Controlled ovarian stimulation and intrauterine insemination vs in vitro fertilisation as the first line treatment for unexplained subfertility - a randomised controlled trial

by

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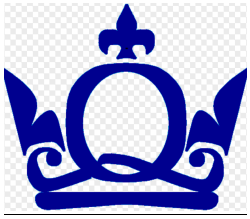

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This thesis is submitted to fulfil the requirement for the degree of Doctor of Medicine by Research, MD (Res) in the Institute of Cell and Molecular Science, Blizard Institute, Queen Mary, and University of London.

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Declaration of originality

I declare that this thesis is the result of my own work.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

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Abstract

Background:

This thesis is based on a randomised controlled trial comparing the effectiveness of intrauterine insemination (IUI) plus Controlled Ovarian Hyperstimulation (COH) versus in vitro fertilisation (IVF) as the first line treatment option for couples with unexplained subfertility.

Subfertility of a couple is classed as unexplained when they fail to conceive after one year of regular unprotected intercourse and when all the standard investigations for ovulation, tubal patency and semen analysis have been found to be normal. It affects 30-40% of couples. The age-old methods of treating these couples have included the empirical use of clomiphene or gonadotrophins to correct any possible subtle defects in ovulation with or without IUI (to overcome any existing cervical barrier to natural conception) or IVF. However, the best treatment options for these couples have yet to be determined. The matter has been made even more controversial by the issue of NICE (National Institute for Health and Care Excellence) guidelines in the UK that suggest IUI be abandoned completely for these women in favour of IVF after 2 years of expectant management.

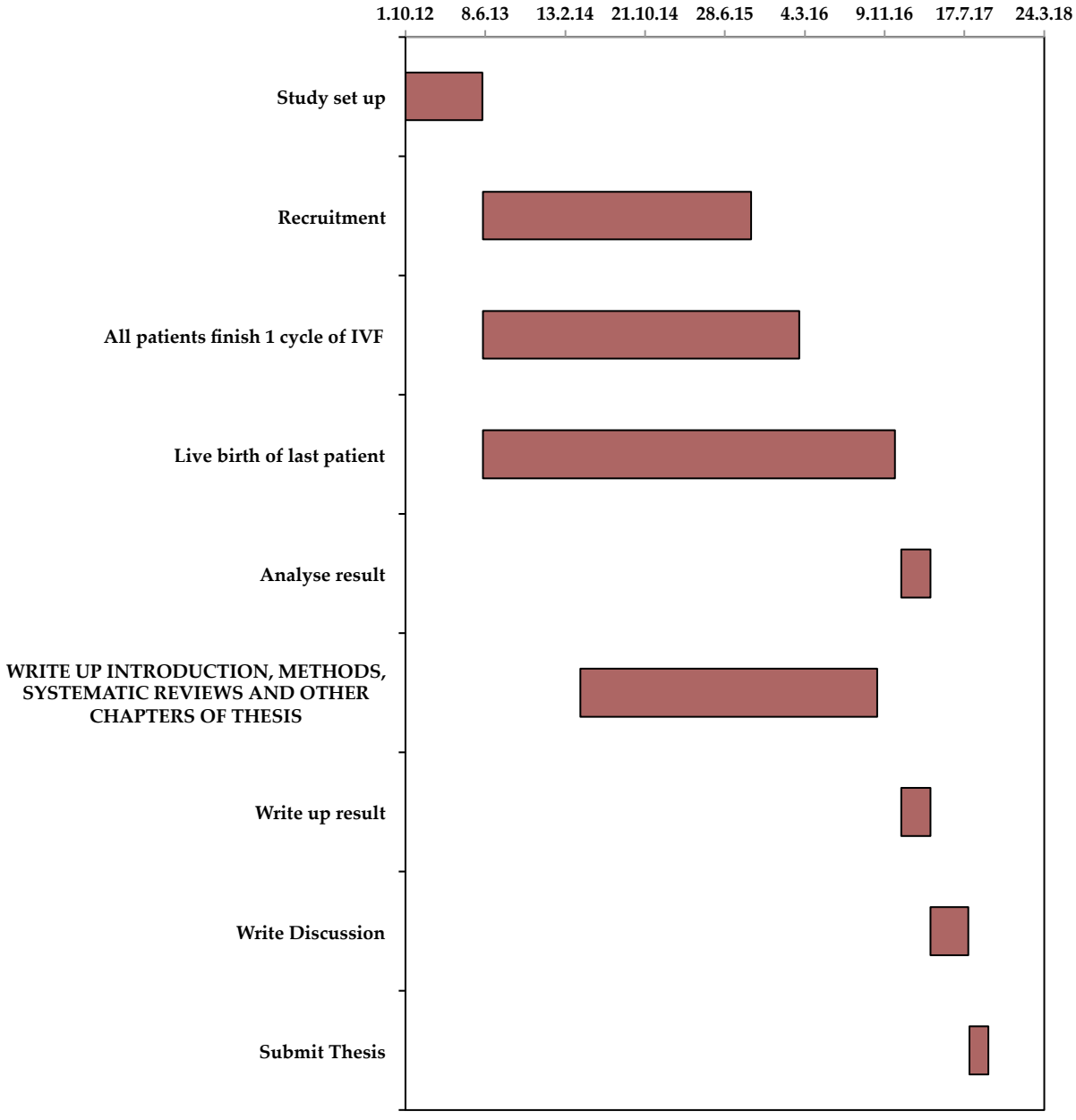
A systematic review of the available literature comparing IUI + COH versus IVF for unexplained subfertility revealed limited numbers of available studies and high clinical and statistical heterogeneity among them.

An online survey was also conducted among fertility specialists to establish the general consensus regarding management of such couples. The results revealed a lack of agreement among fertility specialists with regards to the first line treatment of couples with unexplained subfertility. The mixed

response to this survey demonstrated the ongoing dilemma among practitioners, much of which was due to the lack of robust evidence.

A randomised controlled trial was then designed to examine the effectiveness of COH with gonadotrophins + IUI versus IVF as the first line approach to the treatment of unexplained subfertility (Figure 1). This was the first UK-based randomised controlled trial comparing these two first-line management options for unexplained subfertility.

Figure 1: GANTT chart: schedule for the study and writing up of thesis



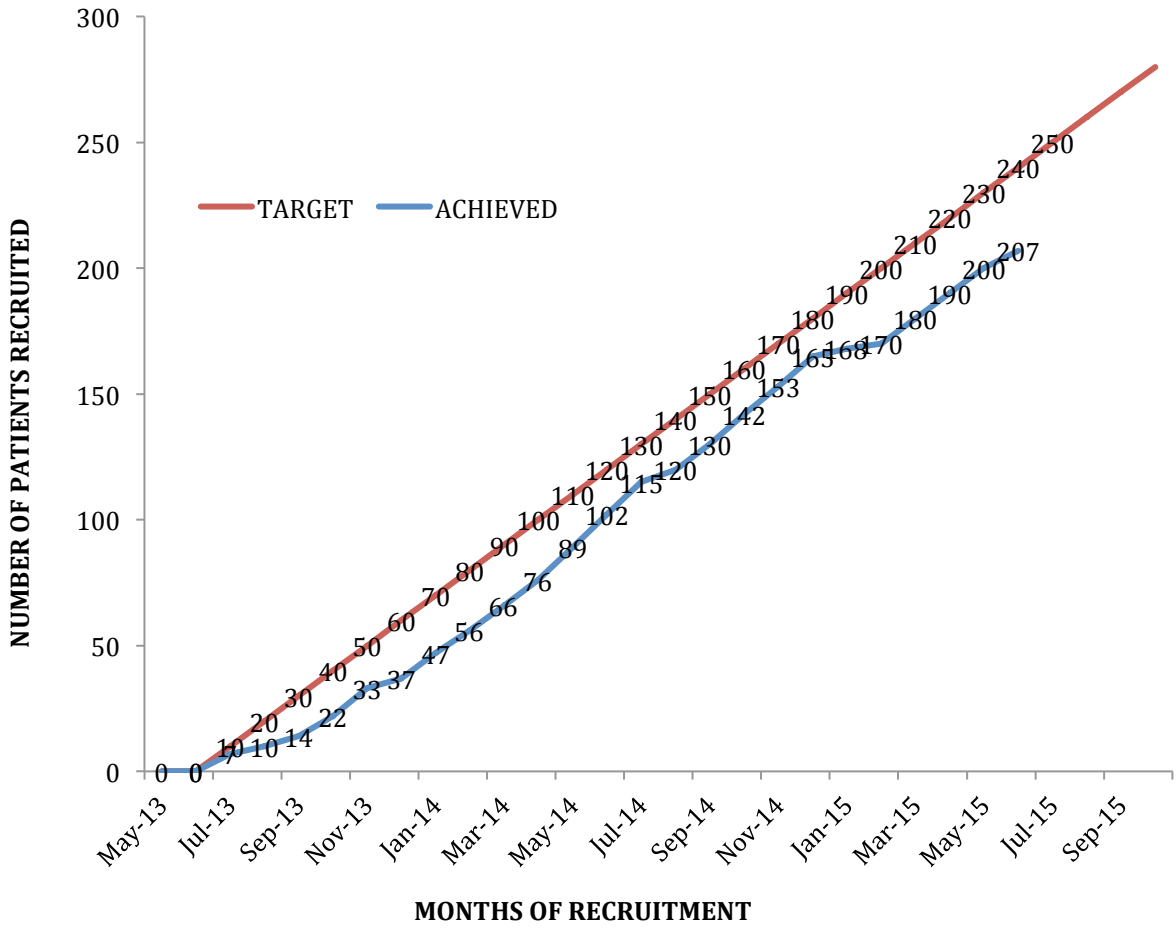
Method:

This randomised controlled trial was initiated by drafting the research proposal and gaining ethical approval for the research. The ethical approval was sought from Brent research ethics committee, ethical approval number being 13/LO/0550. Once the study was registered (ISRCTN43430382), the process of recruiting patients began in a single IVF centre catering for 1200 cycles per year. Couples with female age between 23-37 completed years and diagnosed with unexplained subfertility at the time of first treatment were deemed eligible for the trial. They were randomised to either 3 cycles of COH + IUI or one cycle of IVF, to be completed within a time horizon of 6 months. The primary outcome was the singleton live birth rate. Secondary outcomes consisted of the clinical pregnancy rates, multiple pregnancy rates and spontaneous conception rates. All outcome measures were analysed on an intention-to-treat basis.

Results:

Though the desired sample size was 250, only 207 patients could be recruited for the trial (Figure 2) due to a gradual withdrawal of funding for IUI by the Clinical Commissioning Groups (CCGs) following NICE guidelines.

Figure 2: Recruitment for the trial



Out of 207 couples, 101 couples were allocated to the COH (gonadotrophin) + IUI group, while 106 couples were allocated to the IVF group. In the COH + IUI group, the live birth rate per couple was 28.7% and for the IVF group the live birth rate per couple was 33.9%. There were 25 (24.7%) singleton live births for the IUI + FSH group and 33 (31.1%) for the IVF group, with a relative risk (RR) of 1.3 (95% CI 0.8 to 1.9) and an absolute risk difference of 6.4% (95% CI -5.8% to 18.6%). The multiple pregnancies per live birth were 4 (13.8%) for the IUI + FSH group and 3 (8.3%) for the IVF group, RR 0.6 (95%CI 0.1 – 2.4). There were no cases of ovarian hyperstimulation syndrome (OHSS) for the IUI group and three cases of OHSS (3.7%) in the IVF group. There were 17 live births from spontaneous conception in between treatment cycles (8.2%).

Conclusion:

The singleton live birth rate with one cycle of IVF was not significantly different than three cycles of IUI + FSH.

This MD thesis has taken four years from start to finish. The time allocated for the MD (Res) was four years. Though the study planning started in October 2012, it was only in June 2013 that the recruitment process started and I enrolled for MD in October 2013. The recruitment continued for two years, till August 2015 and then I had to wait for the delivery of the last recruited candidate who conceived before I could start analysing data.

Glossary of abbreviations

AFC	……	Antral follicle count
AMH	……	Antimullerian hormone
bHCG	……	Beta Human chorionic gonadotrophin
BMI	……	Body mass index
CC	……	Clomiphene citrate
CCG	……	Clinical Commissioning Group
COH	……	Controlled ovarian hyper stimulation
CPR	……	Clinical pregnancy rate
EM	……	Expectant management
EPAU	……	Early pregnancy assessment unit
FSH	……	Follicle stimulating hormone
GnRH	……	Gonadotropin releasing hormone
hCG	……	Human chorionic gonadotrophin
ICSI	……	Intracytoplasmic sperm injection
IQR	……	Interquartile range
IU	……	International unit
IUI	……	Intrauterine insemination
IVF	……	In vitro fertilization
LBR	……	Live birth rate
MPR	……	Multiple pregnancy rate
NHS	……	National Health Service
NICE	……	National Institute for Health and Care Excellence
OHSS	……	Ovarian hyper stimulation syndrome
SD	……	Standard deviation
TTP	……	Time to pregnancy

Acknowledgements

There are many people I would like to thank for their support throughout the duration of my research and thesis.

First and foremost, I would like thanking my supervisors, Professor Khalid Khan, Dr Richard Hooper and Professor Roy Homburg. Without their patience and kind support I could not have conducted the trial and written this thesis.

I am grateful to Dr Priya Bhide for helping me run the research trial smoothly.

I would like to thank all my colleagues at the Homerton Fertility Centre, the doctors, embryologists and nurses, for being supportive to me throughout the course of the trial.

I am deeply thankful to all the patients who took part in the study.

Last, but by no means least, I would also like to say a big thanks to my family, my husband and my daughter, for loving me so much and all the sacrifices they made to help me work on my research and thesis.

Signature: ……

Date:……..

Chapter 1: Introduction

Declaration: This chapter has contributed to the publication: Nandi A, Homburg R. *(2016). 'Unexplained subfertility: diagnosis and management'. The Obstetrician and Gynaecologist, 18: 107- 15*.

Unexplained subfertility usually refers to couples who fail to conceive after one year of regular unprotected sexual intercourse and in whom investigations for ovulation, tubal patency and semen analysis have been found to be normal[1, 2]. It affects as many as 30-40% of subfertile couples[3, 4]. While the average cycle fecundity without treatment in these women is 1.3%-4.1%[5], prognosis depends on the age of the female partner, duration of subfertility and previous obstetric history[6,7]. Differences of opinion exist among fertility specialists as to the optimal treatment for these couples[8].

1.1 Potential contributory factors (table 1)

The diagnosis of unexplained subfertility is made by exclusion. However, there are various potential contributing factors that are not detected by routine fertility investigations and could be responsible for the subfertility.

Table 1: Potential contributory factors

BOX 1:

Potential contributing factors

1. Increased age over 35 and low oocyte quality
2. Life style factors
3. Low ovarian reserve
4. Tubal function defects
5. Fertilisation defects
6. Implantation defects
7. Metabolic disorders, immunological and genetic factors
8. Endometriosis
9. Fibroids
10. Adenomyosis

1.1.1. Increased age of the female partner

With increasing age of the female partner, there is a decline in the total number of remaining oocytes and their quality[9], the latter of which can lead to an increase in the aneuploidy rate seen in the embryos from older women, leading to non-implantation and subfertility[10, 11]. A study by Maheshwari et al.[12] demonstrated that women over 35 years of age were more likely to have unexplained subfertility compared to their younger counterparts (OR 1.8, 95% CI 1.4-2.2).

1.1.2 Life-style factors and unexplained subfertility

Various modifiable lifestyle factors can contribute to unexplained subfertility. These include:

Smoking: Both active and passive smoking can adversely affect the potential to conceive by reducing the ovarian reserve and by altering tubal function and the uterine environment[13]. In men, it impairs the fertilising capacity of sperm by reducing mitochondrial activity and increasing DNA damage[14]. Fortunately, this damage can be reversed by quitting smoking[15].

Weight: Both obesity (BMI>30) and being underweight (BMI<19) can impair fertility even in young and regularly ovulating women[16]. Obesity can alter the follicular environment and lead to oocyte incompetence and suboptimal embryo quality[17], and impair implantation by negatively influencing the endometrium[18]. Obesity in men can contribute to subfertility by causing DNA damage in sperm[19] and decreased libido and erectile dysfunction due to conversion of androgen to oestrogen, thereby causing reduced levels of testosterone[20].

Alcohol: Excessive alcohol intake can cause subfertility. In men, even habitual drinking over 5 units per week has been found to have an adverse effect on sperm quality[21]. Alcohol consumption in women can reduce fertility by

decreasing the implantation rate, and by causing luteal phase dysfunction and abnormal embryo development[22]. However, it is not quite clear how much alcohol is actually harmful[23].

Others: Other factors that can have an impact on fecundity include psychological stress, environmental exposure to pollutants, use of illicit drugs and caffeine. The evidence on these is not conclusive due to the difficulty in conducting trials[24].

1.1.3 Ovarian reserve

The ovarian reserve is the size of the remaining follicle pool in the ovary at any point of time, which often indicates the capacity of the ovary to produce an oocyte, which can be fertilised and result in a successful pregnancy. The rate of follicular depletion varies between individuals and hence the ovarian reserve[25]. While the woman's age remains the single most important factor in determining the reproductive outcome, the ovarian reserve is limited to the prediction of ovarian response in an ART cycle[26]. Younger women with a low ovarian reserve are more likely to have cycle cancellation due to poor oocyte yield in in vitro fertilisation (IVF), but once the oocytes are retrieved they achieve near normal pregnancy rates[27].

1.1.4 Tubal function defects

Like tubal patency, the tubal function is also important to achieve successful pregnancy. Optimal tubal functions such as adequate ciliary motion and muscular activity are required for sperm-oocyte interaction and transport of the embryo to the uterine cavity for implantation[28]. Milder forms of gonorrhoea and chlamydia infection can cause tubal function defect without causing overt occlusion[29]. Impaired tubal function in otherwise patent tubes can lead to subfertility in these couples.

1.1.5 Fertilisation defects

Subtle defects in oocyte and sperm, leading to defective fertilisation, could be a possible cause for unexplained subfertility. Sperm defects such as abnormal acrosomes resulting in poor or no zona pellucida binding[30] or defects in acrosome reaction resulting in failure of sperm-zona pellucida penetration, have been proposed to be possible factors leading to subfertility[31]. Sperm DNA integrity has been proposed to be a pre-requisite for normal fertilisation[32]. An otherwise normal semen analysis as per WHO criteria may include sperm with altered genetic material caused by various factors such as defects in chromatin remodelling at the time of meiotic division, post testicular oxidative stress, various environmental factors or advanced male age[32]. High levels of sperm DNA fragmentation could lead to reduced fertilisation and increased miscarriage rate[33, 34]. A variety of in vitro tests are available to detect sperm function defects, such as the ability of sperm to penetrate cervical mucus surrogate, quantification of sperm-zona binding using hemi-zona pellucidae, and various flow cytometric methods to detect sperm DNA fragmentations, including SCSA (Sperm Chromatin Structure Assay), single cell gel electrophoresis (COMET assay) and Terminal Uridine Nick-End Labelling (TUNEL assay)[35]. However, their clinical utility has been undermined by the introduction of intracytoplasmic sperm injection. Hence these tests do not form part of routine investigations[2].

1.1.6 Implantation defects

Undoubtedly a receptive endometrium is essential for successful implantation and pregnancy. Various biochemical factors such as cytokines, LIF (leukemia inhibitory factor), IL-1 (Interleukin -1), and the chemokines CX3CL1 and CCL14, have been proposed to be involved in endometrial receptivity[36, 37]. Alterations of

these factors in the endometrium can cause subfertility. There are no standard tests to detect these defects.

1.1.7 Immunological, metabolic and genetic factors

Dysregulation of the immune system and increased production of auto-antibodies have been postulated to be responsible for unexplained subfertility. Autoimmune antibodies such as anti-thyroid, anti-ovarian, antinuclear, antiphospholipid and anti-smooth muscle antibodies have been associated with unexplained subfertility[38]. While the exact role of these auto-antibodies in the pathogenesis of unexplained subfertility is unclear, various theories have been put forward, including reducing fertilisation rate, interfering with early implantation and modulating the function of FSH and thereby influencing ovarian function[38, 39]. In addition to altered immune response, there are suggestions that thrombophilic gene polymorphism, such as the MTHFR (methylene tetrahydrofolate reductase) gene polymorphism, could be a cause of unexplained subfertility[40]. Again, the possible mechanism could be by causing early implantation failure; however, more evidence is needed to confirm this[41]. Oxidative stress due to an imbalance between reactive oxygen species and anti-oxidants can be caused by various factors, including obesity, smoking, alcohol, recreational drug use and environmental exposure to various toxins. Oxidative stress has been linked with not only male subfertility by causing damaged sperm[42], but also with female subfertility, although in this latter case the mechanism is not clear[43].

1.1.8 Endometriosis

About 30% of asymptomatic women with otherwise unexplained subfertility are diagnosed with mild endometriosis following laparoscopy[44]. The fecundity of women with mild endometriosis is similar to women with unexplained

subfertility[45]. There is no evidence that medical treatment of mild endometriosis improves fertility in these women. Moreover, laparoscopic ablation only improves live birth rate to a small extent [46,47,48]. As per the European Society of Human Reproduction and Society (ESHRE) guideline on management of endometriosis, for women with American Society of Reproductive Medicine (ASRM) stage I/II endometriosis, excision of endometriosis lesion, ovarian endometrioma and adhesiolysis is recommended as it increases the spontaneous conception rate. However, patients should be counselled about the risks of reduced ovarian reserve and loss of ovary after the surgery[127].

1.1.9 Fibroids

The role of fibroids in causing subfertility is unclear. The submucosal component of fibroids could be associated with reduced conception but evidence remains scarce[49, 50]. There is insufficient evidence that myomectomy for intramural or subserosal fibroids improves pregnancy rates[51]. The recent ASRM guideline on treatment of myomas in asymptomatic patients to improve fertility recommends myomectomy (laparoscopic or hysteroscopic) for cavity distorting myomas only. For asymptomatic patients with non-cavity distorting myomas, myomectomy may be considered only in presence of severe pelvic distortion to improve access to ovaries for egg retrieval during IVF[52].

1.1.10 Adenomyosis

The impact of adenomyosis or its treatment on fertility remains unsubstantiated due to paucity of data[53]. Therefore, subfertility in women with adenomyosis remains unexplained for the time being.

1.2 Investigations for unexplained subfertility (table 2)

The tests performed to diagnose unexplained subfertility are not without their limitations and even the most sophisticated tests can fail to detect subtle causes of subfertility.

Table 2: Investigations for Unexplained Subfertility

Investigations for Unexplained Subfertility

1. Detection of ovulation
    a. Urinary LH estimation
    b. Urinary pregnanediol glucoronide
    c. Mid-luteal progesterone
    d. Ultrasound monitoring of follicular growth and confirmation of follicular rupture.
2. Tubal patency test
    a. Hysterosalpingogram (HSG)
    b. Hystero contrast sonosalpingography (HyCoSy)
    c. Laparoscopy and dye test
3. Semen analysis
4. Pelvic ultrasound and saline infusion sonography
5. Ovarian reserve testing
6. Laparoscopy in symptomatic women
7. Hysteroscopy in known uterine anomaly or pathology

1.2.1 Detection of ovulation

While there are various strategies to detect ovulation, none of these tests can detect the quality of the oocyte. Tests such as the urinary Luteinising Hormone (LH) estimation, pregnanediol glucoronide, mid-luteal phase progesterone levels and ultrasound monitoring of follicular growth might detect ovulation; however they might fail to diagnose ovulation if not performed at the right time of the menstrual cycle[2,54]. The presence of a regular menstrual cycle in itself is a fair indicator of regular ovulation and the chances of anovulation in a woman with regular menstrual cycle are rare[2,55].

1.2.2 Tubal patency test

Assessment of tubal patency can be achieved by various methods such as hysterosalpingogram (HSG), hystero-contrast sonosalpingography (HyCoSy), and laparoscopy and dye test. None of these methods can detect tubal function defects that can potentially contribute to the subfertility of the couple.

1.2.3 Semen analysis

This remains the most important investigation of the male partner. In 2010, new WHO (World Health Organisation) criteria for semen analysis were released using lower reference limits (table 3)[2, 56]. While the result of semen analysis yields evidence of concentration, motility and morphology of sperm, it provides no assessment of sperm function[57], which could potentially affect fertility.

Table 3: World Health Organisation 2010 criteria for normal semen analysis

Criteria	Parameters
Volume	≥1.5ml
PH	≥7.2
Sperm Concentration	≥15 x 10^6 /mL spermatozoa
Total sperm count	≥39 x 10^6 spermatozoa
Total Motility	≥40%
Progressive motility	≥32%
Vitality	≥58% live spermatozoa
Morphology	≥4% with normal morphology

1.2.4 Ovarian reserve tests

Tests available for ovarian reserve are basal FSH (early follicular phase - day 2-5 of the menstrual cycle), inhibin A and B, anti-Mullerian hormone (AMH), antral follicle count, ovarian volume, clomiphene citrate challenge test, and the exogenous FSH ovarian reserve test[58]. Though basal FSH is the most frequently

used, it presents significant intra- and inter-cycle variability, which limits its reliability. AMH on the other hand can be measured at any time during the menstrual cycle and both AMH and antral follicle count have good predictive value for response to ovarian stimulation[59]. While these tests predict the response to ovarian stimulation during IVF, they are quite limited in their accuracy to predict chances of spontaneous conception[60,61]. However, according to the American College of Obstetricians and Gynaecologists it is reasonable to encourage a woman to attempt to conceive sooner rather than later if her ovarian reserve is found to be diminished, as her window of opportunity to conceive might be shorter than anticipated[62].

1.2.5 Diagnostic laparoscopy

Women with unexplained subfertility with tubal patency confirmed by normal HSG findings can still have peri-tubal adhesions and/or endometriosis, which can lower the chances of their spontaneous conception[63]. However it is difficult to predict who is going to benefit most from the surgery and the concerns are increased cost along with surgical risks and patient anxiety. Both ASRM (The American Society for Reproductive Medicine) and NICE suggest laparoscopy only in women with symptoms of comorbidities[2,64]. In 2010, Badawy et al showed in a prospective randomised controlled trial that diagnostic laparoscopy could be postponed until 3-6 failed cycles of ovarian stimulation and timed sexual intercourse[65]. While it is reasonable to postpone laparoscopy in asymptomatic women with normal HSG and no previous history of pelvic infection or surgery, it might be of value in selected patients who have experienced multiple failed ovarian stimulation with or without intrauterine insemination[66, 67].

1.2.6 Hysteroscopy

Hysteroscopy is a reliable way to diagnose and treat uterine cavity anomalies such as fibroids, polyps, septum and adhesions[68]. Women with unexplained subfertility might benefit from hysteroscopic removal of submucous fibroids and polyps to improve their chances of conceiving[50]. Where facilities are available, saline infusion sonography along with 3-D ultrasound can offer a less invasive outpatient method to assess the uterine cavity with accuracy similar to hysteroscopy[69].

1.3 Treatment options for unexplained subfertility:

In the absence of a definitive diagnosis, the treatment of unexplained subfertility remains empirical[4]. Though various treatment strategies are available, evidence is lacking to confirm the superiority of one over the other.

Table 4: Treatment for Unexplained Subfertility

Treatment for Unexplained Subfertility

1. Expectant management
2. Ovulation induction (clomiphene citrate, letrozole, gonadotrophins)
3. IUI with or without ovarian stimulation
4. IVF

NICE guideline recommendations 2013: Do not offer IUI routinely for people with unexplained subfertility who have regular unprotected sexual intercourse. Consider IVF after two years of expectant management.

1.3.1 Expectant management

The chances of spontaneous conception remain high in couples with unexplained subfertility. In a multicentre cohort study with 437 couples with unexplained

subfertility, 74% of couples conceived spontaneously[7]. A Dutch multicentre trial randomised 253 couples with unexplained subfertility and intermediate prognosis of natural conception within 12 months into two groups, one receiving expectant management and the other intrauterine insemination with controlled ovarian hyperstimulation, with both groups undergoing treatment for 6 months. They showed similar on-going pregnancy rates between the two groups (23% for the intervention group and 27% for the expectant management group)[70] and a saving of €2616 per couple in favour of expectant management[71]. Though expectant management is a valid option for couples with favourable prognosis, it remains challenging for clinicians to decide the best candidate for this treatment. Various prediction models have been developed to help clinicians in this regard. There are 29 such models. However they have been developed for different patient profiles and lack thorough external validation[72]. Though these models can be used for decision-making purposes for couples similar to the population it was developed for, there remain concerns regarding their generalisability across different patient profiles. On the other hand, expectant management might not be acceptable to many couples as further attempts to conceive naturally add to already existing stress and frustration[73], leading to overtreatment in many of these cases[74].

1.3.2 Tubal flushing or perturbation

The possible therapeutic benefit of tubal flushing during HSG has been known to gynaecologists for over half a century. Various oil-soluble and water-soluble contrast media have been used for HSG and have been linked to an increase in the chance of pregnancy. The latest Cochrane review summarised twelve trials involving 2079 participants and concluded that oil-soluble contrast media increases the odds of live birth in comparison to no treatment (Peto OR 2.98,

95% CI 1.40-6.37), but could not confirm any benefit of oil-soluble versus water-soluble media due to lack of an appropriate trial[75]. Possible mechanism of action are mechanical (removal of tubal debris) or immunological (affecting peritoneal cytokines and preventing peritoneal mast cell phagocytosis of spermatozoa) or an effect on the endometrium to promote implantation[76]. However, oil-soluble contrast media have been widely replaced by water-soluble contrast media due to better image quality and early dissipation, which removes the need for delayed films and possibility of granuloma formation with oil-soluble media.

1.3.3 Clomiphene citrate ± intrauterine insemination

Clomiphene citrate acts as an anti-oestrogen, which increases endogenous FSH and thereby stimulates multiple follicular developments. While its effectiveness has been described in cases of oligo-ovulation, questions have been raised regarding its usefulness in otherwise ovulatory women[77]. A Cochrane review summarised 14 clinical trials (1159 participants) and found no clinical benefit of clomiphene citrate in unexplained subfertility[78].

1.3.4 Intrauterine Insemination (IUI)

IUI + COH is widely used in cases of unexplained subfertility before resorting to more invasive options such as IVF. This procedure involves placing washed sperm into the uterine cavity around the time of ovulation. It has been used both with and without ovarian stimulation. A recent Cochrane review has shown that IUI + COH increases the live birth rate more than two fold compared to IUI in a natural cycle (OR 2.07, 95% CI 1.22-3.5)[79]. COH may correct subtle problems of ovulation or slightly increase the number of oocytes available for fertilisation, thereby increasing the chances of pregnancy[80]. A major concern however with multiple follicle development in IUI + COH is multiple pregnancies[81]. Using mild ovarian hyper stimulation and strict cancellation policies, multiple pregnancy

rates can be kept to approximately 10% without reducing pregnancy rates[82]. Two studies failed to show any benefit of IUI with or without COH over expectant management in terms of live birth rates in these couples[70,77]. Based on this evidence, NICE recommends not to routinely offer IUI for couples with unexplained subfertility but to proceed directly to IVF after two years of infertility. However, the success of IUI remains a controversial issue, as it depends on multiple factors[83]. Moreover, a recent survey of fertility clinicians in the UK with a response rate of 33% found that more than 80% would still consider IUI + COH in these patients[8].

1.3.5 In vitro fertilization (IVF)

With advances in assisted reproductive techniques, IVF has emerged as a safe and successful treatment option. However, debate continues as to whether it should be the sole treatment for these couples.

The first randomised controlled trial by Goverde et al. (2000)[84] compared six cycles of IUI in a natural cycle versus six cycles of IUI + COH versus six cycles of IVF in 258 couples with unexplained subfertility and mild male factor. They found that though the pregnancy rate per cycle was better with IVF compared to IUI in natural cycle or IUI + COH (12.2% vs 7.45% and 8.7%, respectively), there was no difference in the cumulative pregnancy rates (38% vs 31% vs 37%, respectively). However over the years pregnancy rates from IVF continued to improve and the current UK IVF success rates stand at 27%-32% for women under 37 years of age (HFEA. *Latest UK IVF figures: 2010 and 2011*). One might argue that the pregnancy rate reported by Goverde et al. is out of date.

Reindollar et al. (2010)[85] showed in a large randomised controlled trial the effectiveness of moving to IVF after a course of clomiphene citrate and IUI

compared to conventional treatments of clomiphene citrate and IUI and FSH and IUI and then IVF. In addition to achieving higher pregnancy rates, IVF allowed women to conceive 3 months faster. The same group compared two cycles of clomiphene citrate and IUI vs two cycles of FSH and IUI vs immediate IVF in 154 couples with older women (38-42 years) and demonstrated superior pregnancy rates and fewer treatment cycles with immediate IVF[86].

Custers et al. (2011)[87] randomized 116 couples with unexplained subfertility and mild male factors and unfavourable prognosis of natural conception into two groups, one receiving one cycle of IVF-eSET (elective single embryo transfer) and the other three cycles of IUI + COH. They showed similar live birth rates, with 24% in the IVF-eSET group and 21% in the IUI + COH group (relative ratio 1.17; 95% CI 0.60-2.30) and found IUI + COH to be more cost effective[88].

The most recent study by Bensdorp et al. (2015)[89] sheds new light on the effectiveness of IUI and IVF for these couples. In this multicentre randomised controlled trial involving 17 centres in The Netherlands, 602 couples with unexplained subfertility and mild male factors and unfavourable prognosis for natural conception were randomised into three groups, one receiving three cycles of IVF and single embryo transfer, the second six cycles of IVF in a modified natural cycle and the third receiving six cycles of IUI and COH. They found comparable singleton live birth rates (52% vs 43% vs 47%, respectively) and comparable multiple pregnancy rates (6% vs 5% vs 7%, respectively) between the treatments.

In 2015, a Cochrane review summarised these trials and failed to prove the effectiveness of IVF over IUI with ovarian stimulation. They did not find any significant differences in multiple pregnancy or ovarian hyperstimulation

syndrome rates between the two treatments[90].

From the existing literature, it appears that though the per-cycle success rate of IUI is lower compared to IVF (9% vs 22%)[91], cumulative success rates are comparable to IVF[89]. From the couple's perspective, IUI remains less invasive, less stressful and less time consuming than IVF. Moreover, perinatal outcomes for singletons are better with IUI compared to IVF[92]. Hence IUI + COH remains a very realistic treatment option.

1.3.6 ICSI (Intracytoplasmic sperm injection)

In 5%-25% of cases of unexplained subfertility, no fertilisation has been reported with conventional IVF procedures[93]. This could be due to occult abnormalities in the sperm or oocyte[94, 95]. Intracytoplasmic sperm injection (ICSI) has been advocated for these couples[96]. However, studies have failed to show any benefits of ICSI over IVF in terms of clinical pregnancy rates (33% IVF vs 26% ICSI)[97] or live birth rates (46.7% IVF vs 50% ICSI)[98]. Recently, a systematic review summarized eleven studies with a total of 901 couples and showed a higher fertilisation rate with ICSI compared to IVF (RR 1.49, 95% CI 1.35-1.65) and the need to treat five patients with ICSI to prevent one case of fertilisation failure[99]. Due to paucity of data they could not analyse the pregnancy outcome with ICSI in comparison to IVF. Neither NICE nor the ASRM practice committee recommend routine ICSI for unexplained subfertility [2, 100]. However routine use of ICSI for at least some oocytes (split IVF-ICSI) offers several benefits. It allows detection of fertilisation defects, reduces risk of failure to fertilise and identifies couples who would need ICSI in subsequent cycles.

1.3.7 Cost analyses

One of the important factors to consider is the cost of the treatments. The difficulty in performing this kind of analysis is due to the differences in the cost of treatment between different countries and between different regions in the same country. The study by Reindollar et al. (2010)[85] found a saving of $2624 per couple in the immediate IVF arm and 0.06 more deliveries. However, they analysed the cost according to the insurer's charge data, which could be quite different from the cost of fertility treatment when government-funded. Likewise, the cost-effective analysis by Chambers et al. (2010)[101] showed IVF to be cost-effective. However, this study can be criticised, as the study population consisted of patients from private clinics and the study design was a cohort study. Cohort studies being observational studies have inherent limitations of selection bias and unrecognized confounding factors, which might distort the results. On the contrary, van Rumste et al.[88] showed a cost saving with three cycles of IUI + COH in comparison to one cycle of IVF-eSET in a randomised controlled trial in the Netherlands where fertility treatments are covered by healthcare insurance. These differences between private and government-funded treatments reduce the generalised applicability of this kind of analysis.

Chapter 2: Review of literature

2.1 Introduction

IUI with controlled ovarian hyper-stimulation (IUI+COH) remains the preferred choice among many women with unexplained subfertility, as it is less time-consuming, cheaper and also less invasive. However, the treatments of unexplained subfertility have always been a matter of debate. While some have questioned the use of agents to induce ovulation in women who are already ovulating[102], others have observed that the use of intrauterine insemination is only a modified substitute for natural intercourse[70]. New NICE guidelines suggest abandoning intrauterine insemination completely for these women in favour of IVF after 2 years of expectant management[2]. Not many RCTs have been conducted to compare the efficacy of IUI and ovarian stimulation to IVF in these couples. A Cochrane review in 2012 (updated in 2015) has admitted that the effectiveness of IVF for unexplained subfertility relative to intrauterine insemination remains unproven[90]. A systematic review and meta-analysis of the existing literature was conducted to examine the effectiveness of IUI+COH vs IVF, the two most commonly used first line management options for unexplained subfertility.

2.2 Methods

2.2.1 Search methods

Medline, Embase, CINAHL, PscyInfo, and Cochrane Library were searched for relevant studies published between 1980 and May 2015. A combination of medical subject headings (MeSH) and text words were used to generate two subsets of citations, one including studies on IVF ('in vitro fertilization', 'in vitro fertilisation', 'fertilization in vitro', IVF), IUI ('insemination', 'insemination, artificial', 'insemination, artificial, homologous', 'intrauterine insemination',

intrauterine insemination) and controlled ovarian stimulation or controlled ovarian hyperstimulation, and another including studies with unexplained subfertility ('unexplained subfertility', 'unexplained infertility', 'idiopathic subfertility', 'subfertility with patent tubes'). These subsets were then combined using 'AND' to generate a subset of citations relevant to the research question. The reference lists of the selected articles were searched to identify any relevant article not picked up by the electronic search. The authors were contacted where necessary. The study protocol has not been registered prospectively with PRISMA. However, there is a definite plan to submit the article for publication in a peer-reviewed journal.

2.2.2 Study selection for the review

2.2.2.1 Type of studies/participants

Only randomised controlled trials were included without language restrictions. The review was restricted to published, full-text articles.

Female patients aged 18 to 43 years with regular menstrual cycles and patent fallopian tube (one or both), mild endometriosis and with a male partner having normal semen parameters or mild male factors, and experiencing at least 1 year of subfertility were included for the review.

2.2.2.2 Type of intervention

Trials comparing IUI+COH (including controlled ovarian stimulation or controlled ovarian hyperstimulation) vs IVF in couples with unexplained subfertility were considered for the review.

2.2.2.3 Outcome measures

The primary outcome was the live birth rate, while the secondary outcome was clinical pregnancy rates, multiple birth rates, miscarriage and OHSS rates.

2.2.2.4 Exclusion criteria

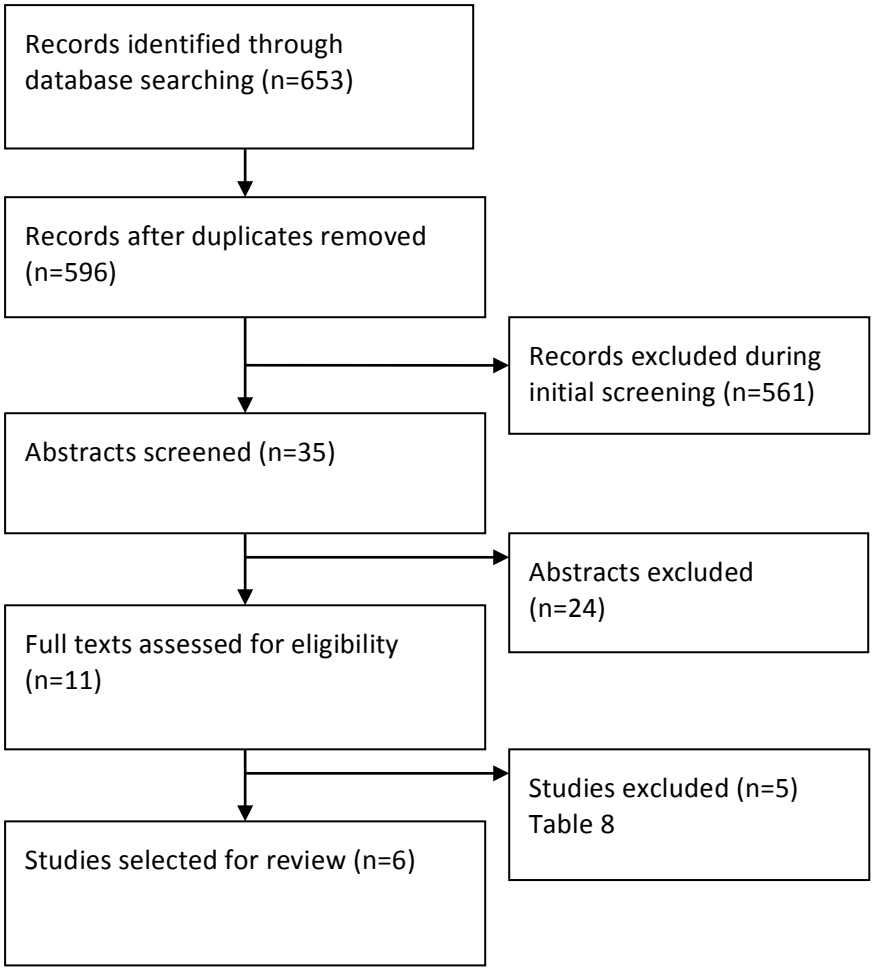
Subfertility for other reasons, such as tubal factors, anovulation, and severe male factors, were excluded. Abstract-only articles or unpublished articles were rejected.

2.3 Results

2.3.1 Study selection

The literature search identified 653 citations. A review of the citations identified 34 abstracts, which were further reviewed to identify 11 eligible studies. Full texts of all 11 studies were retrieved. Six fulfilled all the inclusion criteria and were included in the meta-analysis[84,85,86,87,89, 103] including a total of 1183 couples; the remaining five were excluded[104, 105, 106, 107, 108] (Figure 3, table 5).

Figure 3: Flow diagram of studies



2.3.2 Data extraction and quality assessment

All included studies were assessed for data extraction and quality assessment. Study characteristics, including study type, inclusion criteria, recruitment procedure, intervention, setting, and outcome measures, were extracted from each study (summarized in tables 5 and 6). All studies included were then assessed for trial quality following Cochrane guidelines[109]. Risks of bias in randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other areas were graded for all studies as low, high or unclear (table 7). Reasons for excluding a study were also noted and summarized (table 8).

Table 5: Characteristics of studies comparing IUI + COH vs IVF in unexplained subfertility

Study	Type	Total number of participants	Interventions compared	Intrauterine insemination + controlled ovarian hyperstimulation	IVF	Outcome reported
Custers et al. 2011	Multi-centre RCT	116	One cycle of IVF-eSET vs 3 cycles of intrauterine insemination-COS.	58	58	CPR, LBR
Elzeiny et al. 2014	Single-centre RCT	43	Randomisation was done three to one to intrauterine insemination or IVF.	33	10	CPR, LBR
Goverde et al. 2000	Single-centre RCT	258 (181 with idiopathic subfertility)	Maximum of 6 treatment cycles of lUI in a spontaneous cycle, lUI in a mildly hyperstimulated cycle, or IVF.	61	61	LBR
Reindollar et al. 2010	Two-centre RCT	503	Conventional treatment vs accelerated treatment. Conventional treatment: 3 cycles of clomiphene citrate/intrauterine insemination, 3 cycles of FSH/intrauterine insemination and up to 6 cycles of IVF. Accelerated treatment: 3 cycles of clomiphene citrate/intrauterine insemination followed by 6 cycles of IVF.	169	172	CPR, LBR

Goldman et al. 2014	Two-centre RCT	154	Three arm trial - 2 cycles of clomiphene citrate and IUI vs 2 cycles of FSH and IUI vs 2 cycles of IVF.	52	51	CPR, LBR
Bensdorp et al. 2015	Multi-centre RCT	602	Three arm trial - 6 cycles of IUI and controlled ovarian hyperstimulation vs 6 cycles of IVF in a modified natural cycle vs 3 cycles of IVF and single embryo transfer.	207	201	CPR, LBR and healthy baby

Table 6: Patient characteristics and intervention details of studies comparing IUI + COH vs IVF in unexplained subfertility

Study	Type of sub fertility	Duration of sub fertility (Months)	Inclusion criteria	Exclusion criteria	IUI + COH	IVF	Outcome
Custers et al. 2011	Unexplained sub fertility + mild male factors with chance of natural conception <30%.	12	Age <38 years, at least one tube patent, evidence of ovulatory cycle, total motile sperm count >10 x 10^6. Those with total motile sperm count 3-10 x 10^6 were included as mild male factor.	Severe male factor, cervical factor and polycystic ovary syndrome, female age >/=38 years prior to treatment.	Ovarian stimulation with 50-75 IU of rFSH. Cycle cancelled if > three dominant follicles. Ovulation induced with 5000 -10000 IU of hCG (human chorionic gonadotropin). 0.2 to 1.0ml of semen, processed within 1 hour of ejaculation by density gradient centrifugation followed by washing with culture medium, was inseminated 36-40 hours after HCG administration.	Long agonist protocol with rFSH 100-150 U until >3 follicles >18mm had developed. Oocytes retrieved after 36 hours of hCG. On day 3, one embryo was transferred if >1 good quality embryos were available. If no good quality embryos were available then two embryos were transferred.	CPR: 15 (25%) in the IVF group and 14 (24%) in the IUI + COH group. LBR: 13 (22%) in the IVF group and 12 (21%) in the IUI group.
Elzeiny et al. 2014	Unexplained sub fertility + mild male factors.	12	Age 18-42 years with evidence of ovulation and tubal patency.	IUI or IVF treatment in the previous 12 months, coital disorder, untreated ovulatory disorder or endometriosis (American Fertility	Recombinant FSH 112.5 IU/day starting from day 3. GnRH antagonist (Cetrorelix) 250 µg given when a follicle reached 14mm. Women who achieved 2-3 pre-ovulatory	Recombinant FSH 112.5 IU/day starting from day 3. GnRH antagonist (Cetrorelix) 250 µg given when a follicle reached 14mm. Women who achieved 2-3 pre-ovulatory follicles of	CPR: 4 (40%) for IVF, 4 (12%) for IUI. LBR: 4 (40%) for IVF, 2 (6%) for IUI.

				Society criteria grade 2-4), tubal obstruction, abnormal semen analysis (conc <20 million/ml, progressive motility <25%, abnormal morphology >95% or positive sperm antibodies), or any contraindication for multiple pregnancy.	follicles of >16mm at the time of hCG were randomised to 3 to 1 to IUI or IVF. Final oocyte maturation was induced with 250 microgram of r-hCG when follicles had reached 18 mm and IUI or IVF was scheduled 36 hours later. Fresh semen was collected after 2 days of abstinence and 0.5 ml was used for insemination.	>16mm at the time of hCG were randomised to 3 to 1 to IUI or IVF. Final oocyte maturation was induced with 250 microgram of r-hCG when follicles had reached 18 mm. Oocyte retrieval was performed 36 hours after hCG administration. One or two embryos were transferred at the cleavage stage. Supernumerary embryos were cryopreserved.	
Goverde et al. 2000	Unexplained sub fertility + mild male factors.	Unexplained sub fertility for at least 3 years or male sub fertility for at least 1 year.	Basal body temperature chart, a late luteal phase endometrial biopsy, a post-coital test, a hysterosalpingogram, a diagnostic laparoscopy and at least two semen sample analyses. Unexplained subfertility was diagnosed if no abnormality was found in above tests. Mild male factors were included. No female age is mentioned.	Women with cycle disorders, untreated endometriosis, bilateral occluded tubes or if semen sample yielded less than 1 million progressively motile sperms after centrifugation, if >20% spermatozoa carried antibodies or if >50% sperms had no acrosome.	FSH 75 IU daily until TVS showed at least one follicle with a diameter of 18mm. 10,000 IU hCG was given when urinary test showed LH surge or at least one follicle >18 mm size. Single intrauterine insemination done 20-30 hours after a positive surge or 40-42 hours after hCG.	For women ≤38 years: long agonist protocol with human menopausal gonadotropins 150 - 225 IU for COH. For women >38 years: short stimulation protocol was used. When TVS showed at least one follicle of size 18mm or at least three follicles >16 mm, 10,000 IU hCG were given followed by follicle aspiration 35 hours later. Maximum two embryos (day 2-3) were transferred in women ≤35 years and three embryos were transferred for women >35 years.	LBR: 31 (37%) - live birth in IUI + COH, 33 (38%) - live birth after IVF.
Reindollar et al. 2010	Unexplained sub fertility	12	Age between 21-39 years with at least one ovary and ipsilateral patent fallopian tube, no pelvic pathology, ectopic pregnancy, or previous subfertility	Presence of hydrosalpinges, stage 3/4 endometriosis, donor sperm, the need for assisted reproductive procedures other than	Recombinant FSH (150IU) was given subcutaneously until a lead follicle measured >17 mm and 2-3 follicles >15mm in size were detected. A single IUI was	Long agonist protocol with FSH 225 IU was given until a lead follicle measured >17 mm and there were at least three follicles >15 mm in size. Oocyte retrieval was performed 36	CPR: 50/169 (10.8%) for IUI + FSH in the conventional arm, 145/172 (84.3%) for IVF in the accelerated arm.

			treatment (with exception of up to three cycles of clomiphene without intrauterine insemination. Day 3 FSH of <15mIU/ml and E2 <100 pg/ml and sperm concentration of >15 million total motile sperm or >5 million total motile sperm at intrauterine insemination preparation.	IVF.	performed 36 hours after the hCG was administered.	hours after hCG. ICSI was allowed when <10 million total motile sperms were available for IVF.	LBR: 37/169 (22%) for the IUI + FSH in the conventional arm, 100/172 (58%) for the IVF in the accelerated arm.
Goldman et al. 2014	Unexplained subfertility.	6	Age 38-42 years with at least one ovary, unilateral patent fallopian tube, regular menstrual cycles 21-45 days, no pelvic pathology, ectopic pregnancy or previous infertility treatment (except three cycles of clomiphene without IUI), clomiphene challenge test (100mg clomiphene on cycle days 5-9; FSH values of <15 mIU/mL on cycle days 3 and 10; and estradiol value of <100pg/mL on cycle day 3), normal prolactin and thyroid-stimulating hormone levels and a body mass index (BMI) ≤38, sperm concentration of ≥15 million total motile sperm.	Not fulfilling inclusion criteria.	300 IU of recombinant FSH was started on day 3 for 3 days. 10,000 units of hCG were administered when a lead follicle reached size 17mm or 2-3 follicles of >15mm were detected. Single IUI was performed on second morning after hCG.	Oral contraceptive pills for 21 days followed by 40µg leuprolide acetate twice daily till day of hCG. FSH was started on day 3 of leuprolide acetate with a dose of 300 IU in the morning and 150 IU HMG in the afternoon. This twice-daily FSH was continued for 3 days and then dose was adjusted as per ultrasound and estradiol monitoring. 10,000 units of hCG were administered when a lead follicle reached size 17mm or 2-3 follicles of >15mm were detected. Oocyte retrieval was done 36 hours after hCG and embryos were transferred on day 3. Embryos were transferred as per ASRM guideline.	CPR: 9 (17.3%) after first two cycles of FSH and IUI 25 (49%) after first two cycles of IVF. LBR: 7 (13.5%) after IUI + FSH 16 (31.4%) after IVF.

Bensdorp et al. 2015	Unexplained subfertility + mild male factors with chance of natural conception <30% in next 12 months as per Hunault model.	12	Age between 18 -38 years with at least one patent fallopian tube, ovulatory menstrual cycle, and normal semen analysis with pre-wash total motile sperm count above 10 million. Those with pre-wash total motile sperm count between 3 and 10 million were considered as mild male factor.	Anovulation, bilateral tubal block, severe endometriosis, premature ovarian failure and known endocrine disorders such as Cushing's syndrome, adrenal hyperplasia.	COH was performed with 100mg clomiphene citrate (day 3 -7) or 75 IU FSH. When at least one follicle reached size 17 -18 mm, ovulation was induced with 5000 units of hCG and 36 hours later IUI was performed.	Either long/ short or antagonist protocols were used. COH was started with 150 IU of FSH. When at least two follicles developed to >18mm, ovulation was induced with 10,000 units hCG and oocytes were retrieved 36 hours later. If good quality embryos were available, then one embryo was transferred and the rest cryopreserved. Embryos were transferred on day 3.	CPR: 132 (64%) for IUI + COH, 135 (67%) for IVF. LBR: 116 (56%) for IUI + COH and 118 (59%) for IVF. Healthy child: 97 (47%) for IUI and 104 (52%) for IVF.

Table 7: Quality of studies

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Custers et al. 2011	Computer-generated randomisation LOW RISK	Central Internet-based randomisation LOW RISK	Not mentioned UNCLEAR RISK	Not mentioned UNCLEAR RISK	All missing data and drop outs mentioned LOW RISK	Reported primary, secondary outcomes LOW RISK	Free of other sources of bias LOW RISK
Elzeiny et al. 2014	Computer-generated, adaptive-biased coin randomisation schedule LOW RISK	Sequentially numbered opaque sealed envelopes LOW RISK	Not mentioned UNCLEAR RISK	Not mentioned UNCLEAR RISK	All missing data and drop outs mentioned LOW RISK	Reported primary, secondary outcomes LOW RISK	Initial sample size was 812. Interim analysis of the first 40 subjects indicated the pregnancy rate with IVF was much higher than predicted and that it was unlikely that intraute

							rine insemination would be cost-effective. Hence, trial design was changed and new sample size of 10 subjects in the IVF arm and 30 in the intrauterine insemination arm was calculated. This could potentially be a cause for bias
Goverde et al. 2000	Computer-generated randomisation schedule LOW RISK	Numbered masked sealed envelopes LOW RISK	Not mentioned UNCLEAR RISK	Not mentioned UNCLEAR RISK	All missing data and drop outs mentioned LOW RISK	Reported primary, secondary outcomes LOW RISK	Free of other sources of bias LOW RISK
Reindollar et al. 2010	The biostatistician generated allocation sequence by generating random numbers by a congruence method. Block Randomisation was performed using permuted blocks of varying sizes. LOW RISK	Sealed envelopes LOW RISK	Physicians or patients not blinded. HIGH RISK	The investigators were blinded to all outcome determinations. LOW RISK	Intention to treat analysis was performed and included all couples that were randomised. LOW RISK	Reported primary and secondary outcomes LOW RISK	18 women with hypogonadotrophic hypogonadism anovulation and PCOS, who had not become pregnant after three ovulatory treatment cycles, were included LOW RISK

Goldman et al. 2014	Block randomisation was done using blocks of varying sizes, stratified by woman's age (38^{th}-41^{st} vs 42^{nd}-43^{rd} birthday). An independent biostatistician generated allocation sequence. LOW RISK	Not mentioned. Clinical staff never performed randomisation. UNCLEAR RISK	Not mentioned UNCLEAR RISK	Clinical investigators were blinded to outcome determinants LOW RISK	All missing data and drop outs mentioned LOW RISK	Reported primary and secondary outcomes LOW RISK	Free of other sources of bias LOW RISK
Bensdorp et al. 2015	Computer generated randomisation, using biased coin minimisation, stratified for study centre. Unique number of allocation code was generated after patient's initials and date of birth was entered. LOW RISK	Central Internet-based randomisation LOW RISK	Not blinded HIGH RISK	Not blinded HIGH RISK	All missing data and drop outs mentioned LOW RISK	Reported primary and secondary outcomes LOW RISK	Free of other sources of bias LOW RISK

Table 8: Reasons for exclusion of studies

Study	Reason for exclusion
Karande et al.	Included subfertility for all causes, not only unexplained.
Roya et al.	Unclear if RCT. No email correspondence provided, so authors could not be contacted.
Zayed et al.	Not true RCT. They described as pseudo randomisation, as a few couples who started as IVF were converted to intrauterine insemination due to under response and a few couples who started as intrauterine insemination were converted to IVF due to over response and these were considered as treatment changes and were included in the analyses. Also wishes of patients who wanted to change their allocated treatment were respected.
Van Rumste et al.	This is the economic evaluation of the same study done by Custers et al.
ESHRE multicentre trial	Compared super-ovulation alone, super-ovulation with intrauterine insemination, intra-peritoneal insemination (IPI), GIFT (gamete intra-fallopian

Study	Reason for exclusion
	transfer) and IVF. IPI and GIFT are no longer used nowadays.

2.3.3 Study characteristics

Tables 5, 6 and 7 summarise the characteristics of the studies. Out of the six studies included, two were single-centre trials[84,103], two were conducted at two-centre[85, 86], and two were multi-centre trials[87,89]. Duration of subfertility considered as inclusion criteria by various studies were three years[84], one year [85,87,89,103] and six months[86]. Two studies included cycles using donor sperms[87,89.] Ages of the women included in different studies were ≤38 only[87,89], 18-42 years[103], 21-39 years[85] and 38-42 years[86], and in one study no age limit was specified[84].

2.3.4 Protocol for intrauterine insemination

For IUI cycles, some studies used 75 IU/day of FSH for ovarian hysperstimulation[84,87,89] , some used 112.5 IU/day [103], while others used 150 IU/day of FSH[85] and 300IU of FSH[86]. All of them aimed for 2-3-follicle growths for IUI cycles. Time of IUI was 20-30 hours after urinary LH surge and 40-42 hours after hCG administration in one trial[84], while the rest of the studies performed IUI 36 hours after hCG administration[85, 86, 87, 89 ,103].

2.3.5 Protocol for IVF

One study used long agonist protocol for all women, with 225 units FSH[85], while another used 100-150 units recombinant rFSH[87]. A further study used a long agonist protocol for women ≤38 years and a short agonist protocol for women >38 years with 150-225 units human menopausal gonadotrophins[84], while another used the same protocol for both IUI and IVF using 112.5 IU/day rFSH

starting from day 3[103]. Another study used either a long/short agonist or antagonist protocol with 150 IU FSH[89], and one used a short agonist protocol starting with 450 IU of human menopausal gonadotrophins[86].

Regarding the number of embryos transferred, Custers et al (2011) transferred one embryo on day 3, or two embryos if no good quality embryos were available[87]; Elzeiny et al (2014) transferred one or two embryos at cleavage stage (day 2-3)[103]; Goverde et al (2000) transferred a maximum of 2 embryos on day 2-3 in women ≤35 years, and 3 embryos in women >35 years[84]; Reindollar et al (2010); and Goldman et al (2014) transferred embryos on day 3 (following American Society for Reproductive Medicine guidelines)[110] but did not specify the number of embryos they transferred[85, 86]; Bensdorp et al (2015) adhered to a strict single embryo transfer policy regardless of the quality of embryos[89] .

2.3.6 Study design

In the study by Reindollar et al (2010)[85] couples had previous treatment with clomiphene with IUI up to three cycles before receiving IUI + FSH or IVF, whereas in all other included studies couples did not receive any previous fertility treatment. Custers et al (2011) compared 3 cycles of IUI with one cycle of IVF[87]. Elzeiny et al (2014) compared IUI vs IVF in an allocation ratio of 3:1[103]. Goverde et al (2000) compared 6 cycles of IUI in spontaneous cycle vs 6 cycles of IUI + COH vs 6 cycles of IVF[84]. Bensdorp et al (2015) compared three cycles of IVF and subsequent cryopreserved cycles with six cycles of IUI and six cycles of IVF in modified natural cycle[89]. Goldman et al (2014) compared two cycles of clomiphene citrate + IUI vs FSH + IUI vs immediate IVF[86].

2.3.7 Outcome measures

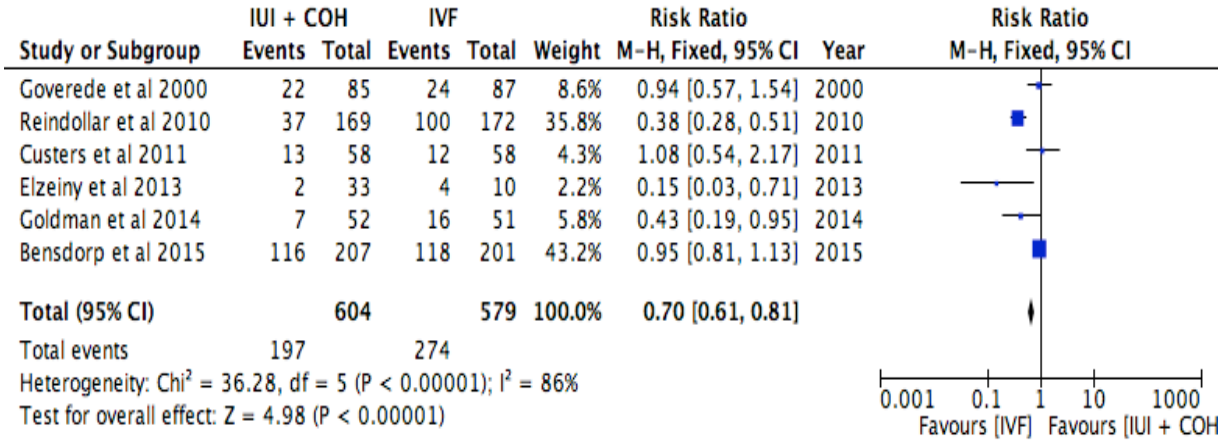
Though all of the studies reported live birth data, none of them, except Goverde et al (2000)[84], reported cumulative pregnancy rates of IUI/IVF cycles. Only Bensdorp et al (2015) included healthy live birth as an outcome measure[89]; Reindollar et al (2010), Goldman et al (2014) and Bensdorp et al (2015) compared time to pregnancy between the interventions[85, 86, 89].

All the studies are considered as low risk with regards to sequence generation, allocation concealment, outcome data reporting and other bias.

2.3.7.1 Live birth rate

All six trials reported the live birth rate. In total, 1183 couples were included, 604 receiving IUI + COH and 579 receiving IVF, with 197 live births in the IUI + COH group and 274 live births in the IVF group. The pooled results showed lower a live birth rate in the IUI + COH group compared to the IVF group (RR 0.7, 95% CI 0.61-0.81, P <0.00001). High statistical heterogeneity was noted among the trials (I^2 = 86%) (Figure 4).

Figure 4: Forest plot: Live birth rate

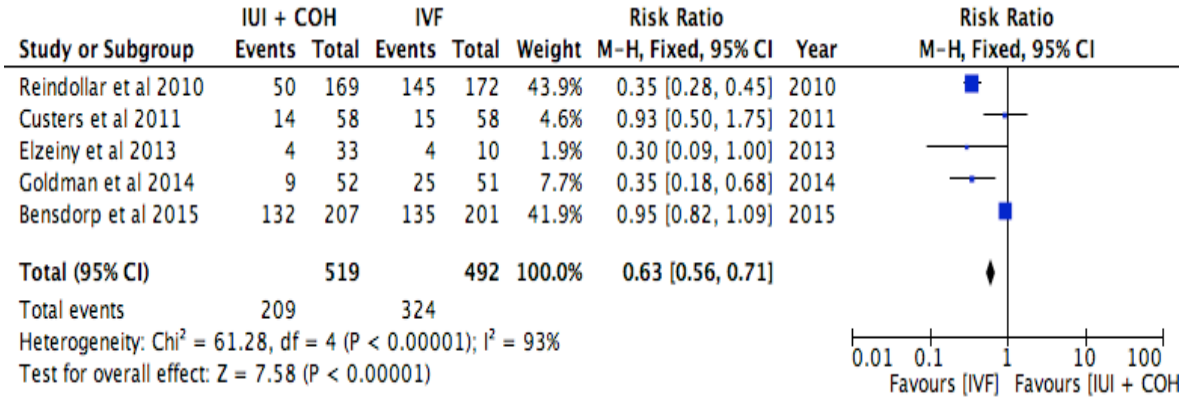


2.3.7.2 Clinical pregnancy rate

5 out of 6 trials reported clinical pregnancy rates. The pooled results showed a lower live clinical pregnancy rate with IUI + COH (RR 0.63, 95% CI 0.56-0.71,

P<0.00001). However, there was high statistical heterogeneity (I^2 = 93%) (Figure 5).

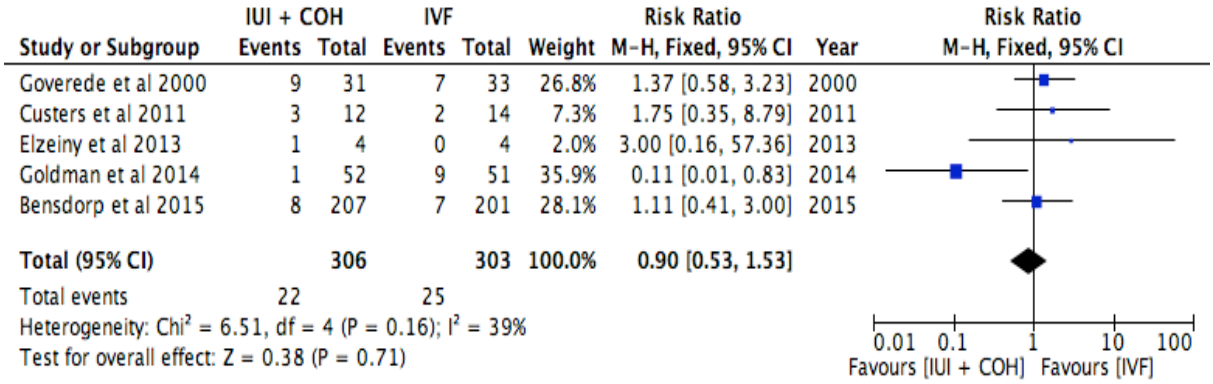
Figure 5: Clinical pregnancy rate



2.3.7.3 Multiple pregnancy rate

5 out of 6 trials reported multiple births. The pooled result from the remaining four trials showed no significant difference in multiple pregnancy rates (RR 0.9, 95% CI 0.53-1.53, P = 0.16, I^2 = 39%) (Figure 6).

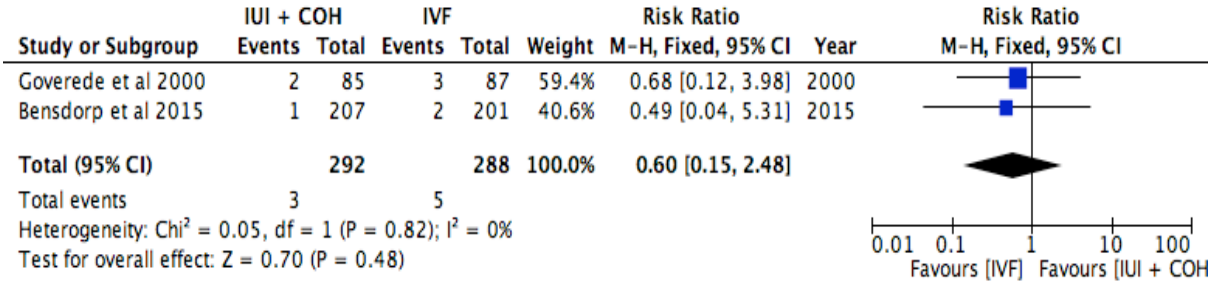
Figure 6: Multiple pregnancy rate



2.3.7.4 OHSS rate

Only data from two studies recorded OHSS. The OHSS rate did not differ significantly between the two groups (RR 0.61, 95% CI 0.15-2.5, I^2 not applicable, P=0.82) (Figure 7).

Figure 7: OHSS rate



2.4 Discussion

2.4.1 Live birth and clinical pregnancy rates

Data presented in this systematic review shows some evidence of lower success with IUI + COH in comparison to IVF, in terms of live birth rate in couples with unexplained subfertility (RR 0.7, 95% CI = 0.61-0.81). However, this must be interpreted with caution, as the number of studies included is small and there is very high heterogeneity between the trials. The FASTT (Fast Track and Standard Treatment) trial by Reindollar et al. (2010)[85] showed no added benefit of gonadotrophin + IUI and shorter time to pregnancy with immediate IVF. It should be noted that all women in this trial received three cycles of clomiphene + IUI prior to receiving gonadotrophin + IUI or IVF. After three cycles of clomiphene + IUI, a good proportion of women who were to achieve pregnancy did so. Hence, adding gonadotrophin + IUI after clomiphene cycles might have negatively influenced its efficacy. It should also be noted that in the immediate arm of the trial, patients received three cycles of clomiphene + IUI prior to IVF, making it questionable whether this is immediate IVF in the truest sense. The FORT-T (Forty and over Treatment Trial) trial by Goldman et al. (2014)[86] included only women aged 38-42 years. With age there is a decline in oocyte numbers and quality, with an increase in the rate of aneuploidy, resulting in reduced fecundity[111]. Hence, the success of assisted conception in general is low

in these women[112]. It would be unwise to extrapolate the outcome of gonadotrophin + IUI in these women to younger women.

2.4.2 Multiple pregnancy rates

One of the main concerns with ovarian stimulation with gonadotrophin is the risk of multiple pregnancies. In our meta-analysis no significant difference between intrauterine insemination + gonadotrophins and IVF were noted in terms of multiple pregnancy rates (RR 0.9, 95% CI 0.53-1.53). In the study by Custers et al. (2011)[87], there were 2 twin pregnancies in the IVF arm and both occurred after transfer of two fresh embryos of lower quality, whereas there were 3 multiple pregnancies (two sets of twins and one set of triplets) in the IUI + gonadotrophin arm. The triplets occurred in an IUI cycle where there were four follicles at the time of hCG administration. In the study by Goverde et al. (2000)[84], they transferred up to two embryos in women ≤35 years and up to three embryos in women >35 years. There were 9 pairs of twins in the IUI + gonadotrophin arm and 6 pairs of twins and one set of triplets in the IVF group in this study. In the study by Elzeiny et al (2014)[103], there was no case of multiple pregnancies in the IVF group and one twin pregnancy in the IUI group, which miscarried at 11 wks. The FORT-T trial[86] transferred day-3 embryos as per the ASRM guideline[110], which allows transfer of up to three day-3 embryos for women aged 38-40 years and up to five day-3 embryos for women aged 41-42 year. There were 12 cases of multiple pregnancies in this trial, one for each of clomiphene + IUI, gonadotrophin + IUI and treatment independent pregnancy, and nine cases of higher order births, including one set of triplets in the IVF arm. In the study by Bensdorp et al. (2015)[89], there was no difference in the multiple pregnancy rates between IUI + gonadotrophins and IVF. There were eight higher order births, including one set of triplets in the IUI arm and seven twins in the

IVF arm. They were strict with their single embryo transfer policy regardless of the quality of embryo and used mild stimulation during IUI. It is quite evident that the stimulation policy during IUI and IVF and the number of embryos transferred differed between different studies. Due to this heterogeneity in practices between different clinics, the results cannot be generalised and should be interpreted with caution.

The risk of multiple pregnancies in the IUI treatment depends largely on the dose of gonadotrophins used and the number of follicles triggered with hCG[80,113]. However, low dose gonadotrophins can result in an acceptable pregnancy rate without increasing the risk of multiple pregnancy[114, 115, 116.] In IVF, elective single embryo transfer can reduce the risk of multiple pregnancy without reducing the overall chance of success[117].

2.4.3 OHSS rates

In our meta-analysis there was no difference between IUI + gonadotrophins and IVF in terms of the OHSS rate. However, data from only two studies could be used for analysis[84, 89]. In one study, two women in the IVF arm and one woman in the IUI arm developed OHSS[89], while in the other study, two women in the IUI + gonadotrophin arm developed mild OHSS and were managed at home and three patients in the IVF arm developed severe OHSS and had to be admitted to the hospital[84].

2.4.4 Time to pregnancy

One of the main concerns of couples presenting subfertility is the time it will take to achieve pregnancy from assisted conception techniques. Hence, TTP should be regarded as an important outcome for any trial comparing various treatment strategies. Out of the six studies included in this review, four mentioned TTP. In

the study by Custers et al, (2011)[87], there were no significant differences in the TTP four months after randomisation between IVF and IUI, with 14 live births (24%) in the IVF arm and 12 (21%) live births in the IUI arm (RR 1.2, 95% CI 0.6-2.3). Similarly, in the study by Bensdorp et al. (2015)[89], the TTP for IVF and IUI were similar, with 8.04 months for IVF and 8.39 months for IUI. The study by Goldman et al. (2014)[86] reported a TTP of 3.0±0.1 months for two cycles of IUI and 5.7±0.2 months after immediate IVF. This reflects the longer time it takes to prepare for and complete one IVF cycle. On the contrary, the study by Reindollar et al. (2010)[85] showed three months of time saving by proceeding to IVF after clomiphene + IUI, and avoiding FSH + IUI.

2.4.5 Spontaneous conceptions

Couples with unexplained subfertility have a good prognosis for achieving spontaneous conception[7]. Hence, it is worth noting the spontaneous pregnancy rates before or in between the treatment cycles. In the study by Goverde et al. (2000)[84], there were 18 spontaneous pregnancies resulting in 18 live births out of 258 participants (6.97%) and a delivery rate of 1.25% per month for unexplained subfertility. Custers et al. (2011)[87] reported a spontaneous pregnancy rate of 3/116 (2.58%); Reindollar et al. (2010)[85,] in their FASTT trial, reported a rate of 7/503 (1.39%) for spontaneous pregnancy; Goldman et al. (2014)[86] reported 14 (9.1%) live births by spontaneous conception before or in between treatments; and Bensdorp et al. (2015) reported 24/408 (5.88%) for spontaneous conception for the IVF and IUI + COH arm[89]. In the study by Elzeiny et al. (2014)[103], out of 135 enrolled couples, 8 experienced spontaneous conception (5.92%).

2.4.6 Cost effectiveness

Cost effectiveness is an important factor in choosing the right treatment option for the patient. It is very interesting to see that in all the European studies in this review, IUI was found to be more cost effective compared to IVF[84,108,118], whereas the American studies found IVF to be more cost effective[85, 86]. In countries like America, fertility treatment is largely self-funded, whereas in European countries treatments are mainly publicly funded[119]. The association between public reimbursement and the use of assisted conception treatments could possibly be a factor contributing to this stark contrast.

The cost effectiveness analysis for the study by Custers et al. (2011)[108] concluded that one cycle of IVF-eSET in their setting would cost an additional €900 per couple compared to three cycles of IUI + COH, for no increase in on-going pregnancy rates or a decrease in multiple pregnancies. The study by Goverde et al. (2000)[84] reported the cost per pregnancy resulting in live birth to be 10,661 Dutch guilders for IUI + COH compared to 27,409 Dutch guilders for IVF (1 Dutch guilders = 0.4791 US$). However, this study was conducted almost 15 years ago and the success of IUI/IVF and costs have changed significantly since. The cost effectiveness analysis for the study by Bensdorp et al. (2015)[118] found IUI + COH to be more cost effective than IVF, with the mean cost per couple being €7187 for IVF and €5070 for IUI-COH, and the mean cost difference between IVF and IUI + COH being €2117 (95% CI: 1544-2657).

The study by Elzeiny et al. (2014)[103] reported the cost per live birth to be AUD 8735 for IVF and AUD 42,487 for IUI. However, the dose of FSH they used for IUI was 112.0IU/day, which is higher than usually used throughout Europe (75IU/day), and they also used a similar dose of 112.5 IU/day of FSH for IVF, which is much lower than usual. Had they used a lower dose for IUI (75IU) and a

higher dose of FSH for IVF (150-225 IU), their costs would have been different. The study by Reindollar et al. (2010)[85] is the only study that included the cost of delivery, and reported a saving of $2624 per couple in the accelerated arm and 0.06 more deliveries. However, the cost they analysed is the insurer's charge data, which might be slightly different from the cost of providing the service. Again, they used an FSH dose of 150 IU/day for IUI, which is higher than the usual dose across Europe (75IU/day).

The interpretation of these figures is hindered by differences in the cost of treatment between different countries and different regions in the same country. There remain differences between private and government-funded treatment, making it harder to generalise findings from one setting to the other.

2.5 Conclusion

This systematic review suggests IVF might be slightly superior to IUI in terms of live birth rate. However, this should be accepted with caution in view of the limited numbers of studies included and statistical heterogeneity that exists among them. All the trials apart from FORT-T trial included couples with mild male factors along with unexplained subfertility. Some trials included those using donor sperm and some included hypogonadotrophic hypogonadism along with unexplained subfertility. This has led to significant methodological heterogeneity.

IUI + COH is less invasive, less time consuming and more patient friendly. There have only been very few RCTs that conducted a head-to-head comparison of IUI + COH and IVF in unexplained subfertility. Further well-constructed RCTs comparing these two treatments are needed.

Chapter 3: An online survey of specialists' opinion of management of unexplained subfertility

Declaration: This chapter has been published: Nandi A, Gudi A, Shah A, Homburg R. (2015). An online survey on specialists' opinion on first line management options for unexplained infertility. Human Fertility, 18(1): 48-53.

3.1 Introduction

The UK National Institute for Health and Care Excellence (NICE) guideline on fertility (2013) suggests that women with unexplained infertility for more than 2 years should not be offered IUI COH through the NHS[2]. They proposed to instead offer IVF to these couples. However, the evidence on which this recommendation is based is not robust. The possible small increase in effectiveness of IVF over IUI + COH should be considered carefully after evaluating its invasiveness and the incremental cost per cycle. Moreover, IUI + COH might be more acceptable to some patients over IVF medically or financially.

Currently there is a lack of agreement among subfertility specialists with regard to first line treatment of couples with unexplained subfertility.

Looking at the controversial nature of the issue, an online survey was conducted among fertility specialists to establish the general consensus regarding management of these couples.

3.2 Method

E-mail invitations were sent to clinicians who were UK members of the British Fertility Society (BFS) to complete an online questionnaire on their usual practice while treating couples with unexplained infertility and their opinion regarding the new NICE proposal on this issue. The BFS list was used, as the

majority of fertility specialists in the UK are members. Only those members who made their email address available to other members were included in this survey. Out of 454 members in the member directory, 420 members were contacted via email. Options to opt out from this survey were provided in the email invitation and all data used was anonymised. Hence, no ethical approval was needed for this study (confirmed with the local Research & Development department). The online questionnaire was set up using Survey Monkey (www.surveymonkey.com), an electronic data collection tool. There were multiple choice questions followed by a comment section for individual comments (table 9). The first email request was sent on 10th March 2013. Two emails bounced back as the emails were non-existent and three members opted out. Two electronic reminders were sent on 19th March 2013 and 3rd April 2013. The survey closed on 30th April 2013.

Table 9: Questions included in online survey

Q1. Following one year of unexplained subfertility, what duration of expectant management would you consider for these couples?	
a. 6 months	
b. 1 year	
c. > 1year	
d. None	
Total	
Q2: Do you consider clomiphene citrate stimulation of ovulation for your patients with unexplained subfertility?	
a. Not at all	
b. Sometimes	
c. Yes, but only in young women <35	

years old	
d. Yes, only if duration is <3 years	
e. Yes, irrespective of age and duration of infertility	
Q3: How many cycles of clomiphene do you consider?	
a. 2	
b. 3	
c. 4-6	
d. NA	
Total	
Q4: Do you consider gonadotrophins + IUI for the treatment of these couples?	
a. Yes	
b. Sometimes	
c. Rarely	
d. Never	
Q5: Do you consider stimulated IUI as a first line treatment option for these patients?	
a. Yes, always	
b. Yes, if age <35 years/duration of infertility <3 years	
c. No, never	
Q6: Do you consider IVF for them as a first line treatment option?	
a. Yes, always, irrespective of age and duration	
b. Yes, if age >35 years/duration of	

infertility >3 years	
Q7: Do you agree with the new NICE guideline that all unexplained subfertility should be considered for IVF after 2 years of expectant management?	
a. Yes	
b. Partly	
c. Unable to comment	
d. No	
Q8: Will you change your treatment strategy now the NICE guideline has been published?	
a. Yes	
b. No	
c. Might do	
d. Unsure	

3.3 Results

3.3.1 Respondents' Characteristics

A total of 136 replied to the survey, which represents a 32.77% response rate. With one person skipping the question, out of the remaining 135, 92 (68.5%) were Consultants (Senior clinicians), 15 (11.11%) were Clinical Fellows (trainees in fertility), 12 (8.88%) were Associate Specialists (Senior clinicians), 2 (1.48%) were General Practitioner's with special interest, 3 (2.22%) were Subspecialty Trainees in reproductive medicine and the remaining 11 (8.15%) were Specialist Registrars (trainees in O&G).

3.3.2 Answers to online survey

Table 10: Answers to online survey

Q1. Following one year of unexplained subfertility, what duration of expectant management would you consider for these couples?	
a. 6 months	13 (12.26%)
b. 1 year	66 (62.26%)
c. > 1year	16 (15.09%)
d. None	11 (10.38%)
Total	106
Q2: Do you consider clomiphene citrate stimulation of ovulation for your patients with unexplained subfertility?	
a. Not at all	65 (50%)
b. Sometimes	43 (33.08%)
c. Yes, but only in young women <35 years old	9 (6.92%)
d. Yes, only if duration is <3 years	3 (2.31%)
e. Yes, irrespective of age and duration of infertility	10 (7.69%)
Total	130
Q3: How many cycles of clomiphene do you consider?	
a. 2	4 (3.20%)
b. 3	21 (16.80%)
c. 4-6	43 (34.40%)
d. NA	57 (45.60%)
Total	125
Q4: Do you consider gonadotrophins + IUI for the treatment of these	

couples?	
a. Yes	53 (40.15%)
b. Sometimes	39 (29.55%)
c. Rarely	17 (12.88%)
d. Never	23 (17.42%)
Total	132
Q5: Do you consider stimulated IUI as a first line treatment option for these patients?	
a. Yes, always	29 (22.48%)
b. Yes if age <35 years/duration of infertility <3 years	61 (47.29%)
c. No, never	39 (30.23%)
Total	129
Q6: Do you consider IVF for them as a first line treatment option?	
a. Yes, always, irrespective of age and duration	18 (16.07%)
b. Yes if age >35 years/duration of infertility>3 years	94 (83.93%)
Total	112
Q7: Do you agree with the new NICE guideline that all unexplained subfertility should be considered for IVF after 2 years of expectant management?	
a. Yes	52 (39.39%)
b. Partly	44 (33.33%)
c. Unable to comment	3 (2.27%)
d. No	33 (25%)

Total	132
Q8: Will you change your treatment strategy now the NICE guideline has been published?	
a. Yes	35 (26.72%)
b. No	39 (29.77%)
c. Might do	38 (29.01%)
d. Unsure	19 (14.50%)
Total	131

3.3.2.1 Specialists' opinion on duration of expectant management

Following one year of unexplained infertility, what duration of expectant management would you consider for these couples with unexplained infertility?

106 out of 136 respondents answered this question. While the majority (95/106 (89.62%)) opted for expectant management, only a few (11/106 (10.37%)) would opt for more active management. The majority said they would take into consideration the female patient's age and would consider a shorter duration of expectant management in older women. Some said that they would also consider AMH, antral follicular count, other co-morbidities and patient's wishes while deciding about expectant management.

3.3.2.2 Specialists' opinion on use of clomiphene citrate

Do you consider clomiphene citrate stimulation of ovulation for your patients with UI?

130 respondents answered this question. While 65/130 (50%) would never use clomiphene in these women, 65/130 (50%) would use clomiphene and of these, 43/65 (66.15%) would use it for 4-6 cycles.

3.3.2.3 Specialists' opinion on use of IUI with or without stimulation of ovaries

Do you consider gonadotrophins + IUI for the treatment of these couples?

132 out of 136 respondents replied to this question. 109/132 (82.57%) said that they would. 53/109 (48.62%) would use it always, 39/109 (35.78%) would use it sometimes and 17/109 (15.59%) would use it rarely. The majority said they would use it depending on individual circumstances such as the couple's age, ovarian reserve tests (AMH, antral follicular count), funding and patient's wish. 90/129 (69.76%) would consider IUI + gonadotrophins as the first line offer for these couples. One respondent said that they would recommend IUI only if the couple had sexual difficulty. Two respondents said that they are achieving success rates of 11-22% for IUI in their centres and hence they support IUI for them.

3.3.2.4 Specialists' opinion on use of IVF as first line option

Do you consider IVF for them as first line option?

We got a response from 112 out of 136. 94/112 (83.93%) said they would use IVF as a first line offer only if female age is >35 years and/or duration of infertility is >2-3years. One respondent admitted that though they give the option to patients, some are reluctant to go to IVF straight away. 18/112

(16.07%) said they would recommend IVF as the first line management for these couples always irrespective of age and duration of infertility.

3.3.2.5 Specialists' opinion on NICE guideline

Do you agree with the new NICE guideline that all unexplained infertility should be considered for IVF after 2 years of expectant management?

We got a reply from 132 respondents out of 136 for this question. While 52/132 (39.39%) agreed with the NICE proposal, the rest partly agreed, did not agree or were unable to comment. Some admitted that there is a long waiting time for NHS patients and believed that some would conceive if offered stimulated IUI while waiting for IVF.

Will you change your treatment strategy now the NICE guidelines have been published?

131 out of 136 responded to this question. While almost half of the respondents (57/131 (43.51%)) were either unsure or might change, only 35/131 (26.72%) said that they would definitely change, and 39/131 (29.77%) said they would not. One said that they would offer a choice to patients, as many women might not wish to proceed directly to IVF.

3.4 Discussion

This survey showed a mixed response among the clinicians, proving the ongoing dilemma among practitioners regarding the best management option for these couples. While the majority (79/106) would offer 6 months to one year of expectant management for these couples after one year of subfertility, 10% would not try expectant management any longer, whereas 15% would continue expectant management for >1 year.

50% of the respondents were in favour of using clomiphene citrate for these patients. Clomiphene citrate has been used for unexplained subfertility both alone and with IUI. One of its advantages is its low cost and ease of application[120,121]. It is believed that it acts by correcting subtle ovulation disorders. However, its anti-oestrogenic effect on endometrium and uterine blood flow affects the pregnancy rate and it has been shown to be no better than expectant management[77,78]. Subsequent to this, an economic evaluation showed clomiphene citrate not to be cost-effective[122]. As per the response received in the survey, it is clear that in spite of the evidence, clomiphene citrate for unexplained subfertility has not completely lost its popularity among practitioners.

The rationale for using IUI in unexplained subfertility is to overcome any existing cervical barrier, correct any subtle defect in ovulation or improve subtle undetected sperm imperfections. It has long been quite popular among patients with unexplained subfertility with lower dropout rates compared to IVF due to its less invasive and less time-consuming nature[123]. Success of IUI depends on many factors, including total washed sperm count[124]. It also depends on the unit offering IUI; according to some of our respondents it is certainly higher in the units which offer IUI only rather than both IUI and IVF. Two of our respondents claimed to achieve success rates of 15-22% for IUI in their centres. IUI + COH remains popular among practitioners as evidenced by this survey, while IVF is not yet quite popular as a first line option for unexplained subfertility.

The 2012 NICE guidelines recommend offering IVF treatment to women with unexplained subfertility after 2 years of expectant management with the exclusion of the COH + IUI option[2]. However, evidence supporting this suggestion is limited. Even NICE has admitted that the evidence on which this recommendation has been made is of low to very low quality. Many of the

respondents have raised concerns about this lack of evidence. One of them raised concerns that many Trusts might use this guideline and stop offering IUI to save money. Some supported IUI as they believed that IUI prepares the patient physically and psychologically for IVF.

Bearing in mind the reduced fecundity of women over 38 years of age due to oocyte senescence, 2 years of expectant management might not be the right choice for them. There has been evidence that IVF is superior to IUI in this group[86]. The majority of the respondents (84%) would consider IVF as a first line option for older women with unexplained subfertility.

3.5 Conclusion:

3.5.1 Strengths of the survey

To the best of our knowledge, this was the first survey conducted to establish current practice in the UK in managing women with unexplained subfertility. The diversity of responses received confirmed the variation in practices among reproductive specialists despite the existence of a National Guideline. It also confirmed the mixed response to the introduction of the new NICE guideline on unexplained subfertility and raised concern as to its wider acceptance, which seemed to be blunted by the lack of robust evidence.

3.5.2 Weaknesses of the survey

However, the survey had limitations. First of all, it was conducted among members of the British Fertility Society only; the policy of reproductive specialists who are not members of the Society could therefore not be assessed. However, a large section of reproductive specialists in the UK are members of the BFS. The return rate was 33%, raising concerns that it might not be a true representation of the overall practice; it did highlight the continued clinical uncertainty. The respondents had a mixture of experience but the majority

(104/135 (77.03%)) were senior clinicians who make treatment decisions. Prior piloting and validation could have improved the response rate.

The diversity in clinical practice in managing women with unexplained subfertility could be due to various reasons. The lack of robust evidence, patients' wishes for the least invasive treatment, and the current system of service provision, which puts patients on IVF waiting lists and delays the start of their treatment, could all lead to this diversity.

Chapter 4: Controlled ovarian stimulation and intrauterine insemination vs in vitro fertilisation as the first line treatment for unexplained infertility: a randomised controlled trial

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4.1 Introduction

Debate continues as to whether IVF should be the sole treatment for couples with unexplained subfertility. Only a few RCTs have conducted a head-to-head comparison of IUI + COH and IVF in unexplained subfertility. Currently, there is a lack of agreement among infertility specialists with regards to the first line treatment of couples with unexplained subfertility[8] and in spite of being aware of the NICE guidelines[2], over 90% of clinics continue to offer IUI + COH to couples with unexplained subfertility as first line treatment[125].

A randomised controlled trial was therefore carried out to examine the following study question.

4.1.1 Study question

What is the best first line management option for the treatment of unexplained subfertility - Controlled ovarian hyperstimulation (COH) with gonadotrophins + intrauterine insemination (IUI) or in vitro fertilisation (IVF)?

4.2 Methodology

4.2.1 Ethical consideration

Ethical approval was sought from a Research Ethics Committee. This study was granted favourable opinion by the Brent Research Ethical Committee, REC ref number 13/LO/0550.

The trial was registered under registration number ISRCTN43430382.

R&D approval: Local Research and Development unit approval was also sought before collecting patient information.

4.2.2 Selection of participants

4.2.2.1 Eligibility Criteria

- Couples with primary or secondary subfertility, of minimum one-year duration.
- The female partner was aged between 23 and 37 completed years. The age limit is based on the concern that age alone affects the success rates of fertility treatment by lowering oocyte quality[9].
- BMI of 19 to 30.
- Evidence of regular ovulation. Women with a regular menstrual cycle of 21-35 days and the mid-luteal serum progesterone level were used to confirm ovulation.
- Day 2 FSH <10 IU/L.
- Confirmed bilateral patent tubes were considered eligible. Women with unilateral blocked tube have some tubal factor already existing and the evidence of the success of IUI + COH in this group is conflicting. Hence, only women with bilateral tubal patency were included the trial. Various methods were used to confirm tubal patency, including HSG or HyCoSy, or

laparoscopy and dye test. HSG was considered as a routine test for all. HyCoSy was considered if there were any suspicions of ovarian cysts and/or fibroids during examination or shown in previous scans. A laparoscopy and dye test was considered if HSG/HyCoSy were equivocal or if the woman had any symptoms of pelvic pain, dysmenorrhea or dyspareunia suggesting possibility of endometriosis.

- Mild endometriosis (American Society of Reproductive Medicine (ASRM) grade I[126], which has been previously surgically treated or patient is asymptomatic were included in the trial[48,127].
- The male partner with normal semen parameters i.e. sperm density >15 million /ml, progressive motility >40% and normal forms >4% (WHO criteria) or total progressive motile sperm count >5 million[128,129] were included in the trial.

4.2.2.2 Exclusion criteria

- Self-funded couples. Self-funded patients were excluded from the trial due to lack of research funding.
- Female partner was <23 years or ≥38 years
- Unilateral or bilateral blocked tubes. Women with previous ectopic pregnancies or those with hydrosalpinges were considered as tubal damage and excluded from the trial.
- Irregular periods suggesting anovulation.
- BMI <19 or >30.
- The male partner had reduced sperm count or motility.
- Women with known uterine anomaly. 3-D ultrasound scan was performed on all participants and if uterine anomaly was suspected in a 3-D scan, then hysteroscopy was performed to confirm it.

- Couples with physical disability or psychosexual problems who had difficulty in achieving vaginal intercourse.
- Couples in a same sex relationship or single women using donor sperm were also excluded, as they do not fall into the definition of unexplained infertility.
- Couples where any of the partners had HIV were not treated in this unit and hence excluded from the trial.
- Those with confirmed endometriosis of Grade II-4 (American Fertility Society Criteria) were excluded from the trial. However routine laparoscopy was not performed in all cases to diagnose endometriosis[127].
- Couples with previous fertility treatment such as IUI or IVF.

4.2.3 Trial design

This was a single-centre parallel group randomised controlled trial with balanced randomisation (1:1), conducted in a tertiary referral centre.

4.2.4 Study setting and funding

4.2.4.1 Study setting

The study was conducted at a tertiary referral unit in London, United Kingdom, catering for 1200 IVF cycles annually and serving couples from all ethnic background. Patients were referred by their General Practitioner or from other hospitals. Eligible couples were identified from the clinics prospectively on the basis that they fulfil the inclusion criteria. Written informed consent was obtained before randomisation was carried out.

4.2.4.2 Funding

There was no external funding for the trial. Patients received IVF or IUI as per their NHS funding.

4.2.5 Recruitment methods

4.2.5.1 Agent responsible for enrolling participants

The chief investigator (Anupa Nandi) offered the study to patients in the majority of the cases. In the absence of the chief investigator, the on-duty doctor introduced the trial to potentially eligible couples.

4.2.5.2 Consent and information

Once the patients had completed all relevant investigations, the chief investigator reviewed them. If patients met the inclusion criteria, they were verbally informed about the trial and were then given the written information leaflet. They were allowed and encouraged to read the information leaflet and given a further follow up appointment after 2-3 weeks.

4.2.5.3 Agent responsible for assigning participants to interventions

In the follow up visit, if patients expressed their wish to participate, they were given a consent form to sign. Both patient and her partner were required to sign the consent form agreeing to participate in the trial. They were allowed to withdraw from the trial anytime without any explanation and without having any effect on their subsequent treatment. Once the consent form was signed, an independent research coordinator opened the sealed envelope to assign the couple to the intervention. The randomisation number along with the assigned intervention was documented in the patient's notes and on the signed consent form. A copy of the consent form along with the patient's details, randomisation number and the assigned intervention was kept in the research file, a copy was given to the patient and a copy was kept in the patient's notes. A computer database was created as a Microsoft Excel spreadsheet, which was updated regularly.

4.2.5.4. Methods to prevent subversion

To prevent subversion, the independent research coordinator randomly checked patients' notes at regular intervals of 2-3 months to correlate the received treatment to the assigned treatment as per the information in the research file.

4.2.5.5. Data protection

To protect patients' confidential information, the research file was kept in a secured research cabinet in an NHS hospital and was monitored by the research coordinator of the unit. It was always kept under lock and key and was accessible only in the presence of the research coordinator or unit manager. The sealed envelopes were kept in the research file. The Excel spreadsheet with patients' details were kept in the NHS computer and secured with a password so that it could be accessed by the chief investigator only.

4.2.6 Randomisation

4.2.6.1 Sequence generation

A simple randomisation procedure was followed. A computerised random number generator was used to generate a list of random numbers[130], assigning participants to one of the two treatment groups in a 1:1 ratio, and distributed in individual, consecutively numbered opaque envelopes. An independent person not involved in the trial performed the sequence generation. The details of the series were unknown to any of the investigators and were kept away from the hospital to be inaccessible to the investigators.

4.2.6.2 Allocation concealment mechanism

The allocation sequence was concealed from the person enrolling the participants by using sequentially numbered, opaque sealed envelopes[131,132]. The type of intervention was typed (Arial size 10) on a separate piece of paper and

folded multiple times and kept inside the envelopes. The opaqueness of the envelopes was checked by two independent people on three separate occasions, in random batches and was confirmed against intense light (sunlight, light bulb, X-ray monitor). The research coordinator for the unit (not a part of the trial) opened the envelope only after the participants had signed the consent forms and the participant's name and details were written on the envelope. The folded card inside the envelope contained the information of the type of treatment the participant would receive and was given to the clinician.

4.2.6.3 Blinding

Due to the nature of the trial, blinding was not possible.

4.2.7 Interventions

Couples were allocated to treatment strategies consisting of 3 cycles of COH + IUI or 1 cycle of IVF within a time frame of 6 months from randomisation. Initially, the protocol was to compare 3 cycles of IUI vs 3 cycles of IVF. Later, the protocol was amended to one cycle of IVF.

4.2.7.1 COH + IUI

A baseline scan was performed between days 2-5 to exclude any ovarian cyst greater than 2cm. The COH was performed with daily subcutaneous injections of 75 IU FSH (Fostimon, a highly purified urofollitropin, Pharmasure) starting from day 2-5 of menstrual cycle onwards. The dose was altered according to the response of the patient and was decided by the attending clinician. The follicular growth was strictly monitored by transvaginal ultrasound. When at least 1-2 follicles with a diameter of 17-18mm were present, final oocyte maturation was induced by sub-cutaneous administration of 250 mcg of recombinant hCG (Ovitrelle, Merck Serono) and 24 hours later IUI was performed. If ≥ 3 follicles of

≥14mm developed then the cycle was cancelled by withholding hCG and IUI and avoiding sexual intercourse due to risk of multiple pregnancies. Semen samples were processed within one hour of ejaculation using density gradient centrifugation followed by washing with culture medium and then used for insemination. A single insemination was done by either the nurse or on-duty doctor[133].

4.2.7.2 IVF

In the IVF group, women underwent down-regulation with GnRH agonist in a long protocol, starting on day 21 of the previous cycle. COH was started with FSH (either human menopausal gonadotrophins or recombinant FSH) with a dose ranging from 150-450 IU depending on the woman's ovarian reserve (as tested by anti-Mullerian Hormone level, basal antral follicle count and day-2 FSH level) and decided by the attending clinician. Follicular tracking was performed by transvaginal ultrasound. When the majority of the follicles were >18mm, ovulation was triggered with 250mcg rhCG (Ovitrelle, Merck Serono) and cumulus-oocyte complexes were retrieved by transvaginal ultrasound-guided oocyte retrieval 36 hours after hCG trigger. ICSI (intra-cytoplasmic sperm injection) was considered if <5million total motile sperms were available post wash.

Women who were deemed high risk for OHSS (AMH>25, AFC>20) underwent a GnRH antagonist protocol for stimulation, when COH was achieved with low dose FSH (150 IU) and starting GnRH antagonist on day 6 of stimulation. Ovulation was induced by GnRH agonist (Buserelin, 0.5 mg subcutaneously)[134] and oocyte retrieval was performed after 36 hours. If over 20 oocytes were collected, embryos were frozen and transferred at a later date in a frozen embryo replacement cycle. In that case, the first frozen embryo transfer cycle

was considered as first cycle and included in the analysis. Data for additional frozen embryo transfer cycles were not collected, as this was not in the study design.

For the frozen embryo transfer cycle, down-regulation was achieved with GnRH agonist starting from day 21 of the previous cycle followed by endometrial preparation with daily estradiol valerate of 8mg for 10-14 days or until endometrial thickness of over 8mm was achieved.

Embryos were assessed daily for morphological grading according to the laboratory's protocol until the time of transfer. If one or more good quality embryos were available, then only one embryo was transferred on either day 3 or 5. If no good quality embryos were available then two embryos were transferred. Luteal phase support was provided with progesterone vaginal pessaries (Cyclogest, 400mg twice daily, Actavis UK Ltd). For frozen embryo transfer cycle or GnRH agonist trigger cycle, where a fresh embryo was transferred, daily estradiol valerate of 8mg and progesterone gel (Crinone gel, Allergan) were given in addition to progesterone vaginal pessaries for luteal support.

All procedures, follicular tracking scan, egg retrieval, embryo transfer and IUI were performed by the on duty doctor (including the chief investigator).

4.2.8 Follow up

After one completed cycle of COH + IUI or IVF, the women underwent a serum pregnancy test (serum hCG) at 2 weeks. If no pregnancy occurred then the next treatment cycle was started as per the protocol. If the pregnancy test was found to be positive then the woman was followed up using ultrasound to locate and confirm viability and number of developing embryos at 5-9 weeks.

4.2.8.1 Biochemical pregnancy

If the urine and serum pregnancy test were positive but never reached a level where an intrauterine pregnancy could be seen on ultrasound scan, it was classed as biochemical pregnancy and considered a miscarriage.

4.2.8.2 Clinical Pregnancy

If an intrauterine gestational sac with or without viable fetus was present on ultrasound scan then it was classed as clinical pregnancy.

4.2.8.3 On-going pregnancy

If subsequent ultrasound scans at 12 weeks showed a viable intrauterine fetus then it was classified as an on-going pregnancy. Patients were registered for their antenatal care in their hospital of choice, which was noted for future correspondence.

4.2.8.4 Ectopic pregnancy

All confirmed or suspected ectopic pregnancies were followed up in the early pregnancy assessment unit (EPAU) with serial bHCG and further scans.

4.2.8.5 Spontaneous pregnancy

Spontaneous conception rates before or in between treatments within the time frame of six months from randomisation were also noted.

4.2.8.6 Dropouts

Not all couples completed all cycles of treatment. All dropouts were checked and the reason documented in the database. This was noted in the flowchart and dealt with during analysis as a part of the 'intention to treat' analysis.

4.2.9 Outcomes

4.2.9.1 Primary

The primary outcome was singleton live birth/couple.

4.2.9.2 Secondary

Further secondary outcome measures were live birth rate, clinical pregnancy, multiple pregnancy and OHSS rates. Spontaneous conception rates before or in between treatments were also noted.

4.2.10 Sample size

Assuming an absolute difference of 15% in live birth rate in favour of IVF with a live birth rate of 30% for one cycle of IVF and 15% for three cycles of IUI[135], 80% power and significance of $P<0.05$, 125 couples were calculated to be required in each arm of the study.

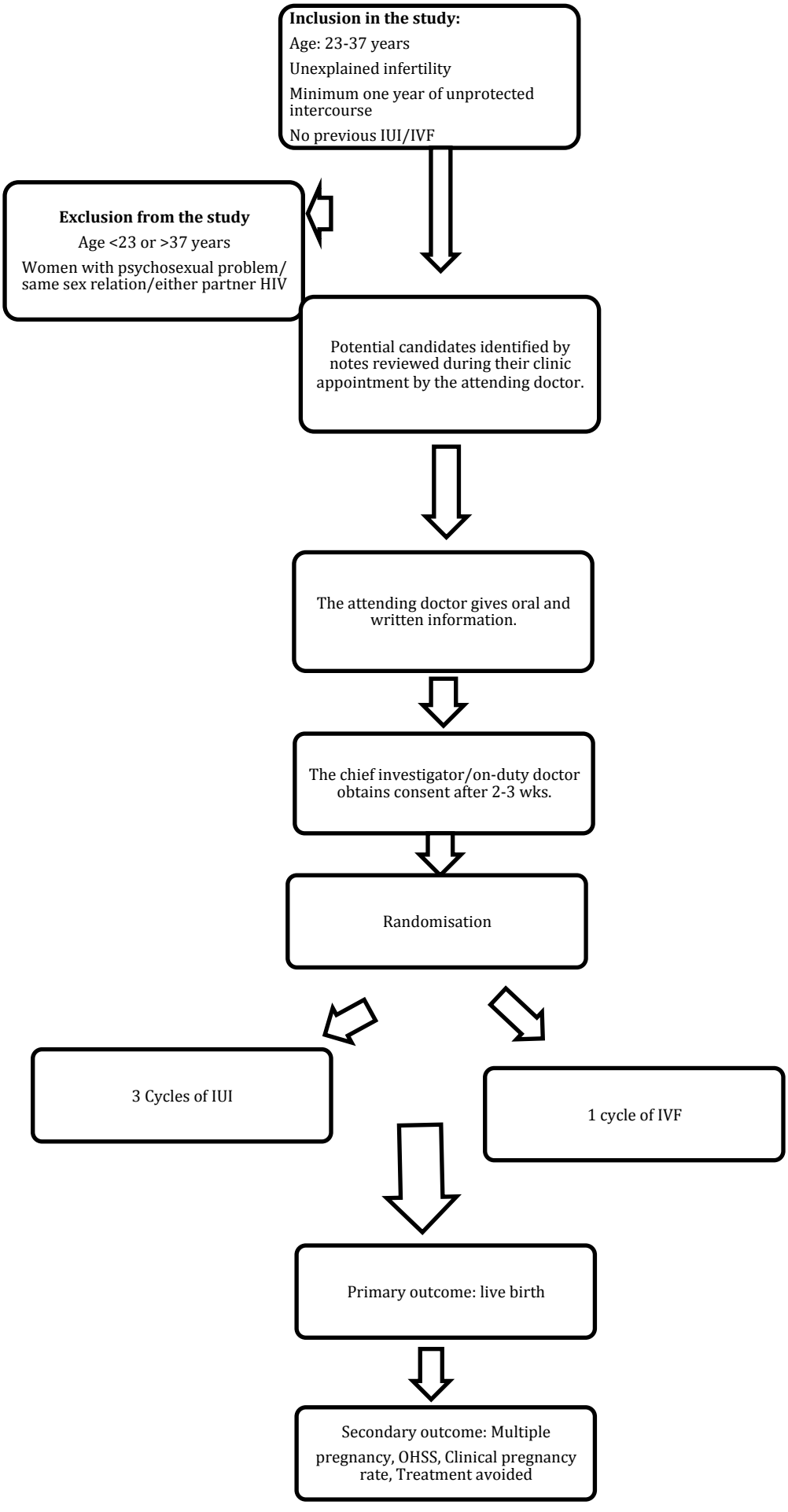
4.2.10.1 Sample size achieved

Following the introduction of the 2013 NICE guideline, there was gradual withdrawal of NHS funding for IUI by most CCGs (Clinical Commissioning Groups). As this trial had no funding and patients received treatment as per their NHS funding, the trial had to be stopped prematurely after recruiting 207 couples.

4.2.11 Statistical methods

Differences in the birth rate per group were expressed as relative risks, with corresponding 95% confidence intervals. This relative risk was unadjusted, following the protocol and analysis plan where no adjustment for confounders was specified. Data were analysed as live singleton birth rates per couple. All randomised couples were analysed in their allocated group as per intention to treat analysis.

Figure 8: Flow chart of the trial



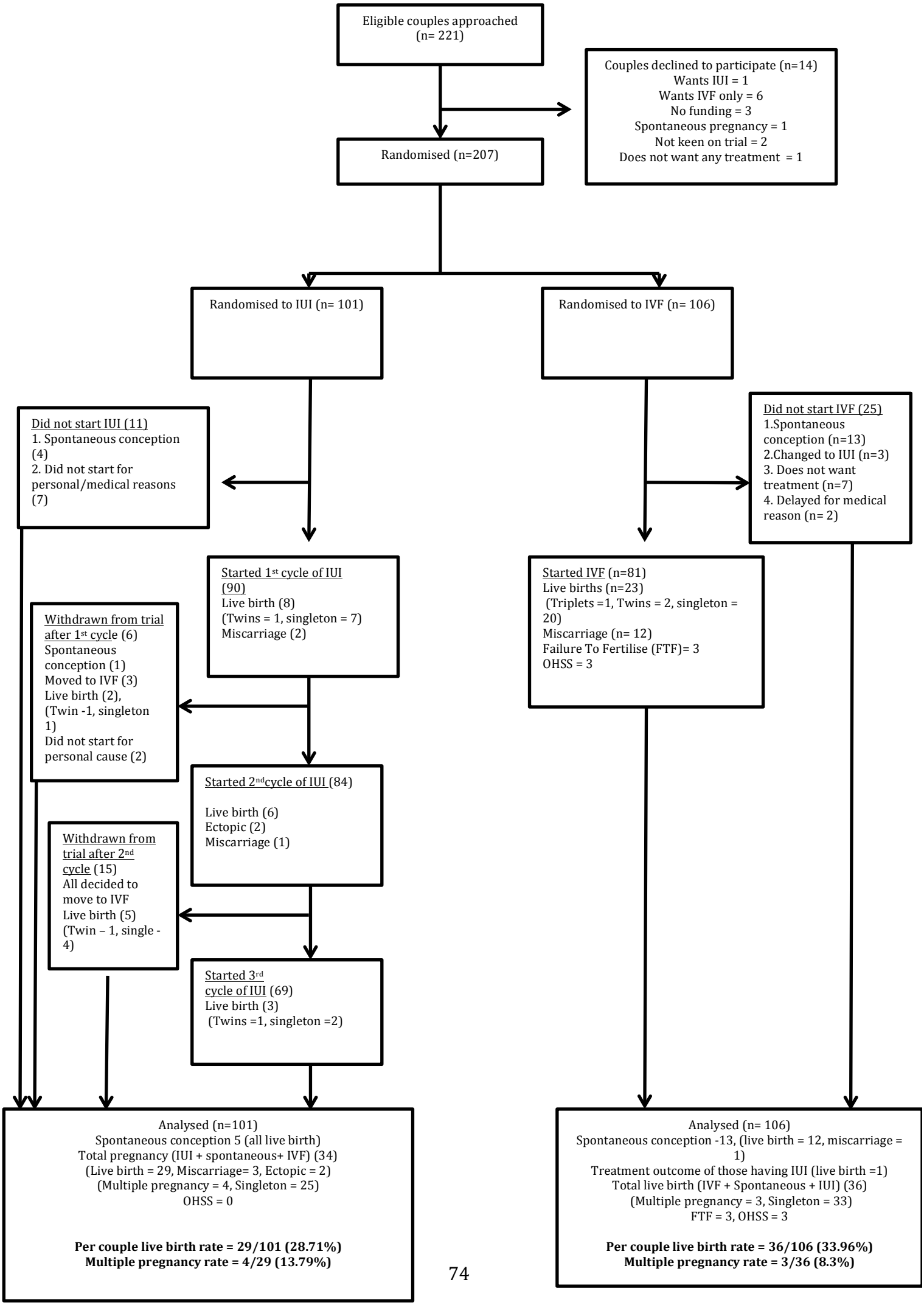


Figure 9: CONSORT flow chart

4.3 Results

Between July 2013 and July 2015, 221 couples diagnosed with unexplained subfertility were approached. 207 couples agreed to participate in the trial and were randomised into three cycles of IUI + COH (101) and one cycle of IVF (106). Overall, the median age of the female partner was 32 years (IQR 30-35), mean BMI 23.6 (SD 3.01), median AMH 19.6 pmol/l (IQR 10.9-31.3) and mean AFC 16.5 (SD 8.2). The median duration of subfertility was 3 years (IQR 2-3). The mean total progressive motile sperm count was 52.4 (SD 11.4).

There were no differences between the two groups in terms of baseline characteristics (table 11).

Table 11: Baseline characteristics of couples randomised

Characteristics	**IUI + COH**	**IVF**
Age median (IQR) years	32 (30-35)	32.5 (30-35)
BMI (mean ± SD)	23.7 ± 3.42	23.5 ± 2.9
Primary subfertility n (%)	83 (82.2%)	93 (87.7%)
Duration of subfertility median (IQR) years	2 (2-4)	3 (2-3)
AMH median (IQR) pmol/l	18.2 (10.5-30.4)	21.6 (11.4-31.1)
AFC (mean ± SD)	16.9 ± 8.2	17.1 ± 8.2
Day 3 FSH (mean ± SD)	5.8 ± 1.8	5.4 ± 1.6
Total progressive motile sperm count - median (million) (IQR)	27.2 (16.2-52.5)	33.5 (15.9-52.2)

Independent *t* test for BMI, AFC and day 3 FSH (normally distributed)

4.3.1 Stimulated IUI group

Out of 101 couples randomised to IUI + COH group, 11 patients did not start treatment either because they conceived spontaneously, or they had changed their mind regarding starting treatment due to personal or medical reasons. 90 couples started their first cycle and 69 couples completed all three cycles. 21 couples withdrew after one or two cycles of IUI and underwent 18 cycles of IVF within the time frame for the trial. There were 29 live births (five were conceived spontaneously in between treatment cycles and seven from IVF cycles that patients underwent after withdrawing from the IUI arm after one or two cycles of IUI) (29/101 = 28.7% per couple). There were three first trimester miscarriages and two ectopic pregnancies. There were four sets of twin pregnancies (4/29 = 13.79%). Two were conceived from IUI and two from IVF. The per couple singleton live birth rate was 25/101 (24.7%).

Out of 101 couples randomised to IUI + COH group, 90 underwent 243 cycles. The live birth rate per cycle was 22/243 (9.1%). The mean duration of stimulation was 9.5 ± 2.7 days. In 55 cycles there were two follicles (22.6%) with stimulation, whereas 170 (69.9%) cycles had monofollicular development. Eight cases were cancelled due to the development of more than three follicles (8/243 = 3.3%) and a further ten cases were cancelled due to miscellaneous causes such as the presence of ovarian cyst, premature ovulation and male partner unable to produce sample on the day of IUI. Out of the multiple pregnancies, two were conceived from IUI cycles and both had two follicles during hCG trigger. The other two were conceived from IVF cycles and both had two low quality blastocysts transferred. The total gonadotropin required per cycle was 932.02 ± 930.5 IU.

4.3.2 Stimulated IVF group

Out of the 106 couples randomised to IVF group, 25 couples did not start due to spontaneous conception, withdrew from trial to have IUI or did not undertake treatment due to personal circumstances or medical reasons. Out of those who underwent IUI, there was one live birth. As per the intention to treat analysis, they were analysed in the IVF group. 81 couples underwent one IVF cycle.

The mean dose of FSH used per cycle was 3239.3 ± 1508.4 IU for a mean duration of 13.1 ± 2.2 days. To reduce the risk of OHSS, in 48 cycles (48/81 = 59.2%) antagonist protocol was used and in 32 (32/81 = 39.5%) agonist trigger was used due to over response. In 28 cases of agonist trigger (28/81= 34.5%) all embryos were frozen for subsequent frozen embryo transfer. There were three cases of OHSS, with two being moderate and one being mild. Both the moderate OHSS cases had GnRH agonist trigger and freeze-all embryos. The mild OHSS case had hCG trigger in an antagonist cycle.

The mean number of oocytes retrieved per cycle was 13.2 ± 6.9. In 56 cycles IVF was used for fertilisation, in two cycles ICSI only was used (due to unexpected low sperm count on the day of oocyte retrieval) and in 23 cycles both IVF and ICSI (oocytes equally divided) were used. There were three cases of failure to fertilise in the IVF only group and in one of them there was no zona binding. There were two cases of no fertilisation with IVF in the IVF + ICSI group (2/23 = 8.7%).

52 had single embryo transfer (SET) (52/81 = 64.2%). There were 11 live births in the SET group (11/52= 21.2%). There were one set of triplets and two twin pregnancies. The couple that had a triplet pregnancy had two day-3 embryos of lower quality transferred. Out of the twin pregnancies, one had two lower quality

blastocysts transferred and the other had two lower quality day-2 embryos transferred. In 43 cycles (43/81 = 53.1%), blastocyst transfer was carried out. The total gonadotropin required per cycle was 3239.3 ± 1508.4 IU.

4.3.3 Outcome measures: (Intention to treat analysis)

Table 12: Outcome measures

Outcomes	IUI + COH (n=101)	IVF (n=106)	RD (95% CI)*	RR (95% CI)**
Singleton live birth rate (per couple) n (%)	25 (24.7)	33 (31.1)	6.4% (-5.8%-18.6%)	1.3 (CI 0.8-1.9)
Live birth rate (per couple) n (%)	29 (28.7)	36 (33.9)	5.2% (-7.4%-17.8%)	1.8 (CI 0.7-1.7)
Clinical pregnancy rate (CPR per couple) n (%)	34 (33.6)	49 (46.2)		1.3 (CI 0.9-1.9)
Multiple pregnancy rate (per live birth) n (%)	4 (13.8)	3 (8.3)		0.6 (CI 0.1-2.4)
Miscarriage/CPR n (%)	3 (12.0)	13 (26.5)		2.2 (CI 0.6-7.0)
Ectopic pregnancy (n)	2	0		
Spontaneous conception leading to live birth n (%)	5 (4.9)	12 (11.3)		
OHSS	0	3 (3.7)		

*RD – Risk difference

** RR – Relative risk

CI- Confidence Interval

4.3.3.1 Primary Outcome

The number of singleton live births was 25 (24.7%) for the IUI + FSH group and 33 (31.1%) for the IVF group, RR 1.3 (95% CI 0.8-1.9) with an absolute risk difference of 6.4% (95% CI -5.8% to 18.6%).

4.3.3.2 Secondary outcome

4.3.3.2.1. Multiple pregnancy rate

The number of multiple pregnancies per live birth rates was 4 (13.8%) for the IUI + FSH group and 3 (8.3%) for the IVF group, with a relative risk of 0.6 (95% CI 0.1-2.4).

4.3.3.2.2 OHSS rate

There were no cases of OHSS for the IUI group and three cases of OHSS (3/81 = 3.7%) in the IVF group.

4.3.3.2.3 Spontaneous conception rate

There were 17 live births from spontaneous conception in between treatment cycles (17/207 = 8.2%).

4.3.4 Per protocol analysis

Since there were a large number of spontaneous pregnancies, we also performed a per protocol analysis as a secondary analysis. Excluding the dropouts and the spontaneous conceptions, there were 18 live births from the IUI group (17 in the IUI group and one from those who withdrew from IVF and underwent IUI instead). 69 couples in the IUI group completed all three cycles of IUI and out of three couples who withdrew from IVF group and had IUI, only one completed all three cycles. Hence as per protocol, there were 18/70 (25.7%) live births per three cycles of IUI. There were 30 live births from 99 IVF cycles (30.3%). According to the per protocol analysis, therefore, three cycles of IUI had a similar live birth rate to one cycle of IVF, RR 1.17 (95% CI 0.7-1.9).

To get a proper head-to-head comparison between IUI and IVF, the live birth rate of the first cycle of IUI (8/90 = 8.8%) was compared against the first cycle of IVF (23/81 = 28.4%), RR 2.3, (95% CI 1.2-4.2) (table 13).

Table 13: Supplementary table

Outcomes	**IUI + COH (n=101)**	**IVF (n=106)**	**RR (95% CI)**
Total gonadotropin requirement per cycle (mean ± SD) IU	932.02 ± 930.5 IU	3239.3 ± 1508.4 IU	
Duration of stimulation (mean ± SD) days	9.8 ± 2.8	13.1 ± 2.2	
Number of oocytes retrieved per cycle (mean ± SD)		13.2 ± 6.9	
Single embryo transfer (SET)/cycle n (%)		52 (64.2)	
Live birth/SET n (%)		11 (21.2)	
Per protocol analysis (live birth) n (%)	18/70 (25.7)	30/99 (30.3)	1.17 (0.7-1.9)
First cycle (live birth) n (%)	8/90 (8.8)	23/81 (28.4)	2.3 (1.2-4.2)

4.3.5 Cost analysis

An evaluation of the full cost analysis is beyond the scope of this thesis. However, a simple direct comparison of the cost of three cycles of IUI and one cycle of IVF was undertaken (table 14). For the sake of simplicity the per-protocol analysis was used to calculate the cost per live birth. In this trial, the cost ratio of IUI/IVF (1:1.3) was higher for one cycle of IVF compared to three cycles of IUI.

Table 14: Cost analysis

	IUI group	IVF group
Average cost per cycle	£700	£3200
Number of cycles	210	99
Total cost for all cycles	£147000	£316800
Number of live births	18	30
Cost per live birth	£8166.66	£10560.00
Cost ratio (IUI:IVF)	1:1.3	

4.4 Discussion

This is the first UK-based RCT comparing IUI + FSH vs IVF. This study gives a head-to-head comparison between three cycles of IUI + FSH and one cycle of IVF in women with unexplained subfertility who had no prior treatment.

The clinical pregnancy rate per couple for one cycle of IVF than three cycles of IUI + FSH (RR 1.3, 95% CI 0.97-1.93), the live birth rate per couple (RR 1.8, 95% CI 0.7 – 1.7) did not reach statistical significance. There was higher miscarriage rate in the IVF group (26. 5%) than that in the IUI + FSH group (12%) (RR 2.2, CI 0.69-7.05). The study dataset did not show an association between particular variables and miscarriage.

In view of the large number of spontaneous conceptions, which could possibly obscure the effects of treatment regimes, a per protocol analysis was also performed. While one cycle of IUI seemed to be associated with a lower success to that of IVF in terms of live birth, three cycles of IUI seemed to lead to a live birth almost equal to that of one cycle of IVF.

4.4.1 Strengths

This trial differs from previous studies in many aspects. All previous studies either included cycles with clomiphene citrate (CC) + IUI as well[87, 89] or patients who had treatment with CC+ IUI prior to FSH + IUI[85]. In this trial FSH only was used for IUI, as the latest Cochrane review showed no evidence of clinical benefit of clomiphene citrate for unexplained fertility[78]; moreover, there is evidence suggesting superiority of FSH over CC when used in conjunction with IUI[136,137].

Unlike previous studies, which included both unexplained subfertility and mild male factor subfertility[84, 87, 89], this trial included couples with unexplained subfertility only. Couples using donor sperm, unlike previous studies[87, 89], were

excluded, as were women with hypothalamic anovulation or polycystic ovary syndrome as used in other trials[85]. This trial represents couples with unexplained subfertility in the truest sense.

This trial was restricted to couples with a female partner between 23 years and < 38 years and excluded those ≥38 years. The age limit was due to the concern that oocyte senescence would reduce the success of IUI or IVF; there is recent evidence that reproductively older woman (≥38 years) would benefit from immediate IVF[86].

In contrast to all previous trials, which included women with a unilateral patent tube[84, 85, 87, 89], this is the first trial to include women with only bilateral patent tubes in HSG or laparoscopy. Women with unilateral blocked tube have an already existing tubal factor and evidence on the success of IUI + COH in this group is conflicting[138,139,140].

The main strength of this trial is its pragmatism, which increases the generalisability of the findings. Previous trials used prognostic models to select a particular groups of patients to be included in their trial[87, 89]. There are over 29 such prediction models developed for different patient profiles which can be used for decision-making in couples matching the population for which it was developed[7, 72].

In this trial prediction models were not used as they are rarely used in the UK in day-to-day clinical practice[141]. All comers with varying prognostic profiles were included, which further increases the generalisability of this trial.

One of the main concerns with IUI + FSH has been multiple pregnancy, the risk of which increases with the number of developing follicles[80]. Hence, in this trial a fixed low dose FSH protocol (75IU) was used and strict cancellation policy was

adopted when there were more than 3 follicles of diameter over 14mm. This is again in contrast to previous trials which aimed for 2-3 follicles and cancelled cycles only when more then 3 follicles developed [87, 89]. There was mono-follicular growth in 70% cases and still a live birth rate of 9% per cycle and 25.7% live birth rate per couple for three cycles of IUI +FSH were achieved. On the other hand, no OHSS was encountered and there was a multiple pregnancy rate of only 9% per live birth. This is in agreement with the randomised controlled trial by Balasch et al. (1994), which compared 75 units of FSH with 50 mg of clomiphene for ovulation induction in IUI cycles in couples with unexplained subfertility and showed a mono-follicular growth of over 91% and on-going pregnancy rate of 13% per cycle for FSH and IUI[142].

To reduce the risk of multiple pregnancies, single embryo transfer was performed in over 60% of cases and the multiple pregnancy rates for IVF was only 8%.

There were 17 live births by spontaneous conception in between treatment cycles, (17/207) 8.2% per couple. These couples did not differ significantly from the rest of the cohort in their baseline characteristics (Table 15).

While expectant management remains a valid option for couples with unexplained subfertility[74], there remains considerable pressure from patients for intervention due to lack of confidence in natural conception.

Table 15: Baseline characteristics of couples who conceived spontaneously

Characteristics	**Spontaneous conception**	**Rest of the cohort**	**P****
Age median (IQR*) years	34 (30 35)	32 (30-35)	0.91
BMI (mean ± SD)	23.5 ± 2.7	23.6 ± 3.0	0.94
Primary subfertility n (%)	12 (70.5%)	151 (79.4%)	
Duration of subfertility median (IQR) years	2 (2-4)	3 (2-3)	0.9
AMH median (IQR) pmol/l	23 (11.4-31.1)	18.9 (10.5-30.4)	0.49
AFC (mean ± SD)	17.8 ± 7.9	16.8 ± 8.2	0.63
Day 3 FSH (mean ± SD)	5.1 ± 1.6	5.6 ± 1.7	0.18
Total progressive motile sperm count – median (million) (IQR)	52.6 (36.6-68.6)	52 (37-67)	0.63

P**<0.05 was considered significant

4.4.2 Limitation

One of the main limitations of this trial is that it had to be closed early after recruiting 207 couples. This was a purely administrative decision and was not influenced by knowledge of the results.

The obstetric and neonatal adverse outcomes associated with IUI/IVF cycles were not looked at. This could be considered as one of the limitations of this trial. The cost analysis carried out here showed IUI to be cost effective. However, it should be interpreted with caution, as it was not a detailed economic evaluation. There is no national tariff for IUI or IVF in the UK and the cost varies between different CCGs. The average cost in general is around £700 for one cycle of IUI and £3200 for one cycle of IVF under the NHS. As all patients who participated in this study received treatment under the NHS, we used the above costs to

perform the cost analysis. I did not include additional frozen embryo transfer cycle from any surplus embryo frozen from one IVF cycle. The reason for not including additional frozen embryo transfer cycle was purely administrative. To finish all the frozen embryo transfer cycle from one IVF cycle in practical sense would take at least one – two years (including time for follow up appointments after failed cycles). It would not have been possible to finish the trial, analyse data and write up thesis within the time frame of four years for my MD (Res). These would be followed up as an additional paper following this trial.

4.5 Conclusion:

The results of this trial suggest that there is no statistically significant difference in live birth rate between one cycle of IVF compared to three cycles of IUI + COH with FSH as per intention to treat and per-protocol analysis. However, due to the relative nature of infertility in this patient population, reflected by the large number of naturally occurring pregnancies, it is possible that expectant management might have been as effective as IUI + COH in these patients.

It is important to balance the cost and invasiveness of IVF and to take patients' wishes into consideration before choosing the right treatment modality.

Chapter 5: Conclusion

This thesis aimed to determine the best first line management option for couples with unexplained subfertility. The absence of a definitive cause for subfertility makes the treatment for these couples empirical. While expectant management is an effective option for some of them, clinicians come under considerable pressure from patients to provide a definitive management due to lack of confidence in natural conception. Various options such as using ovulation-inducing agents, intrauterine insemination with or without ovarian stimulation and IVF have been proposed and used for these couples. However, not many trials have compared these treatments and the best first line treatment option for these couples remains unsubstantiated.

The online survey performed here among current UK fertility specialists clearly shows the on-going dilemma among the fertility experts' in managing these couples. Much of this dilemma is due to the scarcity of evidence. Lack of adequate evidence is also clear as shown by the systematic review carried out in this study. There are high clinical and statistical heterogeneity among the studies included.

Hence, to address the issue, a randomised controlled trial comparing the two most commonly performed treatments —IUI stimulated with FSH versus IVF as the first line treatment option for unexplained subfertility— was conducted. 207 couples with unexplained subfertility participated. They were randomised to three cycles of IUI + FSH or one cycle of IVF. The trial showed that there was no statistical significant difference between three cycles of IUI + FSH in comparison to one cycle of IVF in terms of singleton live birth rates. While there were no

differences in multiple pregnancy rates between IUI and IVF, the OHSS rate was higher for IVF. It is interesting to note that there were large numbers of spontaneous pregnancies in between treatment cycles. This shows the relative nature of subfertility in these couples and that an expectant management remains a valid treatment option for them.

This was the first trial conducted in the UK and provides a head-to-head comparison between the two most commonly performed treatments. The pragmatic nature of the trial makes the results highly generalisable.

Although unprecedented support from the patients was received, as evident by the smooth recruitment for the trial, it was not smooth sailing, especially towards the end of the trial. As the NICE guideline was published in 2013 recommending IVF as the only treatment for this group of patients after two years of trying, the CCGs one by one started to cease their funding for IUI. However, the NICE guideline was not based on robust evidence, which was acknowledged by the NICE guideline development group. In this trial, only couples who had their IVF or IUI treatment funded by NHS were included. Self-funded patients were excluded due to lack of research funding. As the funding for IUI was withdrawn, there was no other option than to stop the recruitment prematurely. However, no interim analysis was carried out and the closure of the trial was done without knowledge of the results. This was purely for administrative reasons beyond the investigator's control. Since the intended sample size was not reached, the results should be interpreted with caution. Larger trials are warranted.

A detailed health economics cost effective analysis was beyond the scope of this trial. However, a very basic cost ratio was conducted considering the average

tariff for IUI and IVF. The cost ratio was higher for one cycle of IVF in comparison to three cycles of IUI. However, there is no agreed national tariff for IUI or IVF in the UK and the average cost varies widely between the NHS and private sectors and also between different CCGs. As all the patients who participated in this trial received NHS funded treatment, the average price for IUI and IVF in the NHS was used to obtain a cost ratio. This is far from a detailed economic evaluation.

Overall, in couples with a female partner of less than 37 years of age, it seems logical to offer expectant management to those trying to conceive for less than two years. A few cycles of IUI + FSH before moving over to IVF might benefit those trying longer than two years.

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