows the average frequencies of consultations in primary and secondary care and the most common investigations performed on participants in the different pathways, showing participants in the conventional pathways had more consultations and investigations compared to participants in the One-stop Pathway.

Table 8. Table of Comparisons of Number of Consultations and Investigations performed in Conventional Pathway versus One-stop Pathway

	Conventional	**One-stop**	**Mann-Whitney U Test p value**
GP Consultation	2.24(1.78)	1.07(0.26)	<0.001
NHS Consultation	3.40(2.14)	1.32(0.54)	<0.001
FBC	0.08(0.32)	0(0)	N/A
U&E	0.01(0.10)	0(0)	N/A

FSH	0.56(0.65)	0.25(0.44)	N/A
LH	0.54(0.63)	0.2(0.44)	N/A
E2	0.43(0.60)	0.21(0.41)	N/A
Semen analysis	0.58(0.70)	0.67(0.81)	N/A
Cystic Fibrosis	0.41(0.20)	0.071(0.26)	N/A
Y-chromosome micro-deletion	0.05(0.22)	0.071(0.26)	N/A
Karyotype	0.05(0.23)	0.071(0.26)	N/A
AMH	0.31(0.48)	0.42(0.50)	N/A
Prolactin	0.40(0.61)	0.32(0.47)	N/A
Testosterone	0.37(0.56)	0.32(0.47)	N/A
TFT	0.31(0.52)	0.32(0.54)	N/A
Progesterone	0.41(0.65)	0.14(0.35)	N/A
Rubella	0.46(0.53)	0.50(0.50)	N/A
HIV, Hep B, Hep C	1.04(0.32)	1(0)	N/A
Chlamydia	0.37(0.51)	0.50(0.50)	N/A
Cervical SMEAR	0.19(0.42)	0.17(0.39)	N/A
Pelvic scan	0.23(0.48)	0.35(0.48)	N/A
HyCoSy	0.12(0.36)	0.17(0.39)	N/A
HSG	0.16(0.36)	0.14(0.35)	N/A
Laparoscopy and Dye	0.05(0.22)	0(0)	N/A
Operative/Diagnostic Laparoscopy	0.04(0.27)	0(0)	N/A
Hysteroscopy	0.005(0.072)	0.71(0.26)	N/A
Female	Conventional	One-stop	
GP Consultations	2.53(1.67)	1.07(0.26)	<0.001
NHS Consultations	3.54(2.14)	1.28(0.46)	<0.001
Male	Conventional	One-stop	
GP Consultations	2.54(1.70)	1.07(0.26)	<0.001

NHS Consultations	3.48(2.04)	1.35(0.63)	<0.001

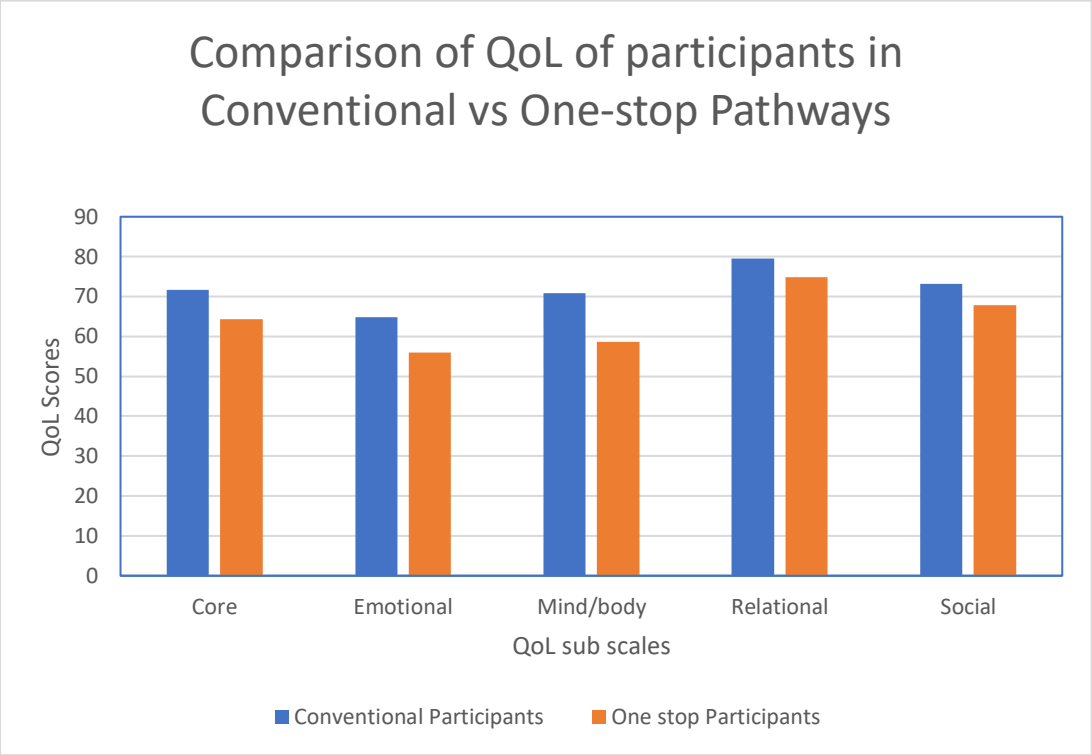
1: Correlation analysis was done using non-parametric Spearman correlation. Findings were considered statistically significant if p value was <0.05.

2: Comparisons of means was analysed using non-parametric Mann-Whitney U Test. Findings were considered statistically significant if the P value of <0.05

4.2.5. Quality of Life (QoL) (Conventional vs One-Stop)

I found that participants going through the Conventional Pathway had a higher mean QoL scores measured by FertiQoL tool for Core, Emotional, Mind/Body, Relational and Social with means of 71.7(14.9), 64.8(22.2), 70.8(18.1), 79.5(14.6) and 73.2(18.1) compared to One-stop pathway participants whose scores were 64.3(16.0), 56.0(19.6), 58.6(22.4), 74.8(14.0), and 67.8(18.9) with p values of 0.008, 0.047, 0.115, <0.001 and 0.145 respectively. These findings were statistically significant for Core, Emotional and Relational sub-scales. The Conventional Pathway FertiQoL mean scores for Mind/body and Social sub-scales were higher than the One-Stop scores, however they were not found to be statistically significant. These results are shown in table 6 above and graphically illustrated in Figure 8 below.

Figure 8: Comparison of QoL of couples in Conventional vs One-stop Pathways



This was an unexpected finding of the study as I expected the QoL to be higher in the One-stop group. I therefore performed a sub-analysis of the QoL of participants based on their sex to further investigate this.

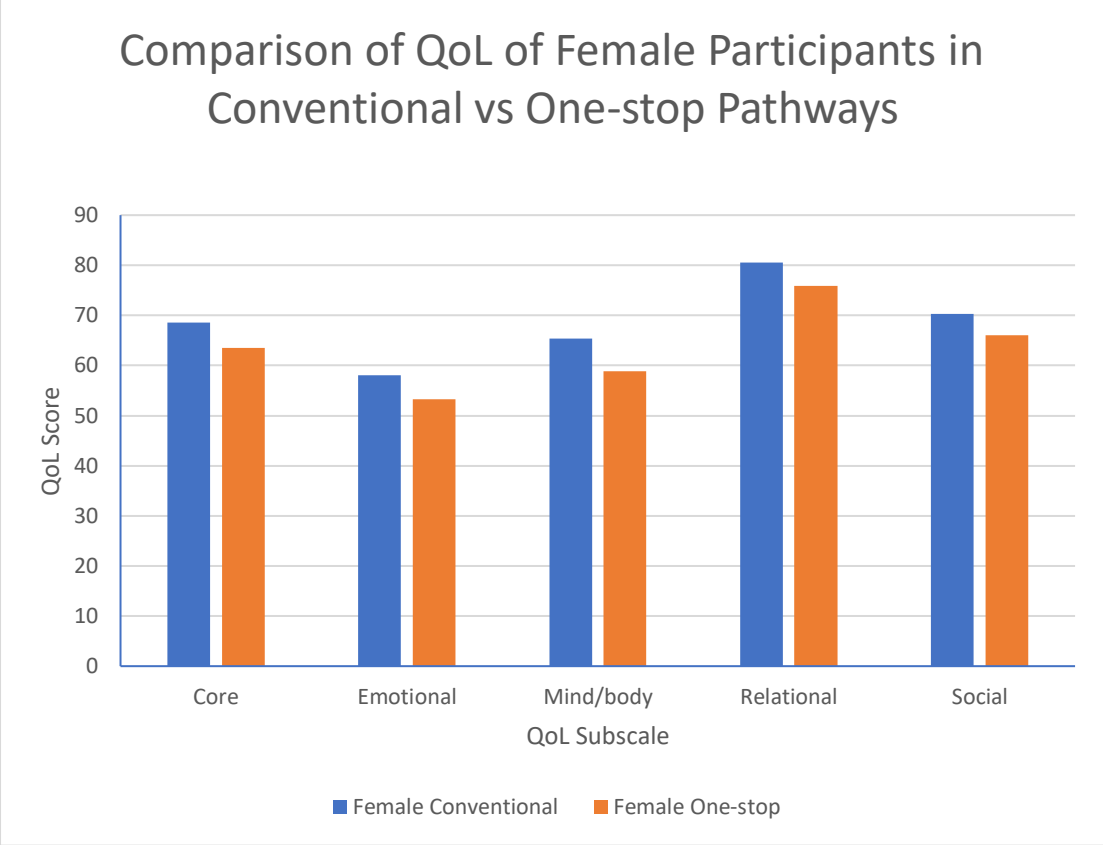
4.2.6. Differences between Female and Male Participants and QoL (Conventional vs the One-stop)

4.2.6.1. Females QoL – Conventional vs One-stop

I found female participants going through the Conventional Pathway had a higher mean QoL score measured by FertiQoL tool for Core, Emotional, Mind/Body, Relational and Social with means of 68.6(14.0), 58.1(22.7), 65.4(18.1), 80.6(13.8) and 70.3(19.3) compared to One-stop pathway participants whose scores were 63.5(16.2), 53.3(22.1), 58.8(23.8), 75.9(13.8) and 66.0(19.4) with p values of 0.215, 0.450, 0.221, 0.234 and 0.439 respectively. All of these

findings were found not to be statistically significant for all the QoL sub-scales. This is shown in table 6 and also graphically in Figure 9.

Figure 9: Comparison of Female QoL in Conventional vs One-stop Pathways



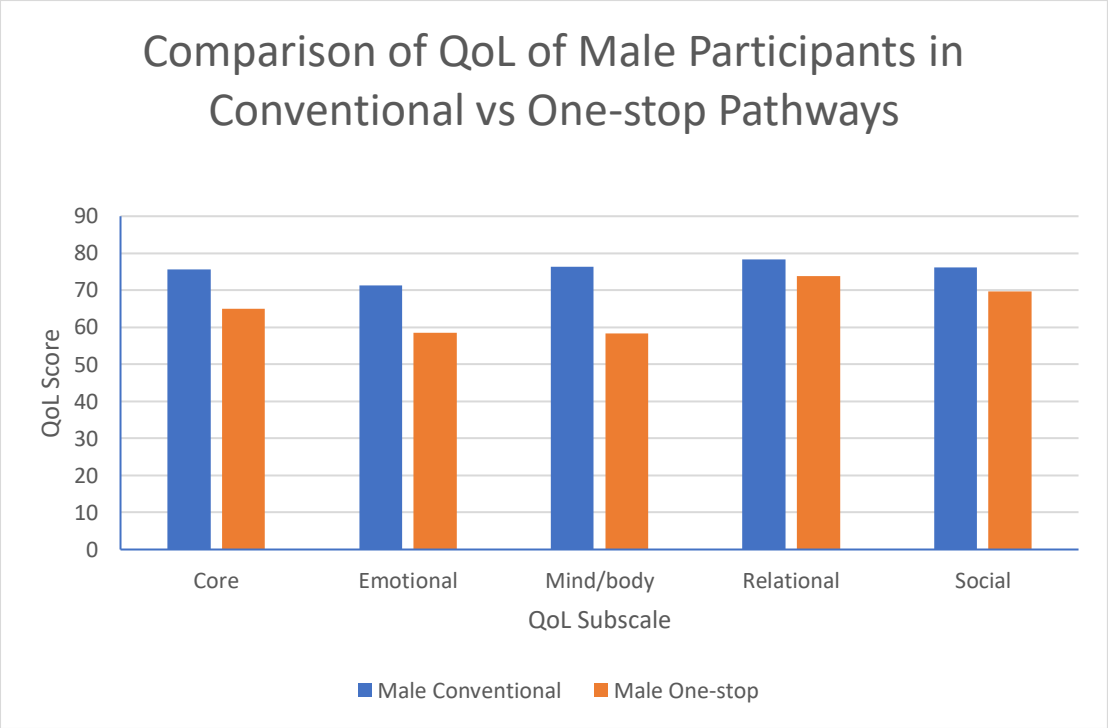
However, the QoL mean subscale scores for Emotional and Mind/body for One-stop participants, 53.3 and 58.8 respectively, were at a level where patients would exhibit signs of clinical anxiety and more concerning, the One-stop females mean Emotional sub-scale score of 53.3 was close to a level expected to demonstrate clinical depression which is below 53.1 on the FertiQoL score. A Dutch validation Study by Aarts et al, comparing FertiQoL scores and patients Hospital Anxiety and Depression Scale (HADS) have found patients exhibited clinical anxiety with a FertiQoL score of less than 58.8 and exhibited clinical depression with a FertiQoL score of less than 51.9 and also showed the link and relationship between infertility and the clinical conditions of anxiety and depression (24). These findings highlight the

importance health professionals and stakeholders to offer patients psychological and emotional support early in the investigative process and not only when ART treatment commences in tertiary care as is the common practice in most fertility services.

4.2.6.2. Males QoL – Conventional vs One-stop

On analysis I found, male participants going through the Conventional Pathway had a higher mean QoL score measured by FertiQoL tool for Core, Emotional, Mind &Body Relational and social with means of 75.6(13.2), 71.4(19.5), 76.4(16.5), 78.4(15.4) and 76.2(16.3) respectively compared to the One-stop pathway participants with scores of 65.1(16.3), 58.6(21.6), 58.4(21.7), 73.8(14.8) and 69.7(19.0) in these sub-scales. with p-values of 0.007, 0.023, <0.001, 0.299 and 0.172 respectively. These findings were statistically significant for Core, Emotional and Mind/body sub-scales but not for Relational and Social. This is illustrated in Table 6 and graphically in figure 10.

Figure 10: Comparison of Male QoL in Conventional vs One-stop Pathways

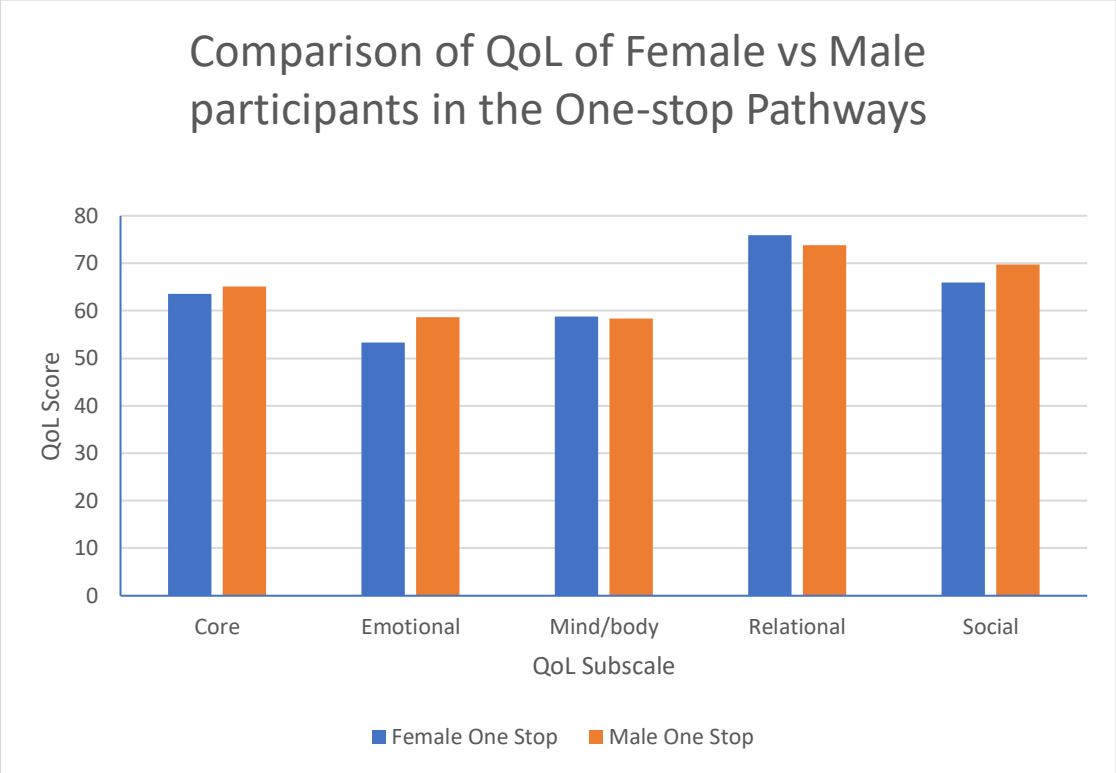


This was a further unexpected finding as the participants in the Conventional pathway exhibited a higher QoL compared to participants in the One-stop pathway and this finding was statistically significant in 3 of the QoL subscales. Also, significantly, the male QoL scores in the One-stop pathway for Emotional and Mind/body were 58.6 and 58.4 which were at a level an individual would be expected to exhibit clinical anxiety and these findings were statistically significant with p values of 0.023 and <0.001 respectively. This would indicate male patients may also exhibit clinical anxiety as they are investigated for infertility and should also have professional counselling offered to provide emotional support that they may need similar to female participants going through fertility investigation and treatment.

4.2.7. Females versus Males QoL in the One-stop pathway

Female participants had lower FertiQoL scores Core, Emotional, Mind &Body and social with means of 63.5(16.2), 53.3(22.1), 58.8(23.8), 75.9(13.7) and 66.0(19.4) respectively compared to male participants with scores of 65.1(16.3), 58.6(21.6), 58.4(21.7), 73.8(14.8) and 69.7(19.0) in these sub-scales. with p-values of 0.764, 0.406, 0.835, 0.763 and 0.549 respectively. These findings were not statistically significant for any of the subscales. These findings are illustrated in Table 7 and also graphically in figure 11.

Figure 11: Comparison of QoL of Female vs Male participants in the One-stop Pathways



It was only the Relational subscale where females in the One-stop pathway had a higher QoL, 75.9 (13.7) compared to male participants who had a mean QoL was 73.8(14.8). This was also replicated in female participants in the Conventional pathway. This could indicate that female felt more secure in their relationship with their partner and felt well supported by their partners. The Male Relational subscale was consistently lower than the females, perhaps indicating that male participants felt less secure in their Relationship and it affected their sexual relationship more than females. Male partners may feel more pressure and fault in the relationship in not able to achieve a desired pregnancy. However, with a p values of 0.426 and 0.763 in the conventional and one-stop groups respectively, this finding was not statistically significant.

4.3. Discussion

Hrehorcak and Nargund (2011) described the One-Stop Fertility Clinic as a comprehensive and quick outpatient service that enables assessment of the reproductive health of both the female and male partners during a single visit(41). One-Stop clinics have been shown to reduce time

spent during the investigative pathway, number repeat visits and investigations and lead to cost savings in other fields of medicine and been very well received and strongly positively rated by patients using these services such as Post-menopausal bleeding One-stop clinics. (41-44).

Prior to designing the One-stop clinic I set up for this study, I studied the pathways other private Fertility clinics, mainly based in the London area, which offered One-stop Fertility pathways commercially, to see how they had incorporated the concept into their private practice. These One-stop clinics which were already available in the private sector did not offer an identical standardized service, but based their approach on the skills on the staff available and other logistical restraints like availability of scans rooms. This clinic specific modelling of the one-stop service dependent on the skills available has also been noted by Magos et al (2005)(42). Although the One-stop clinics were different in design, they followed the same common concept which is to try and complete as many investigations as possible in as few clinic visits as possible. The implementation of the one-stop clinic is based on the skills available from the staff and clinical presentation of the patients. (41, 42)

I designed a one-stop fertility clinic at Oxford for the purpose of this study in collaboration with a few of the referring GP practices, after reviewing the current "conventional" pathway offered to patients, reviewing the current resources available and looking at ways to perform as many investigations as possible in as few visits as possible. The One-stop Fertility pathway I designed, aimed to perform the same of investigations patients would have in the conventional pathway, but only have 1 GP appointment and 1 NHS Fertility Specialist appointment. This was done by engaging receptive local GPs' and advising that when a couple first present to their General Practice, the GP perform the baseline investigations including early luteal FSH, LH, prolactin, testosterone, TFT's, chlamydia screen, rubella serology if indicated, check cervical SMEAR is up-to-date and arrange for a mid-luteal progesterone to check for ovulation and then immediately refer them to the One-stop clinic.

At the One-stop clinic that I set-up at Oxford Fertility, the male partner has a semen analysis (SA) and on the same day as their Initial Consultation in Secondary Care, if the SA was normal or had a Total Motility Sperm Count (TMSC) of 2 million, his partner would then have a HyCoSy scan to check for tubal patency. At the same appointment, they would then be reviewed by a Fertility Consultant/Specialist with all their results and a diagnosis and management plan agreed during the same clinic visit.

The average duration from when they presented in the one-stop clinic to when they completed their consultation was 105mins. This was 60 mins longer than the usual conventional Initial Consultation in secondary care; however, it was shorter than the time they would have spent on individual separate appointments for each appointment to have investigations and then a follow-up to discuss the results. It also meant only one secondary care visit to the Fertility clinic instead of taking several visits to have all the investigations completed. In addition, if the couple was found to have been trying to conceive for more than 2 years, they could then be directly referred for ART, if eligible at the same appointment without need for further appointments.

Figure 1, in the methodology Chapter 2 shows a pictorial flow-chart representation of the 2 investigative pathways.

During the study, due to the slow pace of recruitment, we expanded the study to have a second recruitment centre at Create Fertility at St Paul's in London which also offered ART services to NHS patients to a number of patients. I recruited patients with the same criteria and process as at the initial research site of Oxford Fertility.

At Watford General Hospital, one of the hospitals that referred patients for ART treatment to Create Fertility in London, according to their protocol, the One-stop clinic patients did not have their early follicular FSH/LH and E2 bloods for ovarian reserve and instead only a serum Anti-Mullerian Hormone (AMH). This made it easier for Fertility Nurses to run the service and removed the need for timed blood tests. Mid-luteal progesterone was also omitted if patients had regular periods.

4.4.Cost Savings of One-stop Clinic:

From a Freedom of Information (FOI) request from Oxfordshire CCG, in the 2016 – 2017 business year, the Oxford Fertility Unit saw 746 new couple referrals (1,492 individuals). In the same 2016-17 business year, Oxford CCG funded 110 ART cycles. With further information obtained from the FOI request from Oxfordshire CCG, the average cost of an NHS funded ART cycle was £3500. Therefore, in that year Oxford CCG paid approximately £385,000 to fund approximately 110 ART cycles for eligible couples.

In this study, I demonstrated that the One-stop pathway cost £435.1 less than the Conventional pathway (£544.8 vs £979.9) per participant and this was statistically significant with a p value

of <0.001. Female and male participants in the conventional pathway average cost of investigation were £1081.1 and £875.5 respectively verses Female and male in the One-stop pathway £674.1 and £415.5 respectively. The average total cost to the NHS for a couple in the conventional pathway was £1956.6 compared to £1089.6 in the One-stop pathway. This would imply a savings of £867.0 per couple going through the One-stop pathway.

However, female and male participants attended the same GP and NHS Consultations but in calculating average female and male costs, both participants had the cost of the same appointment added to their total and therefore this calculation would "double" bill the NHS for the same single appointment attended by 2 participants at the same time and make the savings appear larger than they actually are.

Therefore, to calculate a more accurate cost per couple, I first removed the cost of the average number of GP and NHS appointments in each pathway from the cost per participant to get the cost of the specialist investigations only per participant by sex. I then added cost of investigations of the two-sexes to give the average cost of investigations per couple. I then finally added the average cost of GP and NHS appointments per pathway to give a cost per couple in the Conventional and One-stop pathways. The cost per couple in the Conventional pathway was £1185.76 compared to the cost per couple in the One-stop pathway which was £736.42. Therefore, the One-stop pathway led to an average savings of £449.34 per couple investigated through the NHS.

Extrapolating this savings to the 1,492 new referrals to Oxford Fertility each year, the estimated savings would be £670,415.28. This savings would exceed the £385,000 that the Oxfordshire CCG currently spends on ART. These savings could be ring-fenced to maintain or even fund extra ART cycles in Oxfordshire for the local population.

4.5.Quality of Life (QoL) Discussion

In this study, I found that participants going through the Conventional Pathway had a higher mean QoL score measured by FertiQoL tool for the sub-scales of Core, Emotional and Relational with means of 71.7, 64.8 and 79.5 compared to the One-stop participants with scores of 64.3, 56.0 and 58.6 with p values of 0.008, 0.047 and <0.001 respectively, which were statistically significant findings.

The Conventional Pathway FertiQoL mean scores for Mind/body and Social sub-scale were also found to be higher with scores of 70.8 and 73.2 compared to the One-stop participants mean scores of 58.6 and 67.8 respectively. However, none of these findings were not found to be statistically significant with p-values of 0.093 and 0.153 respectively.

These finding were unexpected as previous studies, such as Karabulut et al (2013) have shown that prolonged duration of infertility have a negative effect on QoL(25). One-stop participants had a mean shorter duration of investigation 207.1 days compared to conventional pathways whose mean was 634.0 days, my findings would indicate that a shorter duration does not necessarily mean participants would have a better QoL. This pattern was also seen in the correlation analysis of QoL against Duration in the Conventional pathway with no improvement in QoL seen with a shorter duration of investigation.

The negative effect of shorter duration on QoL that I found may represent the participants had increased anxiety at going quickly through the investigative pathway. They may be overwhelmed with the clinical involvement in their care and not had time to fully settle and cope with their new diagnosis and treatment. The One-stop pathway may bring on its own distress and anxiety as patients go through a new environment at a faster pace than the conventional pathway. It may signify the need for earlier psychological support of couples going through the investigative pathway in line with the clinical support provided by the doctors and nurses seen by the couple. This was also shown in my sub-analysis by sex female QoL in the One-stop group for Emotional and Mind/body subscales was 53.3(22.1) and 58.8(23.8) indicating clinical anxiety with the Emotional subscale approaching the level of clinical depression. The male scores for the same subscales were 58.6(21.6) and 58.4(21.7) which were again indicating levels of clinical anxiety.

NICE, The European Society of Human Reproduction and Embryology (ESHRE) and other independent studies have shown and advocated that specialist counselling and support during investigation and treatment of infertility helps couples deal with stress better and lead to improvement the QoL (1, 45).

Participants who take longer having their investigations undertaken perhaps have more time to be able to adjust and receive alternative support from each other, family and friends to help them through this process.

4.6.Kübler-Ross Change Curve® Model of Grief pattern seen in QoL

I also considered the Kübler-Ross Change Curve® Grief model to explain my findings. Many individuals consider the initial feelings of having difficulty trying to conceive and later diagnosis of infertility as a form of "loss" and Isla et al (2008) described the same model applying to the alignment of patients adapting to the new diagnosis in chronic disease such as in Diabetes. Their dealing with a new disease has been compared to going through a "Loss" and a grieving process(39). The Kübler-Ross Change Curve® has a Wave pattern with time and QoL as depicted in Appendix 3 in the appendix. And moral (QoL) peaks and troughs as time proceeds.

This model prescribes that there are 5 stages humans go through when they encounter a loss, and they are:

1: Denial

2: Anger

3: Bargaining

4: Depression

5: Acceptance

Individuals do not necessarily go through all 5 stages at the same pace or even through all the stages. Although the Kübler-Ross Change Curve® model was initially studied and modelled with patients going through grief with terminal illness, the same pattern has been shown to occur when patients have been informed of a new diagnosis of a disease such as diabetes(39), or as in this studies case, coping with the new diagnosis of infertility.

Though unexpected, the. results appear to show this pattern when looking at the subscales of the QoL affected with a shorter duration i.e., the Emotional and Mind/body subscales of QoL were more affected and exhibiting levels of anxiety, compared to the Core, Relational and Social. This could reflect organic support with couples finding support in their own relationship and from social, family and professional network. However, their Emotional wellbeing is under more pressure, and they feel at loss of control of their plans (mind/body) and only regain this later during their journey/pathway as they start to accept (their new reality of infertility) with Acceptance the final stage in Kübler-Ross Change Curve® pathway which also has patients

with higher morale and QoL. This is also demonstrated in the Kübler-Ross Change Curve® of patient Morale versus Time (duration) in Appendix 3.

This indicates that clinicians and support staff should look-out for signs of anxiety and depression early in the investigative process of infertility and offer counselling and support early, especially to female patients whose QoL scores are lower than male patients and bordering on depression levels.

4.7.Limitations and recommendations for future work

I had hypothesised at the start of the study that a shorter duration of investigation would lead to an improvement in the QoL of participants as suggested in previous studies. However, this study found no correlation between duration and QoL. This could be due to the sample size of this study. However, my study's results could be used to make a power-calculation, to determine an appropriate sample size for future Fertility studies that aim to explore the relationship of duration on QoL based averages of both the Conventional and One-stop pathway participants and the standard deviations found in my study. Hopefully a larger sample size may reveal more information and a better understanding on the relationship between duration of investigation and QoL of fertility patients.

The results of the QoL in this study may only represent the state of well-being of the participants at the point they were recruited and filled in the Questionnaire. In my study, the QoL of participants was also only measured when they were referred for ART treatment. However, it may have been more informative to have measured the QoL at different stages of the pathways such as:

a) When the patients first see their GP.
b) When they are first seen by a Fertility Specialist.
c) When they are referred for ART, and:
d) After they have completed their first ART treatment.

This would be a longer and more complex follow-up study to plan, but would give more insight into the QoL of patients through their investigative and treatment pathway. QoL is not a static measure in participants, it changes depending on the environment, both within the patient and

around the patient. A dynamic study would help understand this complex relationship in the field of fertility.

Some couples conceive spontaneously during the time they are waiting to start ART treatment. These pregnancies would save the NHS money and could be an advantage to a longer duration of investigation before the start of ART. Future studies can be designed to collect data on couples who conceive while waiting to start ART. This can be assessed alongside the saving from One-stop clinics to get a more complete NHS Health Economics assessment of duration from when patients first present with problems conceiving to the start of their ART treatment.

4.8.Conclusion

The "One-stop" Fertility pathway in this study has been shown to reduce the duration of investigation of participants (TDCC) by an approximate mean of 426.9 days. This has been shown to be statistically significant with a p value of 0.016. In addition, the One-stop pathway has been shown to reduce the Total cost of investigations (TCI) of participants by an approximate mean of £435.1 and this was also statistically significant with a p value of <0.001. The savings in duration and cost was mainly due to reduction in consultations, but also some contribution by decreasing the repetition of some clinical investigations.

However, in this study, the One-stop clinic pathway has been shown to have a lower QoL for participants compared to those going through the Conventional pathway. This was an unexpected and complex finding as it was assumed that QoL of participants would be improved by a faster more efficient cost saving pathway. The Kübler-Ross Change Curve® of Grief may explain this finding as couples whose investigative process has been shortened have not had the time to fully adjust emotionally and psychologically to their new clinical circumstance and a longer duration may have allowed them to adjust and cope better and this may have led to a better QoL. However, this is a complex finding and more studies are needed to be undertaken to fully investigate the relationship of duration and QoL.

Sub-analysis of QoL showed that female participants had a lower QoL compared to male participants in both pathways. Female participants in the Conventional pathway had a lower Emotional and Mind/body subscale mean of 53.3(22.1) and 58.8(23.8) compared to male participants with 58.6(21.6) and 58.4(21.7). Both female and male participants had average scores were similar to patients expected to exhibit signs of anxiety reflecting the stress that.

Infertility and infertility investigations place of patients and the need for Fertility Treatment. Services to offer early psychological and emotional support. Female participants Emotional subscale score of 53.3(22.1) was close to the level experienced with patients with clinical depression and this finding should prompt planning for more tailored support for females going through fertility investigation and treatment.

5. Chapter 5: Results of High Multiple Pregnancy (HMP) study and possible influence of ART treatment in the UK and Overseas at the John Radcliffe Hospital, Oxford between 2010-2017:

5.1. Hypothesis on possible influence of ART treatment in the UK and overseas on High Multiple Pregnancy (HMP) in the UK.

This study proposes that the number of High Multiple Pregnancies (HMP) increased during the 7-year study period and this increase may be related to more women seeking ART treatment overseas. The study also aimed to show that these HMP pregnancies were leading to a significant cost to the NHS that was much greater than any savings hoped to be realised by decreasing funding for NHS ART funded cycles thus making a case for "ring fencing" possible savings from one-stop clinics to be used to maintain or even further increase NHS funded ART cycles.

Below are the results from this study.

5.1.1. Maternal Demographics and Summary of Maternal results

Patient Demographics

There were 10 hospitals that referred patients with HMPs for all or part of their care at The John Radcliffe Hospital. A total of 42 patients were seen during the study period. 15 (35%) were originally from Oxford, 11 (26%) from Swindon, 6 (14%) from Reading, 4 (9.25%) from Northampton and then Aylesbury, Milton Keynes, Windsor, Coventry, Birmingham, Peterborough and Nottingham all referred 1 (2.25%) patient each. This information is displayed in Table 9.

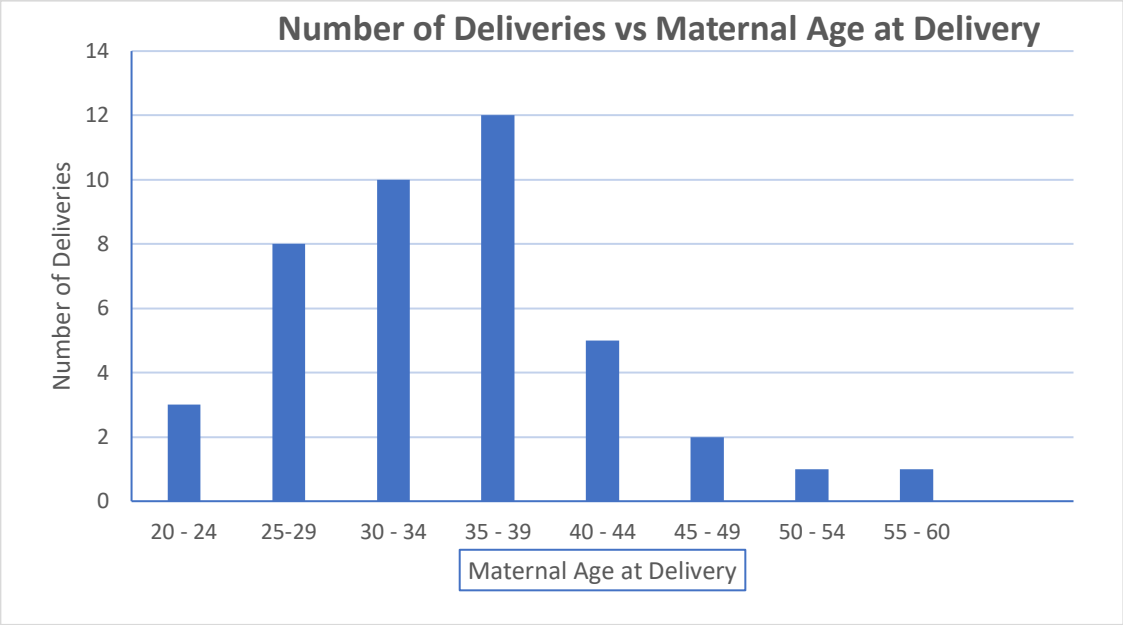
Table 9: Table of Patients Local Referral Area.

Patient Referral Local Area:	**Numbers**	**Percentage**
Oxford	15	35%
Swindon	11	26%
Reading	6	14%
Northampton	4	9.25%
Aylesbury	1	2.25%
Milton Keynes	1	2.25%
Windsor	1	2.25%
Coventry	1	2.25%
Birmingham	1	2.25%
Peterborough	1	2.25%
Nottingham	1	2.25%
Total	**42**	**100%**

5.1.2. Age at Delivery

The average age of the patients was 34.44 years (7.55), with the youngest patient 20 years old and the oldest patient 59 years. The age distribution is depicted in the Figure 12 and in Table 15. The average age of patients who delivered at Oxford was 35.11 (7.30) and the average age of patients who delivered at their original referral hospitals, or other hospitals, was 33.31 (7.82). There was no statistical difference in the patients' average age.

Figure 12. Graph depicting Maternal Age at Date of Delivery.



5.1.3. Method of Conception.

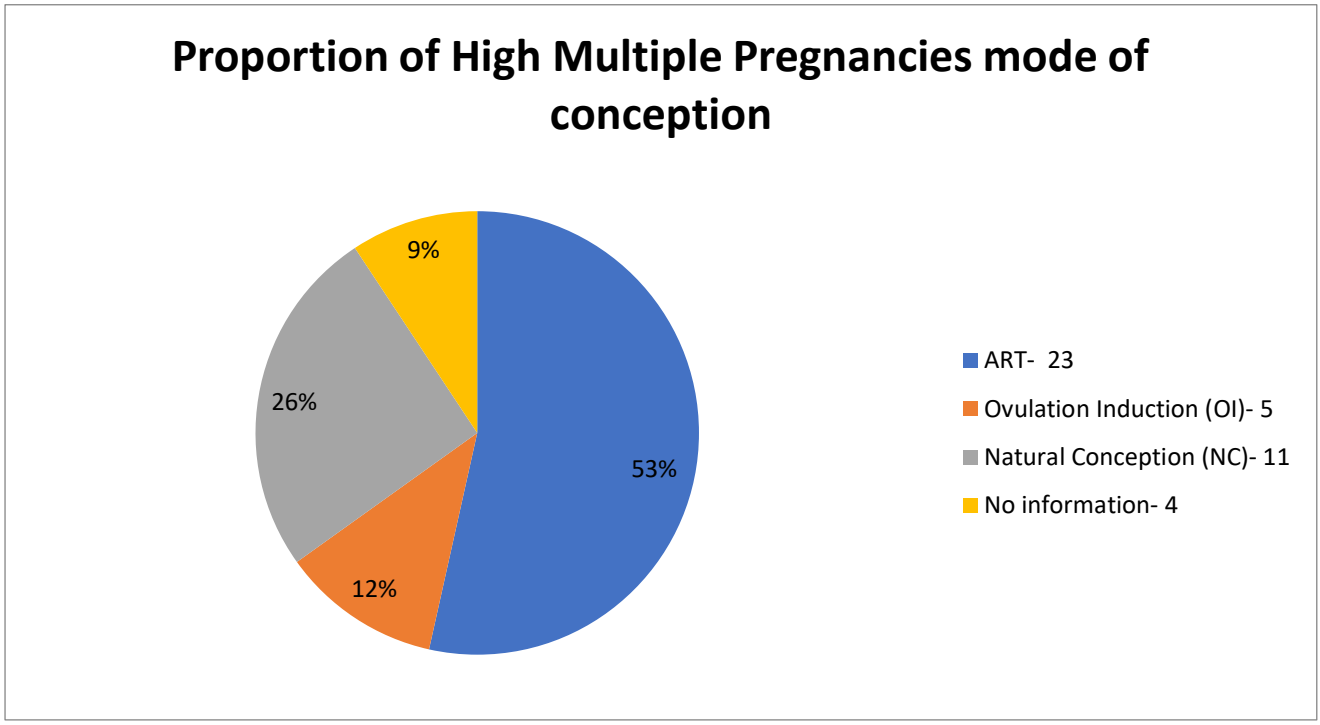
The method of conceptions of these pregnancies and percentages, are displayed in Table 10, while Graph 2 shows the percentages contributions. ART accounted for 23 (53%) of all the high multiple births. There were 11(26%) pregnancies that were naturally conceived and 5 (12%) conceived by ovulation induction. There were a further 4 (9%) pregnancies where there was no information available as to mode of conception, these pregnancies could have been conceived via ART, naturally or by OI, however there is no information currently collected to correctly identify the method of conception.

Table 10: Table of Method of Conception: Total 43 Pregnancies.

Method of Conception	Number	Percentage
ART (IVF/ICSI)	23	53%
Ovulation Induction	5	12%

Natural Conception	11	26%
Unknown	4	9%

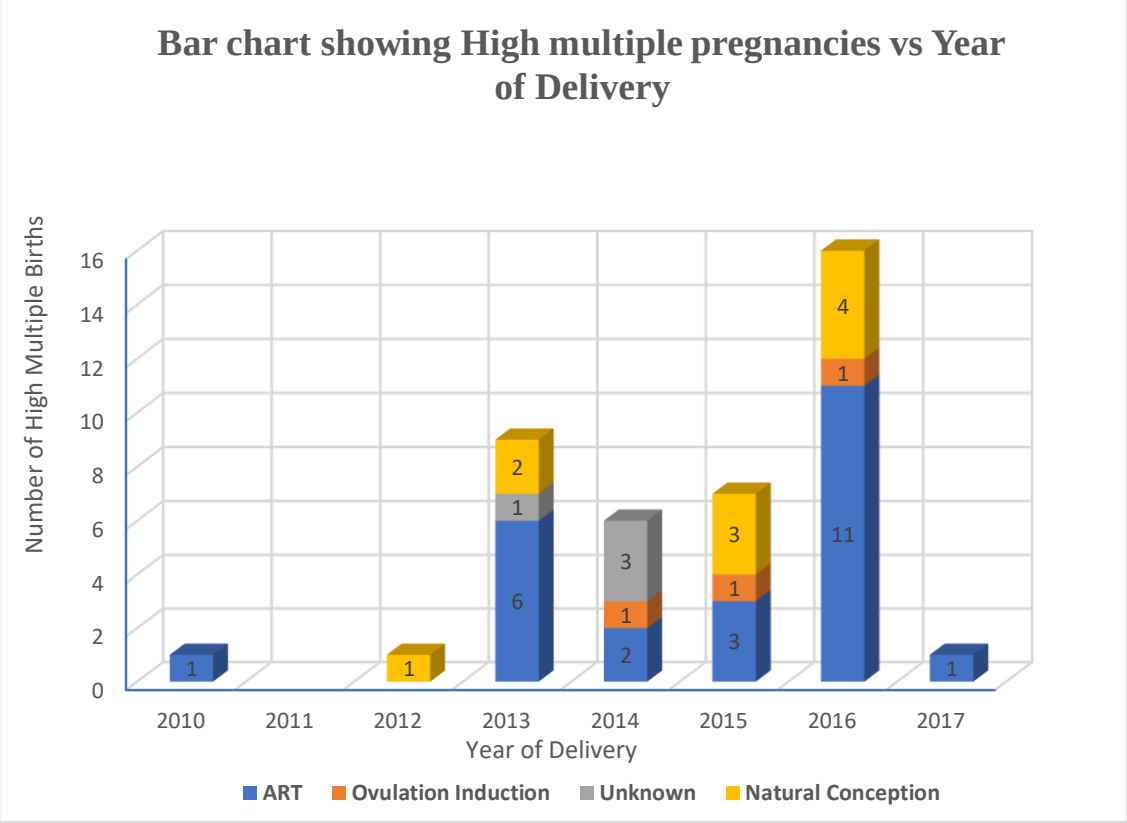
Graph 2: Graph showing Distributions of Different Mode of Conceptions of HMP.



5.1.4. Frequency of High Multiple Births Per Year at the John Radcliffe Hospital.

The Number and frequency of High multiple births per year at the John Radcliffe Hospital is illustrated in Figure 14. This is further illustrated in the Figure 23 of the number of multiple births as well as the proportion that the different mode of conceptions accounted for per year. This shows a trend of increasing number of high multiple pregnancies conceived from 2010 to 2017. In 2010-2012, there were a total of 2 HMPs, in 2013-2015 there were a total of 22 HMPs and in 2016-2017, there were a total of 17 HMPs, all reflective of this trend.

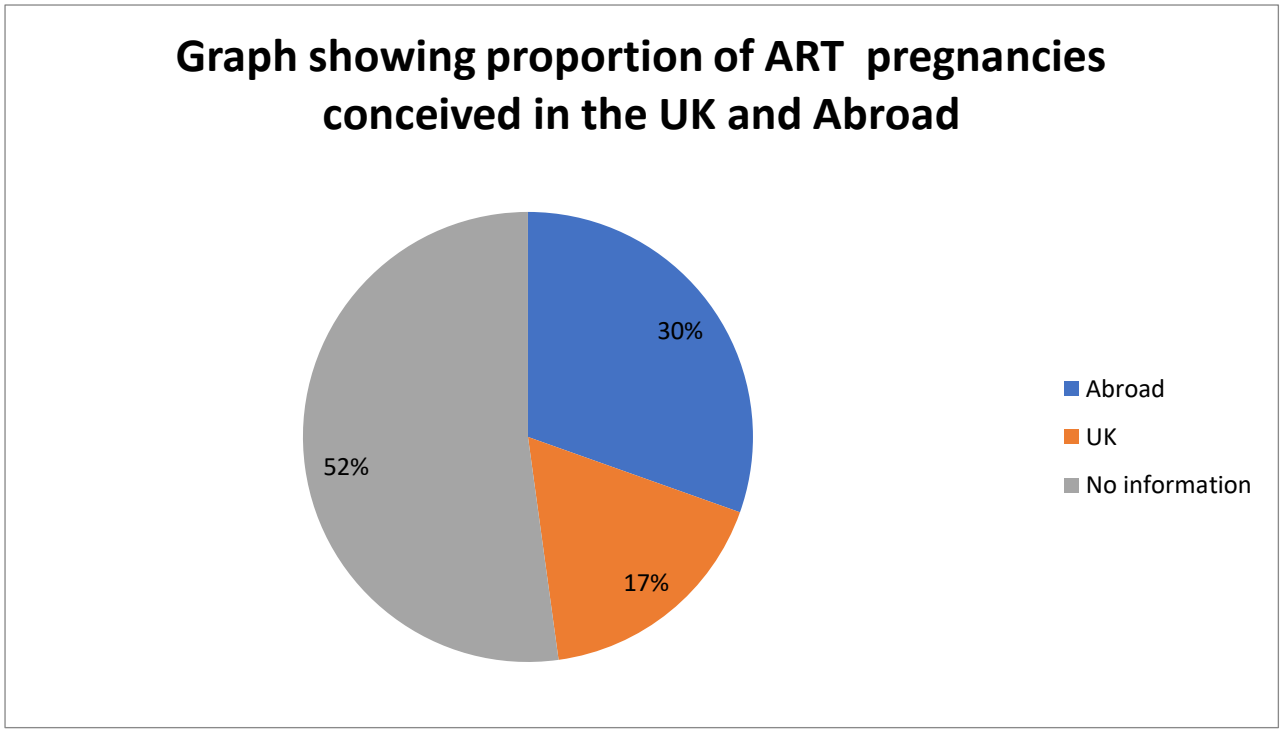
Figure 14: Graph Showing Year of Delivery vs Type of Conception of High Multiple Pregnancy (HMP).



5.1.5. Location (UK or Overseas) of ART treatment.

Some of the patients had their ART treatment in the UK and others had it overseas. There were some patients who there was no data as to the location of their ART treatment, this data is recorded as unknown. Seven (7) patients (30%) of patients had their ART overseas and four (4) patients (17%) had their ART in the UK. For 10 patients (43%), there is no information identifying the location of their ART treatment. Figure 15 shows the distribution of location the pregnancies were conceived.

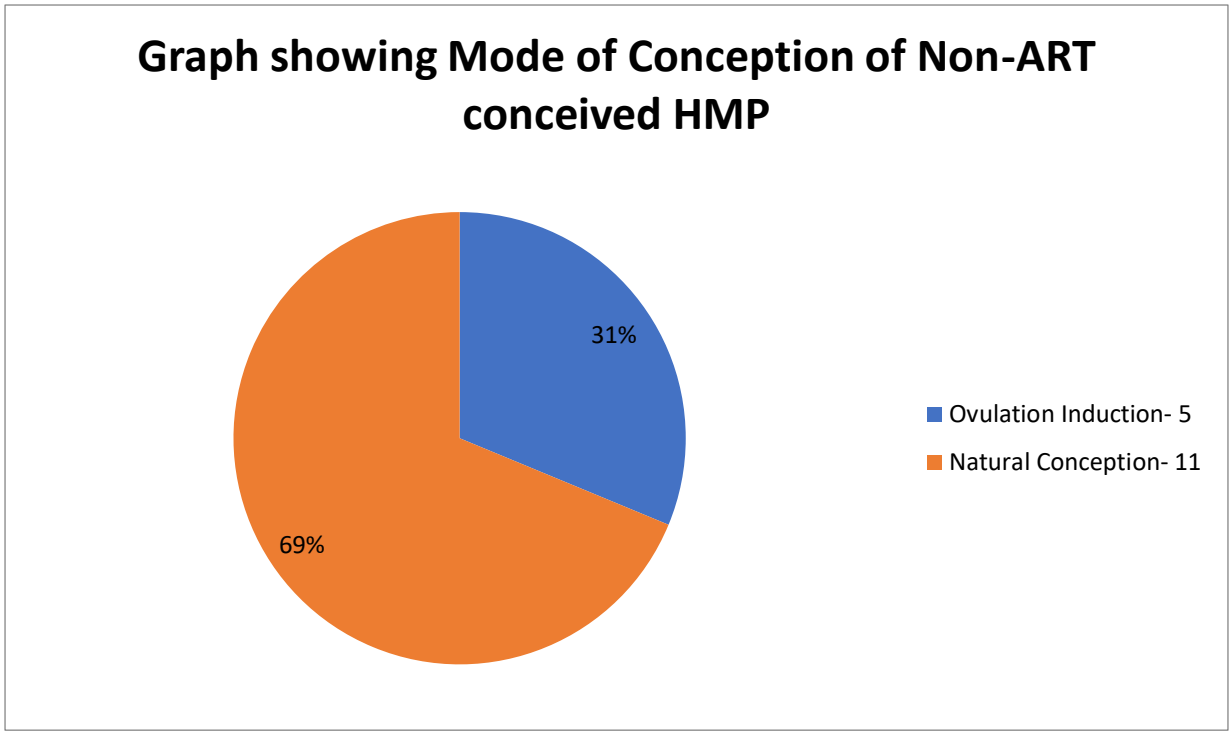
Figure 15: Graph showing percentage and location of ART treatment of HMP.



5.1.6. Non-ART conceived High Multiple Pregnancies (HMP).

There were 16 Non- ART conceived pregnancies that we had information of and this account for 37% of all the HMPs in this study. Of these pregnancies, eleven (11) women (69%) pregnancies were naturally conceived, and five (5) women (31%) conceived following the ovulation induction (OI). This is illustrated in Figure 16. However, this also illustrates the impact non-ART treatment can have on HMPs as Ovulation Induction accounts for 12% of these pregnancies and is performed at different levels of care including NHS, private and tertiary fertility clinics.

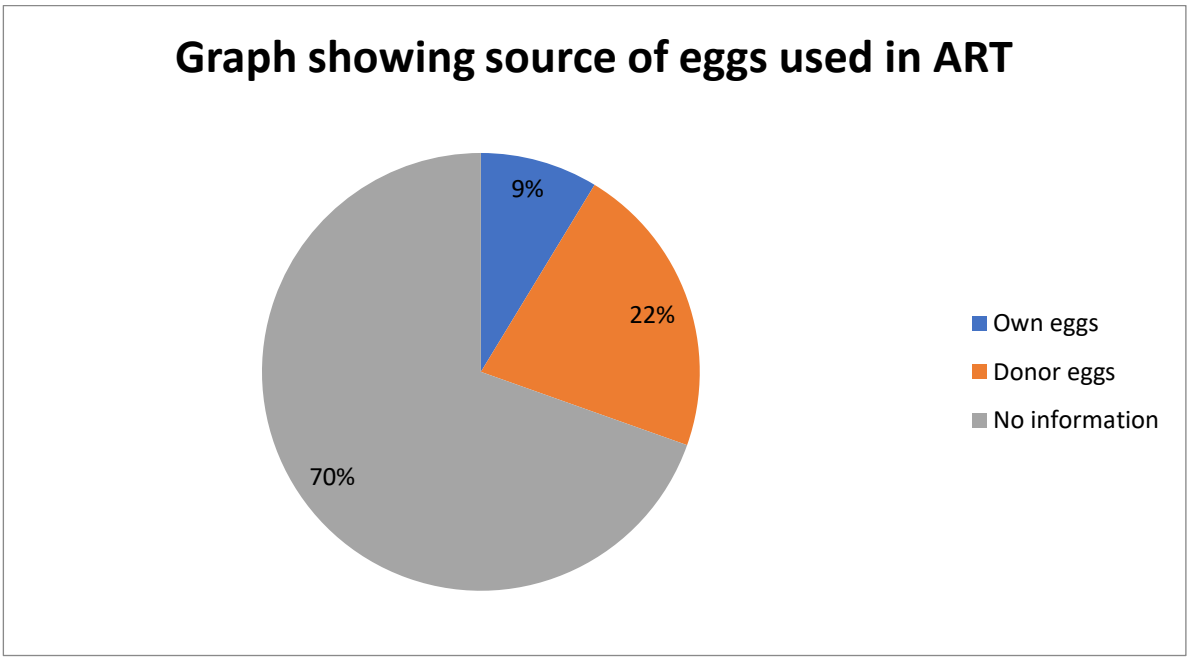
Figure 16: Graph showing Mode of Conception of Non-ART conceived HMP.



5.1.7. ART with use of Own or Donor Eggs.

Information as to whether conception was with their own eggs (autologous oocytes) or donor eggs (donor oocytes) was also recorded in some cases and is displayed in Figure 17. Craft et al (2005) had noted due to the UK anonymity laws, there was a shortage of egg donors in the UK causing waiting lists ranging from 1 to 2 years for treatment and this could influence patients to seek treatment overseas where waiting lists may be shorter. (46)

Figure 17: Graph showing whether autologous or donor eggs used in ART.



Sixteen (16) patients (70%) either having IVF in the UK or overseas had no information as to whether autologous gametes or donor gametes were used, only 7 patients (30%) had information on the type of oocytes used. This is displayed in Figure 17.

Table 11: Table of Location of ART Treatment and type of Oocytes Used.

Country of ART	Number (%)	Own Eggs (%)	Donor Eggs (%)	Egg source unknown (%)
UK	4 (17%)	1 (25%)	0 (0%)	3 (75%)
Overseas	7 (30%)	0 (0%)	2 (29%)	5 (71%)
Unknown	12(43%)	1 (8%)	3 (25%)	8 (67%)

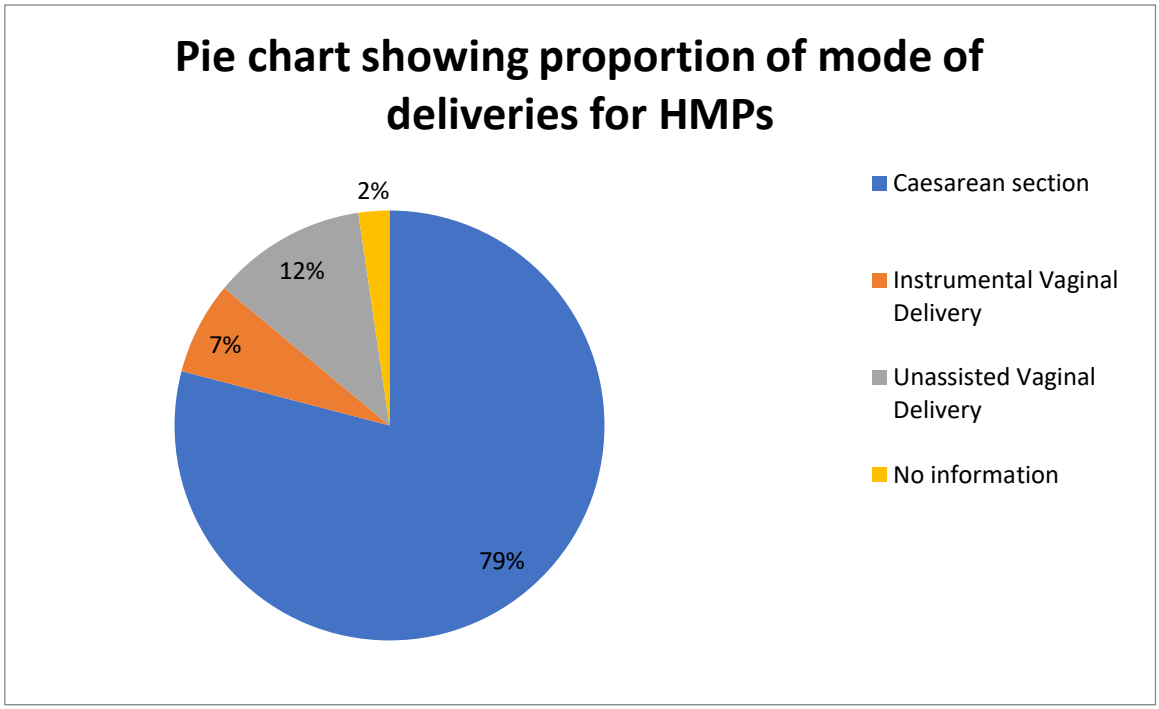
5.1.8. Method of Delivery

Of the 43 patients who had an HMP, for the mode of delivery, 34 (79%) had a Caesarean section, 3 (7%) had an operative vaginal delivery (instrumental delivery), 5 (12%) had a vaginal delivery and 1 (2%) patient the method of delivery was unknown. A summary of the mode of delivery of the 43 patients is illustrated in Table 12 and as percentages in Figure 18. There was only information on 42 patients as one patient came from Peterborough and returned to her locality for delivery and no further information was available. It shows 79% of the deliveries were by Caesarean Section (2)

Table 12 Table of Method of Delivery.

Type of Delivery	Number (%)
Caesarean Section	34 (79%)
Operative Vaginal Delivery	3(7%)
Vaginal Delivery	5 (12%)
Unknown	1 (2%)

Figure 18: Chart Illustrating Mode of Delivery for the HMP.

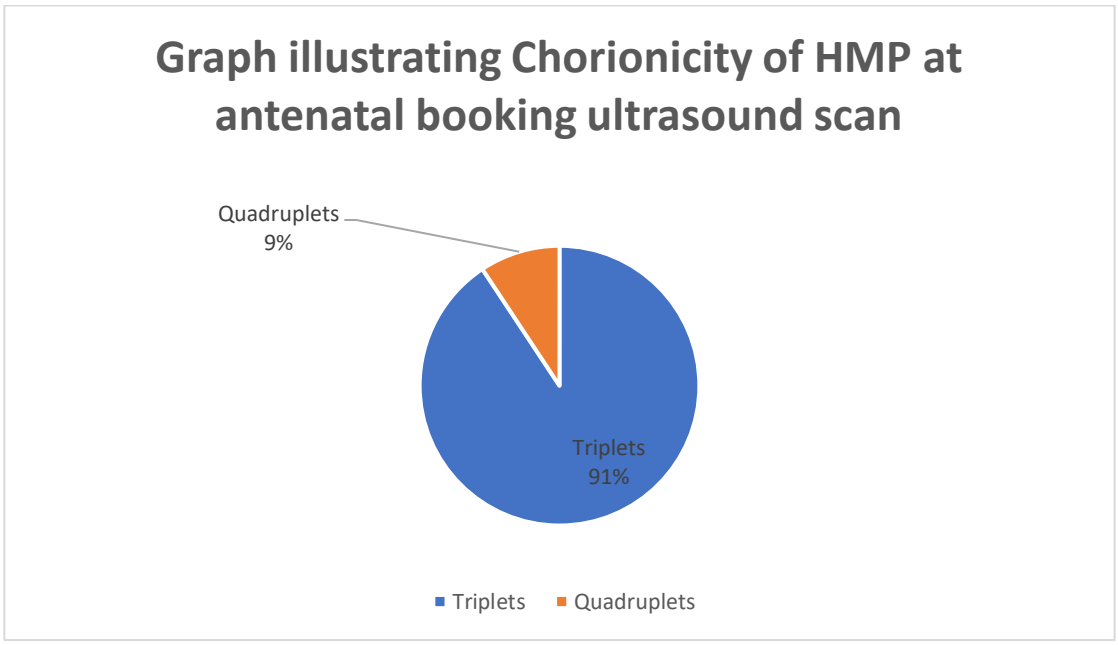


5.2.Summary of Neonatal Results

5.2.1. Chorionicity of Pregnancies

There were 4 Quadruplet Pregnancies (9%) and 39 Triplet Pregnancies (91%) when the patients booked in for their antenatal care, the distribution by percentage of these is displayed in Figure 19. Only 1 Quadruplet pregnancy had all 4 babies delivered alive and this was at 30weeks gestation in. Two other Quadruplet pregnancies were reduced during the pregnancy to a mono-chorionic Diamniotic pregnancy and the final pregnancy reduced the pregnancy to a singleton pregnancy by the mother's own choice.

Figure 19: Graph illustrating Chorionicity of HMP at antenatal booking ultrasound scan.



5.3. Neonatal Outcomes of Pregnancies

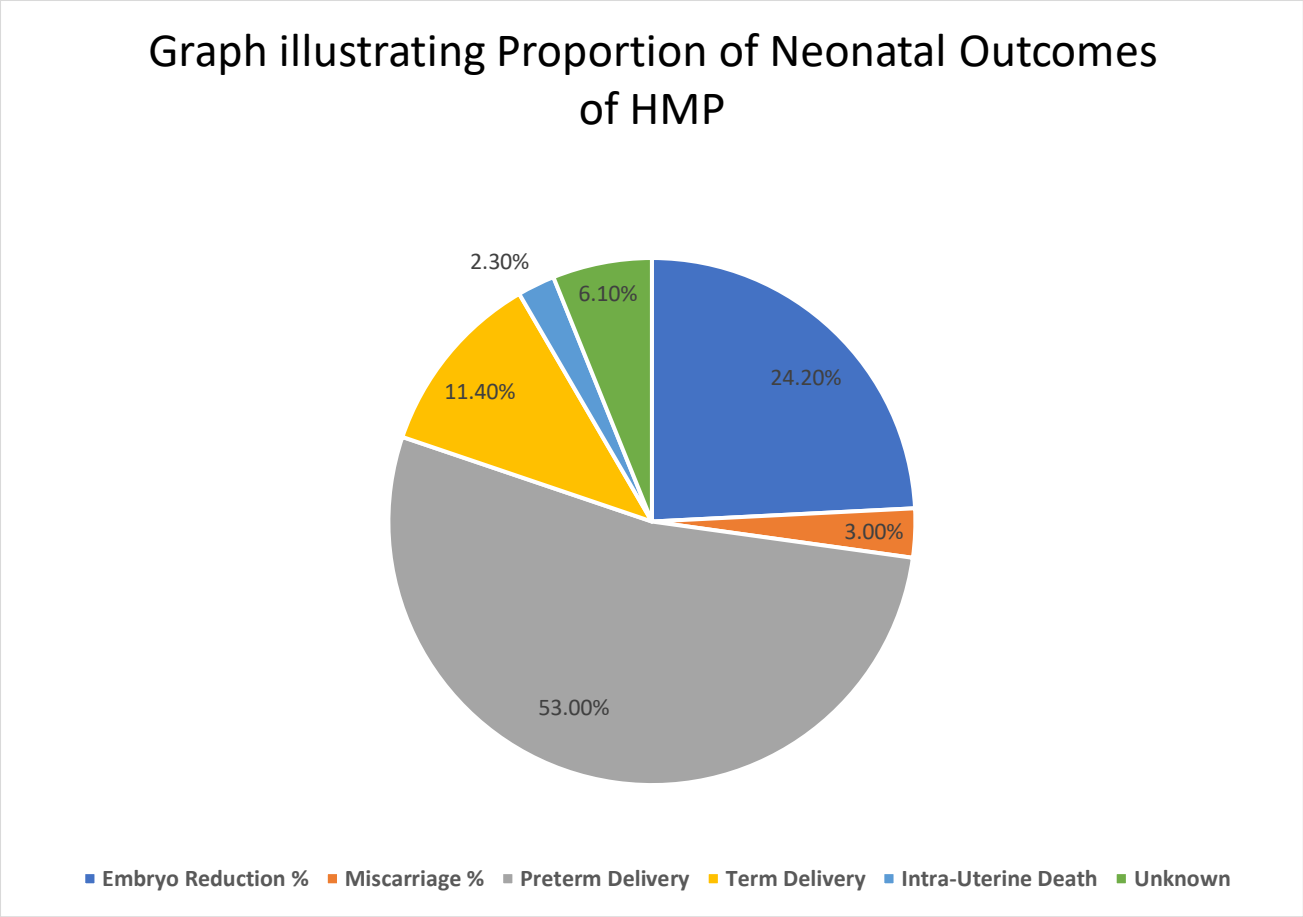
There were 4 quadruplet pregnancies and 39 triplet pregnancies, giving 133 viable foetuses initially. In Table 13 is the record of the outcomes of each of the foetuses. The outcomes included 19 embryo reductions (14%), 17 miscarriages (13%), 70 Preterm deliveries (53%), 15 term deliveries (11%), 3 Intra-uterine Deaths (IUD) (2.3%) and 11 fetuses where the outcome was unknown (6.1%). These categories are also illustrated as percentages of outcomes in Figure 20 to highlight their individual contribution to the overall number. Figure 21 is a bar graph showing the distribution of gestations at delivery of the viable babies born in this group.

In addition, there was a triplet delivery at 28 weeks where the babies survived for only 7 to 9 days, all having a neonatal death which was not reflected in the graph.

Table 13: Table of foetal outcomes.

Foetal Outcomes	Number	Percentage
Embryo Reduction	32	24.2%
Miscarriage	4	3.0%
Preterm Delivery	70	53.0%
Term Delivery	15	11.4%
Intra-Uterine Death	3	2.3%
Unknown	8	6.1%

Figure 20: Graph illustrating Neonatal Outcomes of HMP.



5.3.1. Preterm deliveries:

Preterm delivery rate is 82% in this study. Figure 21 and Table 14 illustrate the distribution of deliveries of these HMB. Only 18% (15 babies) of these babies were born at term which is more than 37weeks gestation. In this study, 33% (28 babies) of the babies were very Pre-Term, and 11% (9 babies) were extreme Pre-Term being delivered at less than 28 Weeks gestation.

Figure 21: Chart Illustration the Distribution of Gestation at Delivery of HMP.

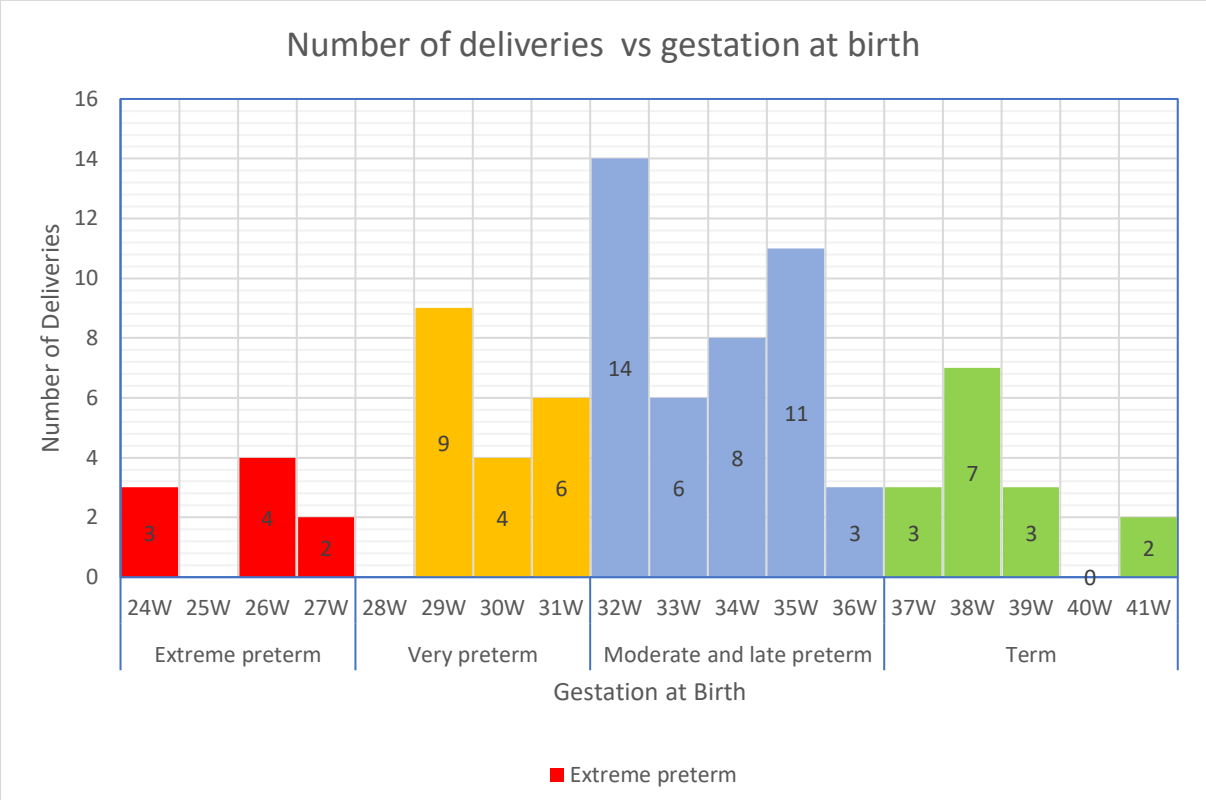


Table 14: Table of Category of Term at Birth

Category of Birth	Number	Percentage
Extreme Pre-term (<28 weeks)	9	11%
Very Pre-term (28-31 weeks)	19	22%
Moderate to Late Preterm (32-36 weeks)	42	49%
Term (>37 weeks)	15	18%

5.4.Maternal complications

The women who carried these HMPs also had co-morbidities associated with these pregnancies. This led to increased antenatal admissions, increased antenatal surveillance during the pregnancies including extra antenatal appointments and scans. The complications are listed in Table 19 and include:

1: Gestational Diabetes Mellitus (GDM)-3 (7%)

2: Preterm Prelabour Rupture of Membranes (PPROM)-3 (6.9%)

3: Ante-Partum Haemorrhage (APH)-2. (4.6%)

4: Pre-eclampsia Toxaemia (PET)- 8 (18.6%)

5: HELLP-1(2.3%)

6: Acute Intermittent Porphyria (AIP)- 2 (4.6%)

7: Twin-to-Twin Transfusion Syndrome (TTTS)-1(2.3%)

8: Growth Discordance- 1 (2.3%)

9: Thrombocytopenia-1 (2.3%)

10: Deep vein Thrombosis (DVT)-1 (2.3%)

11: Cardiac Disease- 1 (2.3%)

12: Psychiatric Disease- 1 (2.3%)

13: Cervical Incompetence -6 (13.9%)- (15 cervical suture procedures were performed in this. group of patients as some patients had the procedure repeated.

14: Placenta Percreta-1 (2.3%)

15: Placenta Praevia-1 (2.3%)

16: Chorioamnionitis- 2 (4.6%)

17: Postnatal Pancreatitis-1 (2.3%)

18: Manual Removal of Placenta (MROP)-1 (2.3%).

19: Major Obstetric Haemorrhage (MOH) more than 1000mls blood loss at delivery-4 (9.3%)

20: Hysterectomy-1 (2.3%).

5.5.Neonatal complications of HMPs.

The neonates from these HMPs also had complications arising from these pregnancies. This led to increased admissions to neonatal intensive care, special care baby units, medical interventions and overall hospital stay. The neonatal complications and their frequency expressed as a percentage, observed in this study are listed in table 20 and include:

1: Prematurity-70 (53%)

2: Intra-uterine Growth Restriction (IUGR)-59 (44.7%)

3: Intra-Uterine Death- 3 (2.3%)

4: Respiratory Distress Syndrome (RDS)-3 (2.3%)

5: Twin-To-To Transfusion Syndrome (TTTS)- 6 (4.5%)

6: Hypoglycaemia-2 (1.5%)

7: Cardiac abnormalities (Patent Ductus Arteriosus-PDA, Left-sided Hypoplasia)-2 (1.5%)

8: Jaundice- 3 (2.3%)

9: Retinopathy of the New-born- 3 (2.3%)

10: Meningomyelocele requiring spinal surgery- 1 (0.8%)

11: Dysmorphic Facial Features- 1 (0.8%)

12: Sepsis- 3 (2.3%)

13: Anaemia- 1 (0.8%)

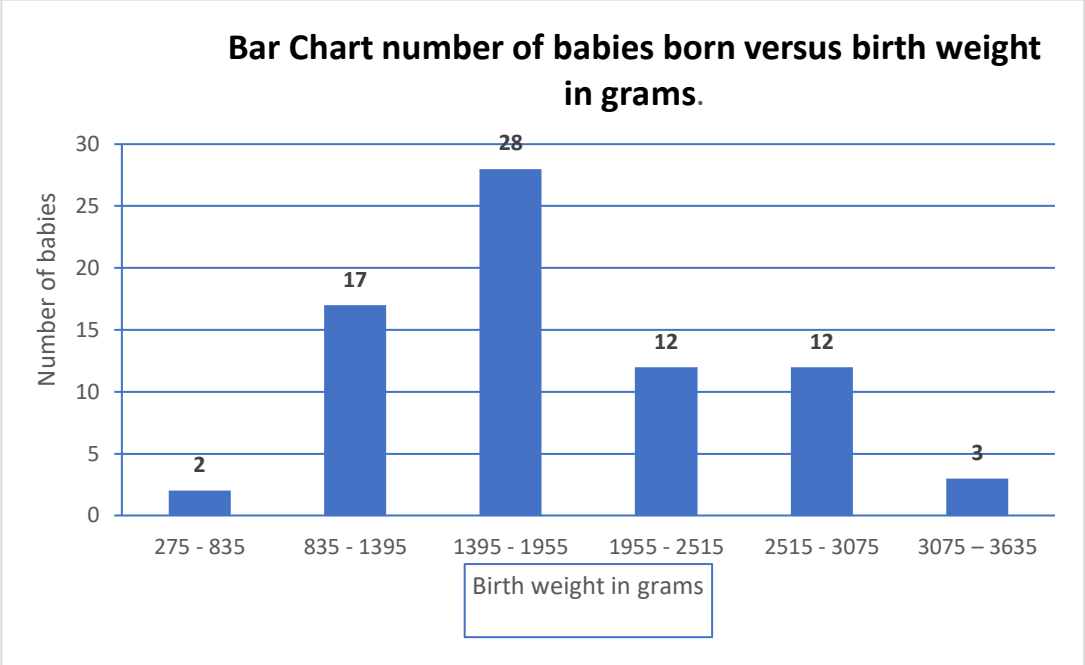
14: Haemangioma- 1 (0.8%)

These complications occur at a much higher frequency than would be expected in singleton pregnancies. Bhattacharya et al (2013) showed that maternal mortality was increased almost 3-fold from 5.9 to 14.9 per 100,000 deliveries. In the same study by Bhattacharya, prematurity, identified as the main cause of neonatal morbidity and mortality increased from 8% in singletons to 42% in twins. Twins faced a 6-fold and triples a 10-20-fold increase in mortality compared to singletons. The same study showed transferring of 3 embryos compared to 2 embryos in ART increased the risk of high multiple births, but did not improve the chance of live birth (47).

5.5.1. Intra-uterine Growth Restriction (IUGR)

Intra-uterine Growth Restriction (IUGR)/SGA (Small for Gestational Age) was defined as birthweight below the 10th centile in this study. In Figure 22, is a distribution graph of the birthweights. There were 89 viable babies born and 59 (66%) of these babies were classified as IUGR or SGA. Majority of these babies were born with under 2 kilograms birthweight. Low-birth weights has long-term implications and is associated with developmental delays and mental health illness in later life.

Figure 22: Graph demonstrating Year of Birth and Distribution of Birth weight in Grams



5.6. Out-patient appointments and In-patient admissions

High Multiple Pregnancies require more antenatal specialist care, scans appointments and deliver babies of lower birth weight requiring longer hospital admissions and care compared to singleton pregnancies. In table 15, I have displayed the average number of hospital antenatal appointments, antenatal scans, average postnatal admission and neonatal admission on Neonatal Intensive Care Unit (NICU) and Special Care Baby Unit (SCBU) and Postnatal Wards (PNW). On average, an HMP had 8.18 (5.51) Antenatal appointments and 8.18 (5.51) antenatal ultrasound scans. The mean Gestation for delivery was 33.44 (5.23) weeks with the earliest gestation 24 weeks and latest 41weeks gestation. Mothers spent an average of 7.52 (4.22) days in post-natal admissions after delivery and the neonates spent an average of 38.07 (60.74) days either on the Neonatal Intensive Care Unit (NICU) or Special Care Baby Unit (SCBU) with 3 days being the least number of days and 270 days being the longest a baby spent in hospital after delivery.

Table 15: Table of Averages of Maternal and Neonatal investigations and Costs of HMP.

Maternal Care	All Hospitals	Oxford	Other Hospitals	Mann-Whitney U Test p value
Maternal Age	34.44 (7.55)	35.11(7.30)	33.31(7.82)	0.603
Out-patient appointments	8.18 (5.51)	10.59 (5.30)	4.12 (2.55)	P = <0.001
Ultrasound scan appointments	8.18 (5.51)	10.59 (5.30)	4.12 (2.55)	P = <0.001
Gestation at Delivery (Weeks)	33.44 (5.23)	32.88 (4.13)	35.46 (4.06)	P = <0.001
Duration in post-natal in-patient stay (Days)	7.52 (4.22)	7.41 (4.28)	**N/A**	-
Average Cost of Maternity Care	**£13,791.28 (£7,975.87)**	**£17,919.05 (7,153.24)**	**N/A**	-
Neonatal Care				
Neonatal Birth Weight (grams)	1831.26 (658.26)	1772.95 (582.93)	1990.31 (824.90)	P = 0.047
Neonatal in-patient stay (Days)	38.07 (60.74)	38.07 (60.74)	**N/A**	-
Average Cost of Neonatal Care (£)	£35,448.53 (£56,553.78)	£35,448.53 (£56,553.78)	**N/A**	-
Average Total Cost of Pregnancy Care (£)	**£68,222.34 (£131,924.40)**	**£104,571.01 (£156,278.50)**	**N/A**	-

1: Comparisons of means was analysed using non-parametric Mann-Whitney U Test. Findings were considered statistically significant if the P value of <0.05

5.7.Cost of High Multiple Pregnancies to the NHS:

Of the 43 pregnancies, only 26 (56%) pregnancies had their antenatal care, delivery and post-natal care at the John Radcliffe Hospital with their record of investigations, treatment and

admission available on the "Viewpoint" software database. Only these 26 pregnancies managed and delivered in Oxford was a reliable robust, complete picture of expenditure possible. Of the remaining 17 HMPs, there were gaps in the information available to calculate the cost to the NHS such as length of inpatient stay after delivery and maternal complications, neonatal admissions to the Neonatal Intensive Care Unit (NICU) or Special Care Baby Unit and neonatal complications encountered after delivery.

The tariffs used to calculate the direct cost to the NHS, derived from the NHS National Schedule of Reference Costs-2017-18 (34, 48). The individual tariffs used are shown in Table 17. Using the tariffs, we were able to calculate and estimate the cost to the NHS of each HMP by multiplying each billable item to the corresponding nationally agreed tariff. I designed a Microsoft Excel sheet and entered the total number of billable items in a row corresponding to a particular patient or fetus. The hospital encounters were entered into the excel sheet and added up to give a total cost per pregnancy. A summary of the total cost of HMPs to the NHS over the 7 years is shown in Table 16.

All HMPs

For all HMPs, the average cost of maternity care was £13,791.28 (£7975.87) and the average cost of neonatal care was £35,448.53 (£56,553.78). The average total cost of all HMPs was £68,222.34 (£131,924.40). This is displayed in Table 15.

Oxford HMPs

Of these pregnancies, the average cost of maternity care for Oxford patients was £17,919.05 (£7,153.24), for Neonatal Care it was £35,448.53 (£56,553.78). The overall average Total cost care of an HMP for Oxford patients was £ 104.571.01 (£156,278.50). This is displayed in Table 15.

Annual Cost of HMPs to the NHS from 2010-2017:

Table 16 below shows the breakdown of the direct costs to the NHS of the HMP that I found. The total expenditure of these pregnancies that had their management in Oxford was £2,823,417 out of the total cost of £2,933,561 for all of the pregnancies. This would suggest that the other 17 pregnancies delivered at the other hospitals only accounted £110,144.

Annual Maternity Costs of HMPs to the NHS between 2010-2017

The average total annual cost of maternity care for all the patients with HMPs was £74,128 (£74,378). The average total annual cost of maternity care for patients who had all of their care in Oxford was £60,477 (£60,713).

Annual Neonatal Costs of HMPs to the NHS between 2010-2017

The average total annual cost of neonatal care for all babies delivered as a result of HMPs was £292,567 (£415,777). The average total annual cost of neonatal care for all babies delivered as a result of HMPs, who had all of their care in Oxford was £292,450 (£415,841). There was little or no information at all about babies delivered at hospitals outside Oxford and therefore the average costs for Oxford and all hospital was almost identical.

Annual Total Costs of Management of HMPs

The average total annual cost of management for all the patients with HMPs was £366,695 (£468,840). The average total annual cost of management for patients with HMPs who had all of their care in Oxford was £352,927 (£455,710).

Table 16: Table of Annual costs of HMP to the NHS

Year of Delivery	Total Cost Maternity Care (£)		Total cost Neonatal Care (£)		Total cost of Management (£)	
	All	Oxford	All	Oxford	All	Oxford
2010	£10,285	£0	£0	£0	£10,285	£0
2011	£0	£0	£0	£0	£0	£0
2012	£19,579	£19,579	£13,965	£13,965	£33,544	£33,544
2013	£164,450	£136,935	£348,194	£348,194	£512,644	£485,129
2014	£82,905	£66,520	£941,241	£941,241	£1,024,146	£1,007,761
2015	£120,939	£110,915	£92,169	£91,238	£213,108	£202,153
2016	£183,065	£138,062	£937,517	£937,517	£1,120,582	£1,075,579
2017	£11,803	£11,803	£7,448	£7,448	£19,251	£19,251
Total	£593,027	£483,814	£2,340,534	£2,339,603	£2,933,561	£2,823,417

Annual Averages	£74,128 (£74,378)	£60,477 (£60,713)	£292,567 (£415,777)	£292,450 (£415,841)	£366,695 (£468,840)	£352,927 (£455,710)

Table 17. Tariffs used in Calculation of Cost of High Multiple Births to NHS: National Schedule of Reference Costs -Year 2017-18- NHS trust and NHS foundation trusts

Procedure:	**NHS National Schedule Reference Cost:**
Antenatal Out-patient Appointment	£135
Antenatal Ultrasound Scan	£151
Cervical Suture	£1482
Chorionic Villus Sampling (CVS)	£1,140
Embryo Reduction	£1,523
Vaginal Delivery	£3,575
Operative Vaginal Delivery	£3,762
Elective Caesarean Section (ELSCS)	£4,204
Emergency Caesarean Section (EMCS)	£6,282
Caesarean Section with Hysterectomy	£6,378
Blood Transfusion	£137
Post Natal Hospital Stay per day	£683
Neonatal Intensive Care Unit Stay per day	£1,445
Special Care Baby Unit (SCBU) stay per day	£520

2

Table 18. Table of Distribution of Types of Multiple Births in the UK in 2018

Type of Pregnancy	**Number of Birth**	**Total Percentage of Births**
Total Number of Births	731,213	
Twin Births	11,010	1.51%
Triplet Births	143	0.02%
Quads of Higher Order	No information available	-

Table 19: Table of Maternal Obstetric Complications with HMP

Maternal Complication	**Observed Frequency**	**Percentage of HMPs (%)**
1: Gestational Diabetes Mellitus (GDM)	3	6.9%
2: Preterm Prelabour Rupture of Membranes (PPROM)	3	6.9%
3: Ante-Partum Haemorrhage (APH)	2	4.6%
4: Pre-eclampsia Toxemia (PET)	8	18.6%
5: HELLP syndrome	1	2.3%
6: Acute Intermittent Porphyria	2	4.6%
7: Twin-to-Twin Transfusion Syndrome (TTTS)	1	2.3%
8: Growth Discordance	1	2.3%
9: Thrombocytopenia	1	2.3%
10: Deep vein Thrombosis (DVT)	1	2.3%
11: Cardiac Disease	1	2.3%
12: Psychiatric Disease	1	2.3%
12: Psychiatric Disease	1	2.3%

[2] The National Tariff does not have direct costs for every single procedure performed by the NHS, for example Cervical Suture is not directly referenced, but the tariff used is for "Ante-natal Therapeutic Procedures, including induction, with CC score 0-1. There was therefore some subjective selection of the tariff that best described the obstetric or neonatal intervention or procedure.

13: Cervical Incompetence	6	13.9%
14: Placenta Percreta	1	2.3%
15: Placenta Previa	1	2.3%
16: Chorioamnionitis	2	4.6%
17: Postnatal Pancreatitis	1	2.3%
18: Manual Removal of Placenta (MROP)	1	2.3%
19: Major Obstetric Haemorrhage (MOH) of more than 1000mls blood loss at delivery.	4	9.3%
20: Hysterectomy-1 (2.3%).	1	2.3%

Table 20: Table of Neonatal Complications recorded from the HMP:

Neonatal Complication.	**Observed Frequency.**	**Percentage of neonates.**
1: Prematurity	70	53%
2: Intra-uterine Growth Restriction (IUGR)	59	44.7%
3: Intra-Uterine Death (IUD)	3	2.3%
4: Respiratory Distress Syndrome (RDS	3	2.3%
5: Twin-To-Twin Transfusion (TTTS)	6	4.5%
6: Hypoglycaemia	2	1.5%
7: Cardiac Abnormalities (PDA, Hypoplasia)	2	1.5%
8: Jaundice	3	2.3%
9: Retinopathy of the New-born	3	2.3%
10: Meningomyelocele requiring surgery	1	0.8%
11: Dysmorphic Facial Features	1	0.8%
12: Sepsis	3	2.3%
13: Anaemia	1	0.8%
14: Hemangioma	1	0.8%

5.8. Discussion of Maternal and Neonatal results

5.8.1. Locality patients referred from to the John Radcliffe Hospital

The John Radcliffe Hospital is a University Teaching and Tertiary Referral Hospital for Obstetric, Fetal-maternal and Neonatal specialist care and has referrals from local, regional and other national hospitals of patients who are considered high risk for some or all of their antenatal, delivery and neonatal care. The most common reason for referral is to access highly specialist care or procedures such foetal reductions or specialist ultrasound monitoring as well as need for neonatal intensive care beds at delivery. Some patients have most of their antenatal care in Oxford, but return to their local hospital for delivery if their local hospital has sufficient specialist staff and resources such as neonatal beds to manage the delivery if the pregnancy has attained a gestation that anticipates a less complicated delivery and neonatal care. Table 9 lists all the 11 local areas that patients with High Multiple Births were referred from in the study period I reviewed.

During the 7-year period reviewed, forty-three (43) women were identified as having been referred for management of an HMP at the John Radcliffe Hospital. Forty-two (4) of these women had their management at the John Radcliffe (JR) Hospital and 26 patients had their deliveries at the same hospital as well. 16 patients had their deliveries at their original referring hospital or another hospital if there were no suitable neonatal beds available at the John Radcliffe hospital at the time of delivery or the patient went into labour and was not close enough to the JR to allow for safe delivery. One (1) patient was from out-of-area and had only part of her ante-natal care at the JR. She gave birth back in her home area of Leicestershire. As a result, no further information on this patient available regarding a) gestation at delivery b) mode of delivery c) birth weight d) number of babies delivered e) comorbidity.

5.9. Method of Conception and Annual Frequency of HMP seen at John Radcliffe Hospital.

The method of conceptions of these pregnancies and percentages, were also recorded and displayed in Table 10, while Graph 2 shows the percentages contributions. ART accounted for 23 (53%) of all the high multiple births. There were 11(26%) pregnancies that were naturally conceived and 5 (12%) conceived by ovulation induction. There were a further 4 (9%) pregnancies where there was no information available as to mode of conception.

ART (using either IVF or intracytoplasmic sperm injection-ICSI) accounted for 53% of all the high multiple births (n=23). Seven (7) women (16%) had their ART overseas, and four (4) women (9%) had their ART in the UK. For twelve (12) women (28%), there was no information identifying the location of their treatment.

Seen in another perspective, of the patients where it was known that they had conceived using ART, seven (7) patients (30%) of patients had their ART overseas and four (4) patients (17%) had their ART in the UK. For 12 patients (52%) of the confirmed ART pregnancies, there was no information identifying the location of their ART treatment. Figure 15 shows the distribution of location the pregnancies were conceived.

The number and frequency of High Multiple Births per year at the John Radcliffe Hospital is illustrated in Figure 14. This is further illustrated in the Figure 23 of the number of multiple births as well as the proportion that the different mode of conceptions accounted for per year. This shows a trend of increasing number of high multiple pregnancies conceived from 2010 to 2017. It also shows a higher proportion of these births being conceived via ART treatment. ART conceptions have shown a generalised trend of gradually increasing and peaking in 2016 at 11 pregnancies. This increasing trend in number of HMP conceived through ART since 2010 is in sharp contrast to the figures released by HFEA which report a decreasing number of multiple pregnancies conceived through ART in HFEA regulated UK clinics. This would suggest that these ART pregnancies are conceived overseas in non-HFEA regulated clinics.

5.9.1. Non-ART conceived High Multiple Pregnancies (HMP)

There were 16 Non-ART conceived pregnancies that we had information of and this account for 37% of all the HMPs in this study. Of these pregnancies, eleven (11) women (69%) pregnancies were naturally conceived, and five (5) women (31%) conceived following the use of ovulation induction (OI). This is illustrated in Figure 16 and also shows possible impact non-tertiary fertility treatment can have on HMPs as ovulation Induction accounts for 12% of the overall HMP pregnancies. The HFEA has noted that only 11% of fertility clinics surveyed confirmed ovulation tracking in at least one cycle of OI. Follicle tracking would help titre the dose of medication used in OI to decrease the risk of multiple pregnancy or cancel a cycle when there is a high risk of an HMP occurring. The HFEA has suggested auditing of follicle tracking for OI as one of the ways of limiting multiple pregnancies (49).

5.9.2. High Multiple Pregnancies Missing information:

There were a further four pregnancies (9%) where there was no information available as to method of conception (Table 10). These pregnancies could have been conceived via ART, naturally or by OI, however there is no information currently collected to correctly identify this. This was a retrospective study and as a result of this design, it was not possible to gather information which was not recorded. A better design for more accurate information would have been to design a prospective study and collect information when the mothers first presented for antenatal care for their mode of conception and location of treatment if the pregnancy was conceived following fertility treatment.

5.10. Neonatal Results Discussion.

5.10.1. Neonatal Outcomes of Pregnancies

There were 4 quadruplet pregnancies and 39 triplet pregnancies, giving 133 viable foetuses initially. In Table 13 is the record of the outcomes of each of the foetuses. The outcomes included 19 embryo reductions (14%), 17 miscarriages (13%), 70 Preterm deliveries (53%), 15 term deliveries (11%), 1 Intra-uterine Death (IUD) (1%) and 11 foetuses where the outcome was unknown or no information (8%). These categories are also illustrated as percentages of outcomes in Figure 20 to highlight their individual contribution to the overall number.

The reasons no information was available was because the patients either had their deliveries planned at another hospital which did not communicate the outcome to the John Radcliffe Hospital or they were transferred to another hospital as an emergency for delivery due to no availability of NICU or SCUBU beds at the JR when a preterm delivery was imminent.

In addition, there was a triplet delivery at 28 weeks where the babies survived for 7 to 9 days, all having a neonatal death which is not reflected in the graph.

5.10.2. Gestations at Delivery and frequency and types of Pre-term deliveries

5.10.3. Definitions of Preterm

For the purposes of this study, we used the World Health Organisation (WHO) definitions for classifications of Preterm Delivery.

1: Moderate to Late Pre-term: Delivery at 32 to 37weeks gestation.

2: Very Pre-term: Delivery at 28 to 32weeks gestation.

3: Extreme Pre-term: Delivery at less than 28weeks gestation.

A Term Delivery is after 37weeks gestation

5.10.4. Overview of Preterm deliveries:

The Preterm delivery rate is 82% in this study. Preterm delivery in singletons is 6.6%. and very preterm and Extreme is 1.3%. In developed countries, preterm deliveries account for 75% of perinatal mortality and more than one-half of the long-term neurocognitive, ophthalmological and respiratory morbidity. Prematurity is the leading cause of morbidity and mortality in new-borns. The rate of prematurity in singletons has been decreasing in developing countries, it is only rising in multiple pregnancies with a quoted rate of 47% in 2007.

Figure 21 and Table 14 illustrate the distribution of deliveries of these HMP. Only 18% (15 babies) of these babies were born at term which is more than 37weeks gestation. In this study, 33% (28 babies) of the babies were very Pre-Term, and 11% (9 babies) were extreme Pre-Term being delivered at less than 28 Weeks gestation. These extreme preterm neonates have increased morbidity such as respiratory, gastric and ophthalmic disorders, are underweight and account for a much greater percentage of use of Neo-natal Intensive care bed use compared to their percentage of total births. A list of the of maternal obstetric complications and neonatal complications observed are listed in Table 19 and Table 20 in the results section respectively.

Intra-uterine Growth Restriction (IUGR)/SGA (Small for Gestational Age) was defined as birthweight below the 10^{th} centile in this study. In Figure 22, is a distribution graph of the birthweights. There were 89 viable babies born and 59 (66%) of these babies were classified

as IUGR or SGA. Majority of these babies were born with under 2 kilograms birthweight. Low-birth weights has long-term implications and is associated with developmental delays and mental health illness in later life. All these complications of HMP occur at a much higher frequency than would be expected in singleton pregnancies(47).

5.11. Calculation of Cost of HMP to the NHS.

The tariffs used to calculate the direct cost to the NHS, derived from the NHS National Schedule of Reference Costs-2017-18 (34, 48). The individual tariffs used are shown in Table 17. Using the tariffs, we were able to calculate and estimate the cost to the NHS of each HMP by multiplying each billable item to the corresponding nationally agreed tariff. We designed a Microsoft Excel sheet and entered the total number of billable items in a row corresponding to a particular patient or foetus. These were then added up and gave a total cost per pregnancy. A summary of the total cost of HMPs to the NHS over the 7 years is shown in Table 16.

5.11.1. Breakdown of Expenditure by Department

I found the average cost of an HMP (triplet or quadruplet) in this cohort was £68,222 (SD £131,924). The average cost of maternal (obstetric) care was £13,791.31 (£7,882.64) and average cost of neonatal care was £35,448.53 (56,553.78). The total cost of HMP to the John Radcliffe NHS hospital during this period from 2010 to 2017 was £2,933,561. The average annual cost of HMPs at the JR Hospital in this study is £366,695 (468,840).

I was able to further analyse these figures and separate them into maternity and neonatal expenditure. During this 7-year period, the estimated total cost of Obstetric care was £593,027 and the cost for Neonatal care was £2,340,534. The majority of the neonatal expenditure was due to 8 extreme preterm triplet deliveries delivered between 24 and 29 weeks-gestation and spent between 30 to 270 days in-hospital costing the NHS between £82,859 and £754,110 for their care. The longest duration a mother spent as an inpatient was 18 days compared to 270 days for a neonate. From this study the neonatal department bears the highest direct cost of HMPs.

However, even these figures are not fully reflective of the true cost of the HMP. The data used to calculate these costs was attained through view point, a software application used at the John Radcliffe Hospital. It was only able to retrieve data on medical interventions at the JR Hospital

such as out-patient appointments, type of deliveries, gestation at delivery, birth weight and duration of neonatal in-patient stay. The software also had information of the type of delivery, gestation of delivery and birth weight of babies born at the referring hospitals or hospital patients were transferred for delivery, but no information on complications encountered after delivery, interventions and duration of in-hospital stay of those women and their babies. There was also no information whether the patient's inter-hospital transfer was performed by ambulance at the expense of the NHS or the patients travelled by their own means and expense.

Of the 43 pregnancies, only 26 (56%) pregnancies had their antenatal care, delivery and post-natal care at the John Radcliffe Hospital. Only these 26 pregnancies managed and delivered in Oxford was robust complete picture of expenditure possible. Of these pregnancies, the average cost of maternity care was £17,919.05 (£7,153.24), for Neonatal Care it was £35,448.53 (£56,553.78) and for overall average Total cost care of an HMP was £104.571.01 (£156,278.50).

The total expenditure of these pregnancies that had their management in Oxford had a total cost of £2,823,417 out of the total cost of £2,933,561 which would appear that the other 17 pregnancies delivered at the other hospitals only accounted £110,144.

There was information on where these other 17 mothers had their deliveries, the gestation of their delivery and mode of delivery. However, there was no information on how long these patients or neonates spent in the hospital that they had their delivery, what complications they encountered and whether extra medical care was required.

Although the average expenditure in Oxford was higher, it is unlikely that the other hospitals averages would be as high as the Oxford costs, even if the missing data was found as the JR hospital in its position as a Tertiary Referral Obstetric Hospital most likely had more complicated pregnancies such as Growth discordance, Twin-to twin transfusion syndrome and Intra-uterine Growth Restriction (IUGR) and with a lower gestation at delivery.

The other hospitals delivered pregnancies with a higher gestation and higher average neonatal weight at delivery. The Oxford pregnancies had a mean gestation of delivery of 32.88 (4.13) compared to other hospitals 35.46 (4.06) respectively and average weight at delivery of the babies was 1,772.95(582.93) grams vs 1,990.31(824.90) grams. These findings were statistically significant with p values of <0.001 and 0.047 respectively. The Oxford pregnancies

had more ultrasound appointments during pregnancy of 10.59 (5.30) compared to the other hospitals with 4.12 (2.55) scan appointments. This was also statistically significant with a p value of <0.001. This information is shown in table 15.

A Sheffield study in 2006 led by Professor William Ledger that calculated the cost of a Triplet pregnancy as £32,354 (36). Taking inflation into consideration and that this study was done over 10 years after the Sheffield study, the estimated costs to the NHS of HMPs found in this study would appear to be reflective of the true cost to the NHS.

HMPs account for approximately 1% of Multiple pregnancies with twin pregnancies accounting for almost 99%. Therefore, the total cost of all multiple pregnancies to the Trust would be much higher and ART pregnancies would account for a high proportion of this.

5.12. Discussion of possible impact of ART funding cuts on HMP

Historically, ART treatment is associated with an increase in HMP. The vast majority of this increase has been attributed to multiple embryos transferred during an embryo transfer procedure by clinicians, in an effort to improve the chances of success of ART treatment.

Owing to this, multiple pregnancy rate amongst ART patients had risen to approximately 25% by 2007. Efforts from the HFEA and in collaboration with self-regulation by UK Fertility clinics, especially with the implementation of the elective single embryo transfer (eSET) policy in the UK, has led to a decrease in the percentage of multiple pregnancies amongst ART patients to approximately 10% by 2015 without compromising the overall success rate of ART, which is approximately 23% live birth per embryo transfer procedure.

Professor Ingrid Granne, the Co-supervisor of the study suggested that even if One-stop clinics or any other measures in the fertility pathway were shown to save the NHS or CCGs money by their efficiencies, the CCG may still be reluctant to maintain current ART levels or use the savings to fund more treatment cycles.

I therefore proposed that the study needed to show the disadvantages of reducing NHS funded ART cycles and to make a case for "Ring-fencing" of possible savings that may be realised by utilising the One-stop Fertility pathway. These savings could then be used to maintain or even increase NHS funded ART cycles.

The HFEA has noted an increasing trend of British residents travelling outside the UK for their ART treatment in clinics that are not as regulated as the clinics in the UK, especially in regards to number of embryos transferred during embryo transfer procedure. The HFEA also noted that this could affect the UK multiple pregnancy rate when the same patients return to the UK for their antenatal care and deliveries(3).

According to the Office for National Statistics (ONS), multiple pregnancy rate was 1% was in 1984, 6 years after the 1st IVF delivery in 1978 when ART was in its infancy. This had increased to 1.53% (approximately 1 in every 65 births) by 2016, an increase of about 53% in 32 years. ART births account for approximately 14,000 (2%) births out of the approximately 700,000 births a year in the UK. The ONS also state that ART is 7 times more likely to result in multiple birth than natural conception (50).

According to the ONS, there were approximately 731,000 live births in the year 2018 in the UK. Overall, Multiple births accounted for 11,153 births (1.51%) of total, illustrated in Table 18. This was the lowest rate since 2007 and the 3rd year of consecutive decreases, however it is still almost 0.5% higher than the multiple pregnancy rate in 1984. The UK multiple Pregnancy rate had peaked at 11.5% in 2012. Twin Pregnancies account for over 98% of multiple pregnancies, however, it is the High Multiple Pregnancies (triplets and higher order) that are associated with more severe morbidity and mortality in both mothers and children and cost to the NHS. Overall, all multiple pregnancies account for a disproportionate cost, morbidity and mortality compared to singleton pregnancies (35, 36, 50-53).

An unknown number of British residents travel outside the UK for their ART treatment. The reasons UK patients chose to have their treatment overseas are varied and beyond the scope of this study but include reasons from the list below:

1: Cheaper cost of treatment even when travel and accommodation included.

2: Higher published success rates of clinics overseas.

3: Shorter waiting lists of clinics overseas to receive treatment.

4: Recommendations of previous patients, family or friends.

5: Seeking treatment fertility add-on treatments not available in the UK.

6: Easier accessibility of ART services either limited or not available in the UK such as donor gametes or donor gametes for ethnic minority patients.

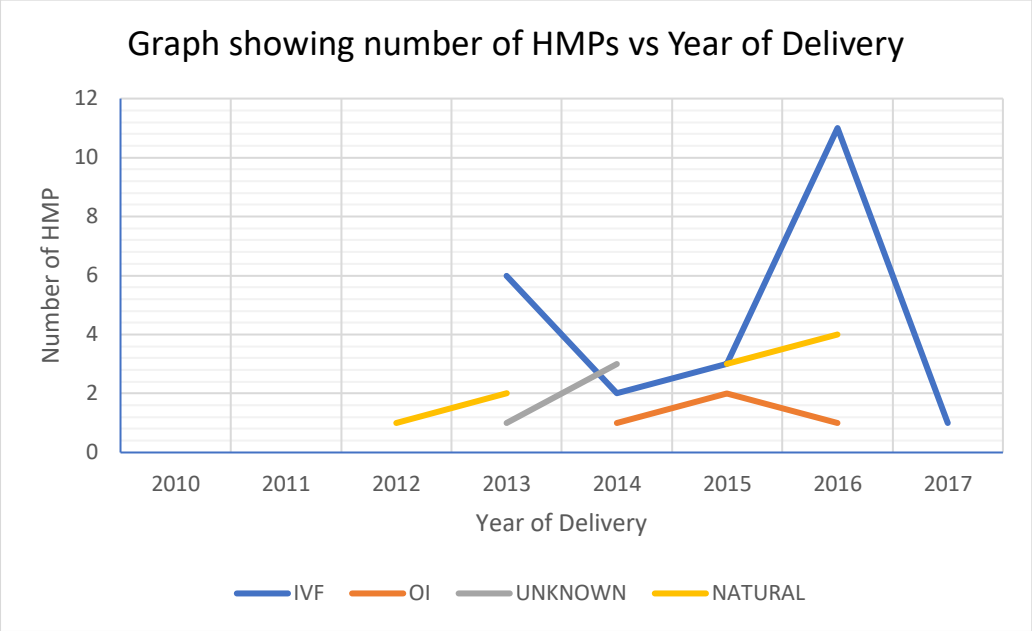
7: Seeking anonymous donors due to long waiting list in the UK.

The cheaper cost of ART overseas is a factor considered by UK patients who chose to travel overseas when they are either are not eligible for NHS funded ART or have used up the ART cycles they are entitled to by their CCG. Popular destinations of ART overseas include Spain, Greece, Cyprus, Turkey, Eastern Europe, India and the United States(20, 53).

5.13. Increasing trend of HMP and Cost to the NHS at the JR Hospital

Despite the HFEA showing a decreasing trend in number of multiple Pregnancies from ART cycles in the UK since the peak in 2012, the number of HMP at the John Radcliffe Hospital in Oxford has been following an upward trajectory since 2013 as shown in Figure 23 below. It also shows of these 43 HMP, 23 (53%) are attributed with ART treatment and 7 (16%) are confirmed to have been treated overseas and with 12 (28%) of these pregnancies, there is no information where the ART cycle was performed. This is illustrated in Figure 14 in the results section.

Figure 23: Graph of Frequency of High Multiple Births and Type of Conception Per Year at the John Radcliffe Hospital



There was a single HMP in 2010 and none recorded in 2011 and then the trend showed an upward trajectory leading to a peak in 2016. Specifically, ART associated HMP births have also shown a trend of gradually increasing and peaking in 2016 at 11 pregnancies in a single year. There was a total of 16 HMP that year. The following year, 2017, there was only one HMP, and it was conceived by ART accounting for 100% of HMP that year.

However, in this same period, 2010-2016, the HFEA recorded a decrease in ART conceived multiple pregnancies in the UK. There was a decrease in NHS-funded cycles and but an increase in total number of ART cycles performed in the UK overall. It can be extrapolated, that as the NHS decreased its funding for ART, there was an increase in patients seeking ART treatment and funding it through private means in HFEA regulated clinics.

However, whereas the HFEA is showing a decreased number of multiple pregnancies from UK clinics that it regulates, Tertiary Hospitals like the John Radcliffe, are showing an increased frequency of High Multiple Pregnancies. It can therefore also be extrapolated, that as HFEA regulated clinics across the UK decrease the number of multiple pregnancies, patients are going overseas for treatment, and this is leading to an increasing percentage of multiple pregnancies that have their antenatal, delivery and postnatal care in NHS hospitals. There is no direct

evidence, but this could point to an increase in HMPs from ART treatment received overseas. Confirming this link is beyond the scope of this study as it would require information from a national database that is currently not available.

Ledger et al calculated in 2006 that the average direct cost to the NHS of a triplet pregnancy was £32,354. These figures were in 2006 and would have increased with UK inflation. In this study I carried out, using the 2017-18 NHS tariffs, I found the average direct cost of an ART HMP pregnancy from this cohort of pregnancies was £31,234 which was close to the direct costs found by the Sheffield team.

In 2013 and 2016 alone there were 6 and 16 HMP pregnancies respectively costing the NHS £1,024,146 and £1,120,582 to care for due to the extreme pre-term deliveries and associated complications. In those years ART accounted for 2 (33.3%) and 11 (68.7%) of the pregnancies respectively. These annual expenditures on HMPs by the NHS at the John Radcliffe, are much higher than the total amount of allocated for NHS funded ART by Oxford CCG (approximately £355,000) and are almost 3 times the amount the CCG would hope to save by a complete ceasing of funding for NHS funded ART cycles in the area.

These expenditures on HMP per year do not include the extra expenditure due to twin pregnancies which account for 98% of multiple pregnancies and also does not consider the cost of long-term care of babies born from HMP when they are discharged from hospital into the community with long-term co-morbidities such as cerebral palsy or other respiratory, ophthalmic or other conditions related to prematurity.

In 2016, a single triplet pregnancy that had a direct cost of £383,054 due to a delivery at a very early gestation of 26 weeks and prolonged stay of almost 200 days on the neonatal intensive care unit (NICU) and special care baby unit (SCUBU). The pregnancy was conceived by ART, but there was no information on whether this patient had her ART in the UK or overseas but it is known she was 27 years old at the time of ART treatment. That same year, there were 15 other HMPs costing the NHS £1,120,582 and was the highest annual expenditure on HMPs' in the 7-year study period.

The small number of pregnancies seen in this observational study make it difficult to draw up robust statistical conclusions for the whole of the UK. However, in the 7 years analysed by myself in this study, High Multiple Pregnancies had a direct cost to the NHS at the John

Radcliffe Hospital of £2,933,561 and the ART conceived pregnancies accounted for 50.8% of these pregnancies. In 2011, there were no recorded HMP, which could be that this study did not identify any such pregnancy due to the retrospect nature of the study as the ONS reported the peak of Multiple pregnancies in the UK was in 2012. There may have been HMPs during this period that were not identified. However, from 2013 there were 6, 2014 there were 2, 2015 there were 3, peaking in 2016 when they here were 11 and 2017 there was 1. The overall trend year on year is showing a steady increase in HMP despite HFEA licensed clinics showing a decrease in HMPs over the years which therefore could suggest treatment overseas as a possible cause for this increase. There is no direct evidence of this as the study also showed there were HMPs which were conceived from spontaneous pregnancies and ovulation induction performed in the UK.

Ten (10) of the women, almost half (45%) of women recorded as having ART to conceive, resulting in high multiple pregnancy in the John Radcliffe Hospital during this study period, there was no information readily available as to whether they had their treatment in the UK or overseas. A further 4 patients (9%) out of the total 43 patients, there is no information as how they conceived.

Of the 23 women conceived via ART, 13% (4) patients used donor eggs, and 9% (2) conceived using their own eggs. Almost three quarters (73%) of ART patients, it wasn't known whether they were using donor eggs or their own eggs to conceive. There are gaps in the information available for determining the true impact of ART, whether received in the UK or overseas, on the finances and resources of the NHS and this should be addressed for better planning of services.

5.14. Psychological Impact of miscarriages, terminations of pregnancies and IUD's from HMP.

Multiple births are the single greatest risk associated with fertility treatment (49). In this study I found, there were 32 embryo reductions (ERs) performed in the 7-year period. Embryo reductions, depending at what the gestation carried out may involve injection of Potassium Chloride into the embryo followed by aspiration of amniotic fluid of early gestation pregnancies. An alternative is ligation of the umbilical vessels in later gestations. There were also 4 miscarriages and 3 Intra-uterine death (IUD). These loses in pregnancy represents almost 30% of the babies seen at the start of this study.

Many studies have shown that miscarriage or termination of an embryo has a significant effect on the psychological well-being of the mother leading to anxiety and depression. There is significant psychological effect on the mothers of these pregnancies, whichever way the loss of an embryo occurs and this can lead to long term psychological and psychiatric pathology requiring expert intervention and treatment. (54)

5.15. Ring-fencing of Savings from One-stop Clinics to fund more NHS funded ART cycles.

One-stop clinics have demonstrated that they can make savings to the NHS if they are substituted for the current conventional pathway clinics of almost £670,000 a year in Oxford. These savings of almost could fund almost twice the current number NHS-funded ART cycles by Oxford CCG. From a FOI request, Oxfordshire CCG funded 110 ART cycles in the 2016-17 business year at a cost of £385,000.

The HFEA has also noted that several CCGs are in Consultation to reduce or stop funding ART cycles. This may however lead to more couples seeking treatment overseas and may also lead to more multiple pregnancies and expense to the NHS (4). This study has demonstrated that HMPs have cost the NHS a much greater figure a year in direct costs, and may even cost more in indirect costs if long-term care of patients and their children is considered. In this study I found it therefore be a valid argument to "ring-fence" savings made from One-stop clinics to at a minimum maintain current funding levels while more studies into the trends and causes of HMP in the UK are carried out.

In 2006, Ledger's study group from the Jessop Wing in Sheffield demonstrated savings to the NHS and reduction in morbidity and mortality from adopting elective single embryo transfer to reduce the multiple pregnancy rate. The same study demonstrated that the direct cost to the NHS of a singleton pregnancy was £3,313, a twin pregnancy £9,122 and a triplet pregnancy £32,354(36). This study of 43 HMP cost the NHS approximately £68,222.34 each leading to a total cost of £2,933,561 over 7 years or on average £366,695 each year.

However, HMP only represent 1% of multiple births, twins would make up approximately 4,300 pregnancies over the same period (7 years) or approximately 600 twin births a year with each birth costing the NHS £9,122 using the 2006 Sheffield study findings and would lead to a total cost of or £5,473,200 a year without taking annual inflation into account.

Considering I demonstrated ART accounted for 54% of the multiple pregnancies in my study, ART could potentially account for £2,955,528 per year in direct costs to the local Oxford NHS due to Multiple Pregnancies, a figure much higher than any savings made by completely stopping NHS funded ART cycles. As the cost of an HMP has almost doubled from the figures calculated by the Sheffield group from £32,354 to £68,222 in 2017 when the calculations were made, multiple pregnancies from ART could be costing the costing the NHS at the JR hospital £6,000,000 a year.

Professor Bill Ledger and the Sheffield study group in 2006 went further and advocated the ring-fencing of the savings to fund more ART cycles to maintain and promote good clinical practice such as. eSET(36). A similar ringfencing of cost savings realized from One-stop clinics to fund NHS funded ART cycles in the UK should be advocated to promote better clinical practice such as eSET and better clinical practice could improve clinical outcomes of pregnancies and improve patient QoL(42).

5.16. National Database for Multiple Pregnancies

There is a need for a national database to keep information on all multiple pregnancies, twins and higher order, type and location of conception and make note of antenatal, delivery and postnatal care and complications as well as long-term complications and care of children born to these pregnancies such as prematurity, ophthalmic, respiratory complications and neurological disorders associated with such pregnancies for a better determination on impact on the NHS and social services provisions in the UK. There is a need for more co-ordination, discussion and corporation between ART service providers, Obstetric fetal-maternal Medicine and Neonatal clinicians on how each service affects their patients and a co-ordinated approach to discussing funding of services with CCGs for a more rounded rather than individualised departmental approach.

It is not known the how many couples travel overseas for ART treatment, or how many cycles occur overseas of UK residents. It is assumed that the number is small compared to the approximated 70,000 cycles registered a year by the HFEA. Having more accurate figures of the number of cycles performed on UK couples overseas would help calculate what percentage of high multiple births foreign fertility clinics contribute and cost to the NHS.

The UK, NHS, NICE and the RCOG are seen across the world as setting high standards of patient care. ART treatment was first performed in the UK in 1978 and it is now carried out in over 140 countries and the UK standards in ART are seen as a benchmark world-wide. This influence as well as advocacy, can be used positively to affect changes in good practice in countries where UK patients travel for ART.

5.17. Limitations of Study Cost Calculations to the NHS and Recommendations of future work:

5.17.1. 1: Costs related to Long-term care of Children born to HMP.

Many of the children born form these pregnancies have long term morbidities associated related to prematurity and low-birth weight such as ophthalmic disorders, respiratory disorders and neurological development disorders. This study did not set out to assess the long-term cost of these pregnancies but other studies have assessed this and it does put a considerable burden on NHS resources.

5.17.2. 2: Study Limited to One Tertiary Referral Hospital.

The John Radcliffe Hospital is a recognized National Tertiary Referral Feto-maternal unit and receives complex pregnancies from across the country and not only the Oxford CCG. This study only gives figures of patients seen during the study period at the John Radcliffe Hospital. The patients were referred from a total of 7 CCGs around the Oxford area referred to as Thames Valley It is not known what proportion of the National figure this represents.

5.17.3. 3: Data on Twin Pregnancies missing

Twin pregnancies (conceived naturally, through ovulation induction and ART), account for make a higher proportion (99%) of all multiple pregnancies. This study was not able to collect data on Twin pregnancies as it was not collected in the "View Point" software. Twin pregnancies would raise and account for a higher number of antenatal consultations, ultrasound scan appointments, neonatal bed admissions, morbidity and cost to the NHS compared to HMB. Knowing the true proportion of twins conceived via ART treatment overseas would give a better reflection of the true cost to the NHS of patients seeking ART treatment overseas.

Knowing this figure would help appreciate the true financial impact of decreasing NHS funding for ART treatment.

5.17.4. 3: Retrospective Data:

All the data used for this study was retrospective data. Retrospective data used in clinical studies is that it may not accurate as encountered in this study with missing information such as location of ART treatment or even type of conception. A prospective study would most likely be more accurate. However, this study does highlight the clinical, financial and psychological impact of HMP and lays the ground work for a more in-depth study.

5.17.5. 4: Post Hospital Discharge Costs to the NHS:

Children born as a result of HMP encounter a higher proportion of associated complications such cerebral palsy, respiratory and ophthalmic complications related to preterm delivery. Collecting such information was beyond the scope of this study, however, such information would most likely lead to an increase in the true cost to the NHS.

5.18. Conclusions and Recommendations:

1: A national registrar of Multiple Births including twins and higher orders. This registrar should contain details of:

a) The method pregnancies were conceived i.e., naturally, ovulation induction or by ART.
b) If OI used, details if there was any follicle monitoring used to reduce risk of MP.
c) If ART was involved, it should be documented the location/country it was performed.
d) If ART was performed, documentation on number of embryos that were replaced at embryo transfer.

2: Ring-Fencing of potential saving made through the adoption of One-stop Fertility Clinics and utilizing these funds to maintain or increase the number of NHS funded ART cycles. This may present patients with an alternative to travelling overseas for ART treatment and may led to a further decrease in number of Multiple Births. Bhattacharya's study group in Aberdeen in 2014 also showed that the reduction in multiple pregnancies was associated with reduction in number of embryos transferred which was also related to NHS funding for ART treatment(47).

3: A larger study to look at all HMP in the UK with more in-depth details of types of conceptions, where the ART treatment was received, the direct and in-direct costs to the NHS as well as costs associated with long-term co-morbidity of children born to HMP as well as the QoL of women who carry these HMPs and the information gathered used to aid decision making on proposed NHS cuts to ART funding.

4: A coordinated approach between ART service providers, Fetal-maternal medicine and Neonatal clinicians about the impact of ART on their patients and budgets.

6. Chapter 6: Conclusions and Recommendations.

Infertility diagnosis and fertility investigation, treatment and its funding are a highly emotive issue in the UK. This study has shown that both females and males diagnosed with having difficulty with fertility have a lower QoL than most individuals in the general public with both their QoL's below the level of clinical anxiety. For female participants specifically, the level falls close to the level of clinical depression.

On an individual level for the patient, there is a strong desire to conceive and have a child or children of their own. Difficulty achieving this can affect their QoL, professional and social wellbeing as well as lead to extra personal expenditure in an effort to achieve a successful pregnancy. However, to the public and at a nationwide level, NHS funded fertility investigation and treatment requires the use of public funds raised through taxes. The wider public expects these funds to be used in the most cost effective and efficient manner and priority to be given to funding investigations and treatments of diseases and conditions perceived to present the highest burden on the public(19).

The government has passed on the responsibility of managing the health budgets of local populations to the different local Clinical Commissioning Groups (CCGs). Increase in public funding for health care has been limited due to pressures outside the scope of this paper, however CCGs are having to make savings through improving efficiencies or reducing services in their local health budgets(4).

Several CCGs have chosen to make some savings through either reducing the number of cycles offered below what NICE recommend i.e., 3 cycles for female patients below 40 years old and 1 cycle for patients between 40 and 42 years old, or withdrawing funding completely of ART service provisions. According to the HFEA, in 2017 many CCGs were carrying out consultations to completely withdraw funding of ART for the populations they serve with the aim of making savings of between £400,000 to £800,000 a year (4, 49).

However, in this study I have shown that whereas most CCGs aim to make savings by mainly reducing or ceasing the provision for tertiary NHS funded ART cycles, there may be alternative solutions. This study shows that one of the possible ways of making savings is by improving the efficiencies in the investigative pathway by way of introducing One-Stop Fertility Clinics. The savings realised by these one-stop clinics may be similar to the savings the CCGs hope to

achieve by the proposed cuts to NHS funded cycles. This study shows possible savings of up to £670,415.28 by introduction of a One-stop clinic to the Oxford CCG.

In this study, I also found that the Quality of Life (QoL) is not associated to the duration of investigation of participants. This was an unexpected finding as it initially assumed that the longer duration of investigation would negatively affect the QoL. However, I did find the QoL of participants is decreased early in the investigative pathway to a level similar to patients showing clinical anxiety. On sub-group analysis, QoL of female participants was lower than male participants and approaching the level of clinical depression and this information can be used to offer and plan emotional support and professional counselling for patients diagnosed with infertility and going through the investigative pathway

A possible cause of female participants having a lower QoL may include that females have more primary investigations and more specialist and invasive secondary investigations performed on them. Female patients may also feel more pressurised by cultural norms as well as pressure on what they believe is their identity and purpose in their personal relationships. These findings highlight the need for offering earlier professional counselling and support to couples having fertility investigation and treatment, even before they start ART treatment in tertiary care which is where most services offer this support. It also highlights the need to only carry out the minimally necessary investigations to avoid anxiety especially in female fertility patients.

In this study, I have also shown that reductions in NHS funding for ART may have unexpected effect of an increase in couples seeking treatment overseas in clinics which are less regulated than in the UK with regards to minimalizing the risk of multiple births. As a result, although multiple pregnancy rates are decreasing in HFEA regulated UK clinics due to adoption of policies such as elective Single Embryo Transfer (eSET) of eligible patients, there may be an increase in multiple pregnancies from couples seeking treatment overseas.

This could lead to an increase in NHS Obstetric and Neonatal expenditure in caring for more Multiple Pregnancies than the savings expected from cuts to NHS funded ART cycles. This therefore makes a strong case for "ring-fencing" potential savings from One-stop fertility services to maintain or even increase NHS funded ART cycles which may lead to less couples seeking treatment overseas.

6.1. Summary of Main Findings from the One-stop Fertility Clinic Study

1: There is a direct correlation between the duration that couples spend in the investigative process and the cost to the NHS, with expenditure increasing the longer patients spend from the time they present to their GP to when they start ART treatment.

2: There is no correlation between the duration that couples spend in the investigative process and the QoL of patients.

3: Fertility patients overall QoL is decreased to the levels similar to patients exhibiting clinical anxiety. The decrease in QoL is more pronounced in female patients and fall close to levels of patients exhibiting clinical depression. This indicates a need to offer counselling and psychological support early in the investigative pathway.

3: Adoption of a "One-Stop Fertility" pathway for patients could lead to an average decrease in duration by approximately 426.9 days for heterosexual couples from when they first present to their GP to when they start ART treatment.

4: A "One-Stop Fertility" pathway for patients could lead to savings to the NHS of approximately £435.1 per patient from when they first present to their GP to when they start ART treatment.

5: The QoL of patients in the "One-Stop Fertility" pathway was decreased compared to patients in the Conventional from an average of 72.1 (SD 14.0) for conventional pathway to 64.3 (SD 16) for One-stop pathway respectively and this was statistically significant with a p value of 0.007. Female patients had a more pronounced decrease in their QoL compared to male participants. This finding and may signify the need closer attention to patients QoL and proactive early referral for counselling and psychological support of patients having fertility assessment and treatment and in particular for female patients.

6.2. Summary of Findings from the High Multiple Pregnancies Study

1: I found that a high proportion of HMP who received care at the John Radcliffe Hospital in Oxford were conceived as a result of ART treatment of UK residents who travelled overseas.

These pregnancies contributed to a significant cost to the NHS and personal morbidity to the patients and their babies.

2: There is a need to provide patients with suitable alternatives within the UK which offer more regulation, surveillance and strategies to reduce the incidence of HMP.

3: Savings made from One-stop fertility clinics could be "ring-fenced" to maintain or increase ART funding to offer potential patients alternative ART treatment within the UK.

4: There isn't a robust database for monitoring the number of multiple births with information of where they are conceived, type of conception, morbidity, mortality and cost to the NHS to allow for better long-term strategic planning for National expenditure.

6.3. Recommendations

6.3.1. 1: Adoption of acceptable and achievable timescales from presentation to start of treatment or referral for specialist treatment.

Female age is the strongest prognostic factor in the success of ART. Long delays can decrease the success rate of ART treatment or increase the cost of successful treatment to the NHS. Setting mandatory timescales from when couples have been trying to conceive or how long they can spend in the primary and secondary care can address delays that may hamper success of treatment and decrease the cost of achieving that success (40).

6.3.2. 2**:** Adopting advances in clinical practice that could lead to cost savings

There have been several improvements in the skill set and training available across the NHS which if taken advantage of, could lead to more efficient ways of managing fertility patients, for example:

A: The Anti-Mullerian (AMH) blood test to replace need for early follicular FSH, LH and E2 levels for assessing ovarian reserve which can save time, need for strict scheduling and unnecessary repetitions if mistimed.

B: HyCoSy and 2D/3D Saline Infusion Sonography (SIS) adoption for tubal patency and uterine assessment to replace HSG and pelvic scan and Hysteroscopy. HyCoSy and SIS involves no radiation and is an outpatient procedure. Additionally, the budget can be retained in the Gynaecology department instead of outsourced to radiology and has as good sensitivity and specificity as the procedures it replaces and additional functionality such as able to ability to assess ovarian reserve by preforming an Antral Follicle Count (AFC) pelvic and. endometrial pathology such as ovarian cysts, fibroids, polyps and adhesions. This could mean fewer outpatient visits which would be benefit to both patients and clinicians.

6.3.3. 3: Offering Early Psychological support for patients presenting with infertility.

This study has shown that QoL is affected at a very early point in the patient investigative pathway. Clinicians and support staff should adopt a more proactive and holistic approach to patients and consider offering professional psychological support and counselling to patients presenting with infertility.

Although NICE do recommend offering psychological support to patients during and after the investigative and treatment process, it is the authors experience that this is only actively offered once the patients are offered ART treatment and rarely if they do not meet the local CCG criteria for ART treatment. This study has shown that the QoL of couples decreases early in the investigative process. Possibly early referral for counselling services may provide such patients with much needed psychological support.

6.3.4. 4: Implementation of a National Database for Multiple births

The study showed that there was a significant cost to the NHS of High Multiple Births. There is a significant lack of an extensively informative database about multiple pregnancies in the UK. This study demonstrates a need for a robust and central national database for all multiple pregnancies in the UK.

More accurate information could lead to better public health planning and help identify areas contributing to an increase in multiple pregnancies to devise and focus strategies that may lead to early interventions that may reduce such pregnancies that result on a greater cost to the NHS. This study group would therefore recommend a Central National Database For Multiple Pregnancies (CNDFMP), which would collect information of method of conception,

location(clinic, hospital, country) of treatment, Obstetric surveillance required and Complications associated with Antenatal Care, Delivery, Postnatal Care, Neonatal Care and Long-term Paediatric care to help plan for the future provision of services. (36)

6.3.5. 6: Better Public Health Education

The study found patients spent an average of 3.5 years from when they first presented to their GPs with difficulty trying to conceive to when they started ART treatment. Indirect evidence suggests patients may also be spending 1.8 years trying to conceive before they present to their GP, almost 0.8 years longer than NICE recommend for the start of investigations. It is known the best prognostic factor in determining success of ART is a woman's age, if these patients present earlier, their ART treatment will most likely be more successful and this will be cheaper for the NHS (40). There is a need for better public health awareness on the issues of reproductive health.

6.4. Criticisms and Recommendations for future work.

6.4.1. Criticisms

On reviewing the study that I have completed, on reflection, there are aspects of this study that I would have designed and implemented differently These include: -

- On reflection, I would have kept data on eligible patients that I approached for the One-Stop Fertility Pathway as this data be interesting to know the acceptability of such studies in the population.
- I would have also recruited patients not eligible for NHS ART funding to see how this affects their QoL and also to see what investigations and treatment are carried out on them by their clinicians and to see how many continue to fund their own ART treatment as this will give a more complete picture of health economics to both the patients and the NHS.
- For assessing QoL, I used the Fertility Specific Tool of FertiQoL which is quickly becoming the Gold-standard for QoL studies in infertility. However, many Health Economics studies have used both a Fertility Specific Tool as well as generic and more recognized validated Tools such as SF-36 to help compare health status of different populations.

- There was a lot of missing data in the HMP study due to the lack of a National Database. Calculating an estimated cost of these pregnancies to the NHS was difficult as a result. A prospective study may have been more appropriate.

6.4.2. Recommendations for future work

I therefore have some recommendations for future studies: -

- I would suggest future studies can be designed to collect data on couples who conceive while waiting to start ART to assess the cost savings of a longer duration of investigation before the start of ART. This can be evaluated alongside the saving realised from decreasing the duration to ART with One-stop clinics to build a more complete Health Economics assessment of duration of fertility investigation and cost to the NHS.
- I would also suggest carrying out QoL measurements of participants at different points of the investigative pathway and not just at the start of ART treatment, as was done in my study to give us a dynamic and longitudinal view of how QoL changes during the investigative pathway.
- For assessing QoL, I would consider using both a generic QoL tool such as SF-36 and EQ5D alongside the Fertility Specific Tool of FertiQoL which would allow for referencing of QoL of the study population to the general public. This would make any future Health Economics studies designed easier to compare.

I would design a prospective study on multiple pregnancies and not just HMP and collect data from women who have multiple pregnancies to find out reasons why they chose to have treatment overseas and also to collect data on what the cost to the NHS is as a result of these pregnancies. I would also involve regional referral hospitals where some of these multiple pregnancy patients are referred from to get a regional overview of the true cost of these pregnancies to the NHS.

6.5. Conclusion

Funding for fertility health-care in the UK is a complex multi-factorial issue affecting healthcare regulatory organisations, health-care providers both public and private and the individuals affected.

A One-stop fertility clinic pathway isn't a single golden solution that will resolve the question of funding for fertility services, however, this study has shown that a One-stop clinic pathway can be part of the solution in reducing cost to the NHS and reducing the duration of investigation for patients (19).

The study has shown that QoL drops early in the investigative pathway to levels below clinical anxiety and close to the levels of clinical depression more so in female patients. It is important for stakeholders to provide early counselling and support for patients in the early stages of investigation. Further research is needed to fully understand the factors affecting QoL of patients undergoing fertility investigation.

This study has also shown there may be a need for a pragmatic and more in-depth analysis of the short and long-term financial, clinical and psychological consequences of reducing fertility services. Reduction in funding will have a direct and indirect effects on primary and secondary Gynaecology care, but can also have major implications on antenatal, Obstetric, Neonatal and psychiatric services.

There is a need to develop a National database to accurately gather information on multiple births across the UK. This database should collect data on how these multiple pregnancies were conceived, where they received their treatment, the complications in the pregnancy and neonatal period. This information would then help build a fuller picture of what fertility interventions are contributing to multiple pregnancies and what burden they are having on antenatal, delivery and neonatal services run by the NHS.

This study raises interesting questions about cuts to NHS funded ART cycles which have implemented to make savings to the NHS. It raises the probability that these cuts may be associated with in-direct costs to other sectors in the NHS which are worth exploring perhaps a larger, prospective dynamic QoL and Health Economics study involving all interested health stakeholders and providers.

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8. Appendix:

8.1. Appendix 1: FertiQoL Questionnaire used in Study.

FertiQoL International

Fertility Quality of Life Questionnaire (2008)

For each question, kindly check (tick the box) for the response that most closely reflects how you think and feel. Relate your answers to your current thoughts and feelings. Some questions may relate to your private life, but they are necessary to adequately measure all aspects of your life.

Please complete the items marked with an asterisk (*) only if you have a partner.

	For each question, check the response that is closest to your current thoughts and feelings	**Very Poor**	**Poor**	**Neither Good nor Poor**	**Good**	**Very Good**
A	How would you rate your health?	☐☐	☐☐	☐☐	☐☐	☐☐
	For each question, check the response that is closest to your current thoughts and feelings	**Very Dissatisfied**	**Dissatisfied**	**Neither Satisfied Nor Dissatisfied**	**Satisfied**	**Very Satisfied**
B	Are you satisfied with your quality of life?	☐☐	☐☐	☐☐	☐☐	☐☐
	For each question, check the response that is closest to your current thoughts and feelings	**Completely**	**A Great Deal**	**Moderately**	**Not Much**	**Not At All**
Q1	Are your attention and concentration impaired by thoughts of infertility?	☐☐	☐☐	☐☐	☐☐	☐☐
Q2	Do you think you cannot move ahead with other life goals and plans because of fertility problems?	☐☐	☐☐	☐☐	☐☐	☐☐
Q3	Do you feel drained or worn out because of fertility problems?	☐☐	☐☐	☐☐	☐☐	☐☐
Q4	Do you feel able to cope with your fertility problems?	☐☐	☐☐	☐☐	☐☐	☐☐

	For each question, check the response that is closest to your current thoughts and feelings	**Very Dissatisfied**	**Dissatisfied**	**Neither Satisfied Nor Dissatisfied**	**Satisfied**	**Very Satisfied**
Q5	Are you satisfied with the support you receive from friends with regard to your fertility problems?	□□	□□	□□	□□	□□
*Q6	Are you satisfied with your sexual relationship even though you have fertility problems?	□□	□□	□□	□□	□□
	For each question, check the response that is closest to your current thoughts and feelings	**Always**	**Very Often**	**Quite Often**	**Seldom**	**Never**
Q7	Do your fertility problems cause feelings of jealousy and resentment?	□□	□□	□□	□□	□□
Q8	Do you experience grief and/or feelings of loss about not being able to have a child (or more children)?	□□	□□	□□	□□	□□
Q9	Do you fluctuate between hope and despair because of fertility problems?	□□	□□	□□	□□	□□
Q10	Are you socially isolated because of fertility problems?	□□	□□	□□	□□	□□
*Q11	Are you and your partner affectionate with each other even though you have fertility problems?	□□	□□	□□	□□	□□
Q12	Do your fertility problems interfere with your day-to-day work or obligations?	□□	□□	□□	□□	□□
Q13	Do you feel uncomfortable attending social situations like holidays and celebrations because of your fertility problems?	□□	□□	□□	□□	□□
Q14	Do you feel your family can understand what you are going through?	□□	□□	□□	□□	□□
	For each question, check the response that is closest to your current thoughts and feelings	**An Extreme Amount**	**Very Much**	**A Moderate Amount**	**A Little**	**Not At All**
*Q15	Have fertility problems strengthened your commitment to your partner?	□□	□□	□□	□□	□□
Q16	Do you feel sad and depressed about your fertility problems?	□□	□□	□□	□□	□□

Q17	Do your fertility problems make you inferior to people with children?	□□	□□	□□	□□	□□
Q18	Are you bothered by fatigue because of fertility problems?	□□	□□	□□	□□	□□
*Q19	Have fertility problems had a negative impact on your relationship with your partner?	□□	□□	□□	□□	□□
*Q20	Do you find it difficult to talk to your partner about your feelings related to infertility?	□□	□□	□□	□□	□□
*Q21	Are you content with your relationship even though you have fertility problems?	□□	□□	□□	□□	□□
Q22	Do you feel social pressure on you to have (or have more) children?	□□	□□	□□	□□	□□
Q23	Do your fertility problems make you angry?	□□	□□	□□	□□	□□
Q24	Do you feel pain and physical discomfort because of your fertility problems?	□□	□□	□□	□□	□□

FertiQoL International

Optional Treatment Module

Have you started fertility treatment (this includes any medical consultation or intervention)? If yes, then please respond to the following questions. For each question, kindly check (tick the box) for the response that most closely reflects how you think and feel. Relate your answers to your current thoughts and feelings. Some questions may relate to your private life, but they are necessary to adequately measure all aspects of your life.

	For each question, check the response that is closest to your current thoughts and feelings	**Always**	**Very Often**	**Quite often**	**Seldom**	**Never**
T1	Does infertility treatment negatively affect your mood?	□□	□□	□□	□□	□□

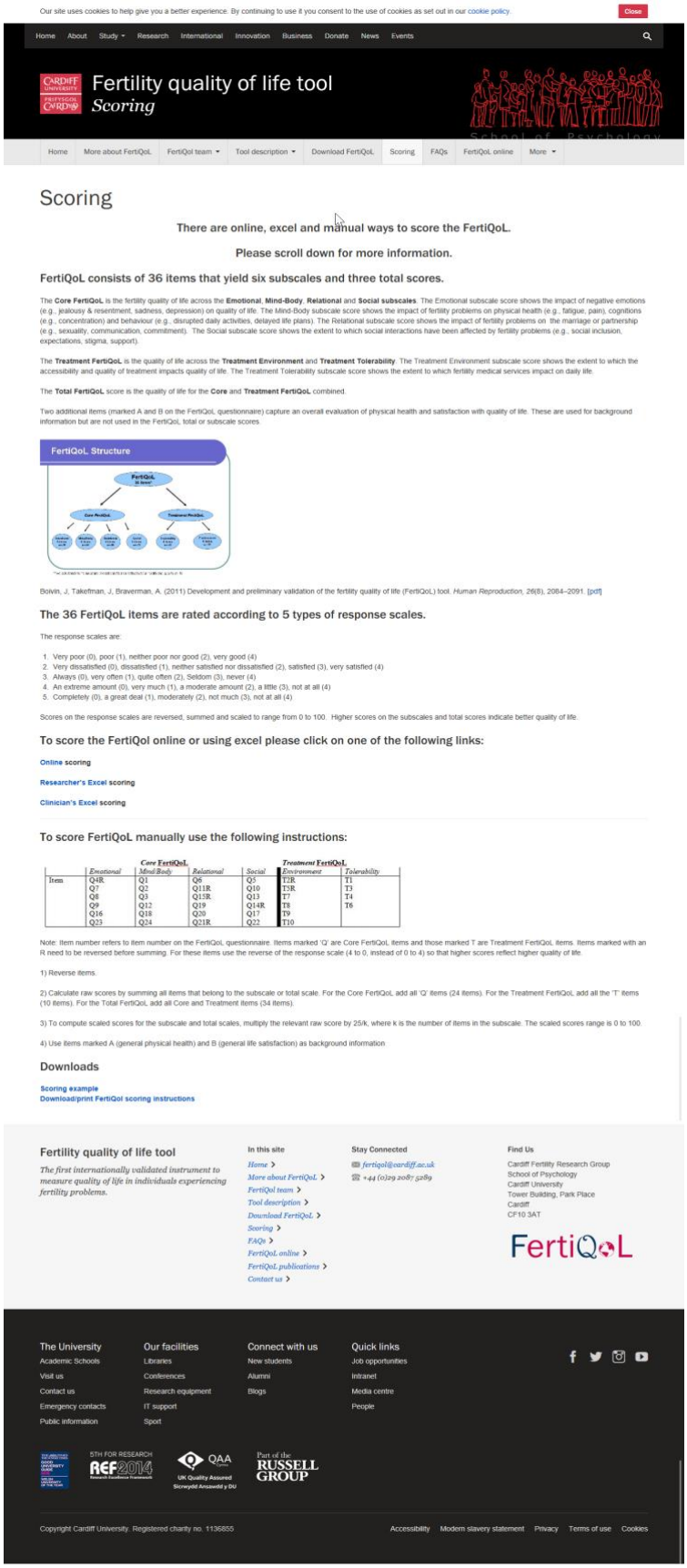
T2	Are the fertility medical services you would like available to you?	□□	□□	□□	□□	□□

	For each question, check the response that is closest to your current thoughts and feelings	**An Extreme Amount**	**Very Much**	**A Moderate Amount**	**A Little**	**Not At All**
T3	How complicated is dealing with the procedure and/ or administration of medication for your infertility treatment(s)?	□□	□□	□□	□□	□□
T4	Are you bothered by the effect of treatment on your daily or work-related activities?	□□	□□	□□	□□	□□
T5	Do you feel the fertility staff understand what you are going through?	□□	□□	□□	□□	□□
T6	Are you bothered by the physical side effects of fertility medications and treatment?	□□	□□	□□	□□	□□

	For each question, check the response that is closest to your current thoughts and feelings	**Very Dissatisfied**	**Dissatisfied**	**Neither Satisfied nor Dissatisfied**	**Satisfied**	**Very Satisfied**
T7	Are you satisfied with the quality of services available to you to address your emotional needs?	□□	□□	□□	□□	□□

T8	How would you rate the surgery and/or medical treatment(s) you have received?	□□	□□	□□	□□	□□
T9	How would you rate the quality of information you received about medication, surgery and/or medical treatment?	□□	□□	□□	□□	□□
T10	Are you satisfied with your interactions with fertility medical staff?	□□	□□	□□	□□	□□

8.2. Appendix 2: Picture of FertiQoL Questionnaire scoring for QoL.



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Fertility quality of life tool
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Scoring

There are online, excel and manual ways to score the FertiQoL.

Please scroll down for more information.

FertiQoL consists of 36 items that yield six subscales and three total scores.

The **Core FertiQoL** is the fertility quality of life across the **Emotional**, **Mind-Body**, **Relational** and **Social subscales**. The Emotional subscale score shows the impact of negative emotions (e.g., jealousy & resentment, sadness, depression) on quality of life. The Mind-Body subscale score shows the impact of fertility problems on physical health (e.g., fatigue, pain), cognitions (e.g., concentration) and behaviour (e.g., disrupted daily activities, delayed life plans). The Relational subscale score shows the impact of fertility problems on the marriage or partnership (e.g., sexuality, communication, commitment). The Social subscale score shows the extent to which social interactions have been affected by fertility problems (e.g., social inclusion, expectations, stigma, support).

The **Treatment FertiQoL** is the quality of life across the **Treatment Environment** and **Treatment Tolerability**. The Treatment Environment subscale score shows the extent to which the accessibility and quality of treatment impacts quality of life. The Treatment Tolerability subscale score shows the extent to which fertility medical services impact on daily life.

The **Total FertiQoL** score is the quality of life for the **Core** and **Treatment FertiQoL** combined.

Two additional items (marked A and B on the FertiQoL questionnaire) capture an overall evaluation of physical health and satisfaction with quality of life. These are used for background information but are not used in the FertiQoL total or subscale scores.

FertiQoL Structure

Boivin, J, Takefman, J, Braverman, A. (2011) Development and preliminary validation of the fertility quality of life (FertiQoL) tool. *Human Reproduction*, 26(8), 2084–2091. [pdf]

The 36 FertiQoL items are rated according to 5 types of response scales.

The response scales are:

1. Very poor (0), poor (1), neither poor nor good (2), very good (4)
2. Very dissatisfied (0), dissatisfied (1), neither satisfied nor dissatisfied (2), satisfied (3), very satisfied (4)
3. Always (0), very often (1), quite often (2), Seldom (3), never (4)
4. An extreme amount (0), very much (1), a moderate amount (2), a little (3), not at all (4)
5. Completely (0), a great deal (1), moderately (2), not much (3), not at all (4)

Scores on the response scales are reversed, summed and scaled to range from 0 to 100. Higher scores on the subscales and total scores indicate better quality of life.

To score the FertiQol online or using excel please click on one of the following links:

Online scoring

Researcher's Excel scoring

Clinician's Excel scoring

To score FertiQoL manually use the following instructions:

	Core FertiQoL				*Treatment* FertiQoL	
	Emotional	*Mind/Body*	*Relational*	*Social*	*Environment*	*Tolerability*
Item	Q4R	Q1	Q6	Q5	T2R	T1
	Q7	Q2	Q11R	Q10	T3R	T3
	Q8	Q3	Q15R	Q13	T7	T4
	Q9	Q12	Q19	Q14R	T8	T6
	Q16	Q18	Q20	Q17	T9	
	Q23	Q24	Q21R	Q22	T10	

Note: Item number refers to item number on the FertiQoL questionnaire. Items marked 'Q' are Core FertiQoL items and those marked T are Treatment FertiQoL items. Items marked with an R need to be reversed before summing. For these items use the reverse of the response scale (4 to 0, instead of 0 to 4) so that higher scores reflect higher quality of life.

1) Reverse items.

2) Calculate raw scores by summing all items that belong to the subscale or total scale. For the Core FertiQoL add all 'Q' items (24 items). For the Treatment FertiQoL add all the 'T' items (10 items). For the Total FertiQoL add all Core and Treatment items (34 items).

3) To compute scaled scores for the subscale and total scales, multiply the relevant raw score by 25/k, where k is the number of items in the subscale. The scaled scores range is 0 to 100.

4) Use items marked A (general physical health) and B (general life satisfaction) as background information.

Downloads

Scoring example
Download/print FertiQol scoring instructions

Fertility quality of life tool

The first internationally validated instrument to measure quality of life in individuals experiencing fertility problems.

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8.3. Appendix 3 Picture of Kübler-Ross Change Curve®.

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Appendix 3