"Demographics of infertility and management of unexplained infertility"

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Abstract

The cause of infertility is unexplained in approximately 22-28% of all infertile couples. The prognosis for spontaneous pregnancy in such couples is better than in those with diagnosed causes of infertility. Traditional treatment options in this group have included expectant management, Clomifene citrate, intrauterine insemination with (SO + IUI) or without (IUI) super ovulation and in-vitro fertilisation (IVF). Despite being more expensive, empirical Clomifene and IUI in an unstimulated cycle do not improve the chances of live birth compared to expectant management. Although unlikely to be more effective than no treatment in couples with a reasonably good prognosis, SO + IUI has been shown to be more effective than IUI. Any potential advantage of SO + IUI has to be balanced against the relatively high risk of iatrogenic multiple pregnancy. IVF remains the treatment of choice in longstanding unresolved infertility and, when coupled with the use of elective single embryo transfer, can minimise the risk of multiples. There is a relative paucity of data from randomised trials confirming the superiority of IVF over expectant management.

Key words: unexplained infertility; expectant management; intra uterine insemination; super ovulation; Clomifene citrate; in-vitro fertilization.

Introduction

Infertility has been defined as failure to conceive after regular unprotected sexual intercourse for one year [1, 2]. This definition reflects the prognostic approach to this condition, based on the knowledge that, in a general population, 84% of all women are expected to conceive within one year of regular unprotected sexual intercourse. This figure rises to 92% after two years, and 93% after three years [3]. The term 'unexplained infertility' refers to infertile couples in whom standard investigations, including tests of ovulation, tubal patency and semen analysis are normal. The prevalence of unexplained infertility has been shown to vary from 22% to 28% [4, 5]. A more recent

study puts the prevalence among couples attending a fertility clinic to be 21% in women under 35, and 26% in women over this age [6].

Standard work up for infertility

The basic fertility work up needs to balance the cost and invasive nature of currently available investigations against their value in informing clinical decision making. National Institute of Clinical Excellence (NICE) in the United Kingdom and American Society of Reproductive Medicine (ASRM) in the United States have recommended the following essential tests: semen analysis, assessment of ovulation and evaluation of tubal patency by hysterosalpingogram (HSG) or laparoscopy [7, 8]. The place of laparoscopy versus HSG continues to be debated but it is felt that laparoscopy should be considered when severe endometriosis, pelvic adhesions or tubal disease is suspected [8].

The predictive value of the Post Coital Test has been questioned and the result of a randomised trial has not demonstrated improved pregnancy rates in women undergoing this investigation [9]. Tests of ovarian reserve have been shown to be useful in predicting follicular response to controlled ovarian stimulation in in-vitro fertilisation (IVF) but their role in predicting pregnancy outcomes in infertile women is limited [10].

Causes of unexplained infertility

Standard fertility investigations are far from comprehensive and unable to identify subtle abnormalities in the reproductive pathway. The etiology of unexplained infertility is therefore likely to be heterogeneous, with proposed causes ranging from endocrinological, immunological and genetic factors [11]. In addition, compromised ovarian reserve is a factor which, while not always captured in the diagnostic pathway, can be responsible for a diagnosis of unexplained infertility in older women.

Some authors have questioned the validity of the term 'unexplained infertility' as it is sensitive to the number, nature and quality of the tests used [12]. Others have argued that the limited number of treatment options and the overwhelming dependence on assisted reproduction means that increasing the number of expensive and invasive tests is unlikely to change the treatment strategy in these couples [13].

Prognosis

Couples with unexplained infertility have a higher chance of spontaneous pregnancy than those where definite barriers to conception have been identified [14]. A number of prognostic models have attempted to determine factors associated with spontaneous livebirth [14-16]. A synthesis of these models has been produced by Hunault et al. and validated in a Dutch population [17-19]. Prognostic factors are gradually emerging as key in terms of informing clinical decision making. The chance of pregnancy leading to live birth is influenced by female age, duration and previous pregnancy [14]. For example, a woman aged 28 with 2 years of unexplained infertility has been shown to have a 36% chance of conceiving over the next 12 months [14]. The decision to treat a couple with unexplained infertility should therefore take into account their chances of spontaneous conception.

Management options

Expectant management

The relatively high possibility of spontaneous pregnancy in unexplained infertility supports the strategy of expectant management, i.e. active medical intervention. Couples are made aware of the fertile period and advised to continue regular unprotected intercourse. Observational data supporting this policy come from a number of sources. Snick et al. reported a cumulative pregnancy rate of 27.4% at 12 months in a cohort of couples seen in primary care while Collins et al. observed a

live birth rate of 14.3% at 12 months in the absence of treatment in a secondary/tertiary care setting [14, 16]. In a more recent study, the majority of pregnancies occurring in a group of Dutch couples with unexplained infertility have been shown to be conceived spontaneously with limited contribution from IVF [20, 21].

In a Scottish randomised controlled trial 17% of women, with a mean age of 32 years and a median duration of infertility of 30 months, had a spontaneous pregnancy leading to live birth following 6 months of expectant management [22]. A health economic evaluation based on data from the same trial suggests that, despite being more expensive, empirical Clomifene citrate and unstimulated intrauterine insemination (IUI) do not offer substantially better outcomes in this context [23]. Dutch data on long term follow up of couples with an intermediate prognosis, randomised initially to a 6 month period of either expectant management or super ovulation (SO) and intrauterine insemination show no difference in terms of pregnancy rates between the groups – but an estimated saving of 2616 € in those managed expectantly [24].

Clomifene citrate

It has been believed that oral Clomifene citrate acts in unexplained infertility by correcting subtle ovulatory dysfunction and inducing multiple follicular growth. Women have been traditionally advised to start treatment with Clomifene citrate at a dose of 50 mg once daily from day two to six of a menstrual cycle. A transvaginal ultrasound scan for follicle monitoring is advisable on day 12 in order to minimise the chance of multiple pregnancy. Couples are advised to have timed intercourse from day 12 of the cycle. Where excessive ovarian response is suspected the cycle is cancelled and the couple asked to abstain from intercourse till the next period.

The use of Clomifene has been very popular in couples with unexplained infertility – mainly because it is inexpensive, non-invasive and requires little clinical monitoring [25]. Concerns about multiple pregnancies induced by clomifene and a potential risk of ovarian cancer, however, underline the

need to weigh the risks and benefits [26]. In a randomized controlled trial comparing Clomifene with expectant management, live birth rates in the two treatment groups were comparable (OR 0.79, 95% CI 0.45 – 1.38), suggesting no benefit associated with Clomifene use [22]. The number needed to harm (NNH) with Clomifene citrate was 33, i.e. treating 33 more women with Clomifene would yield one fewer live birth compared with a strategy of expectant management.

A Cochrane review by Hughes et al. was unable to demonstrate improved pregnancy rates associated with Clomifene citrate versus expectant management after pooling data from two trials (OR 1.03, 95% CI 0.64 – 1.66) [27]. Aggregation of data from two studies where Clomifene was used along with a human chorionic gonadotrophin (hCG) trigger also failed to show any benefit following active treatment (OR 1.55, 95% CI 0.58 – 4.60). Multiple pregnancy rates were similar in both the groups (OR 1.01, 95% CI 0.14 – 7.19) (Table 1).

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Wordsworth et al. evaluated the cost effectiveness of empirical Clomifene vs expectant management in unexplained infertility. The cost per live birth was £72 (95% CI £0 - £206) following expectant management and £2611 (95% CI £1870 - £4166) after treatment with Clomifene. Clomifene was more expensive as well as less effective than expectant management [23].

Intrauterine insemination

Intrauterine insemination with or without super ovulation has been an important component of the traditional approach to the treatment of unexplained infertility. It has been believed that increasing the density of motile spermatozoa within the uterus and bringing sperm in close proximity to one or more eggs has the potential to increase the monthly probability of pregnancy. IUI can be performed with or without concomitant ovarian stimulation. In a super ovulation cycle, more oocytes are available, thus increasing the possibility of fertilisation and pregnancy.

Where IUI in a natural cycle is planned, women are asked to monitor either urinary or serum luteinising hormone (LH) levels daily from day 10-12 of the treatment cycle. A single intrauterine insemination is planned after 20-30 hours following the detection of an LH surge. Semen is prepared either by a swim up technique or a density gradient method and the processed sample is re-suspended in a sperm buffer. Between 0.2 ml to 1 ml of the prepared inseminate is introduced aseptically into the uterine cavity using a fine catheter. Couples are advised to abstain from intercourse from the day of LH monitoring until the insemination day. No luteal support is advised.

For SO + IUI cycles, either oral anti estrogens (Clomifene citrate), gonadotrophins or occasionally a combination of the two are used [28]. The aim of ovarian stimulation is to achieve ovulation from more than one (ideally two) mature follicles.

In stimulation protocols using Clomifene citrate, a 50 mg oral dose is administered once daily from day two to six of the treatment cycle. A transvaginal ultrasound for follicle monitoring is planned on day 12. Once a follicle with a diameter of 18 mm is documented, urinary LH or serum LH levels are estimated to rule out endogenous surge. If no endogenous surge has occurred, a (hCG) trigger which mimics endogenous LH surge is administered intramuscularly and IUI planned 36-40 hours later.

For stimulated cycles using gonadotrophins, a day 3 ultrasound is performed during the treatment cycle. Thereafter a daily dose of 75IU of gonadotrophin (Human menopausal gonadotrophin; HMG intramuscularly or follicle stimulation hormone; FSH subcutaneously) is started from day 3 and transvaginal ultrasound is performed from day 8 to monitor follicular growth.

Once a follicle of 17 mm is documented, urinary or serum LH levels are estimated to rule out an endogenous surge and a human chorionic gonadotrophin (hCG) trigger administered. Intra uterine insemination is planned 36-40 hours after the hCG trigger. In the case of excessive response (> three follicles of more than 15mm), the cycle is cancelled to avoid the risk of high order multiples [29]. Usually no luteal support is advised.

In combination cycles using Clomifene and gonadotrophins together, Clomifene (50 mgs orally) is started on day 2 and continued till day 6 of cycle. Gonadotrophins (either HMG or FSH at a dose of 75IU) are given on days 3, 5 & 7 and follicular monitoring is performed on day 8. The rest of the protocol is similar to the gonadotrophin protocol.

IUI vs expectant management

In a Scottish multicentre trial, 507 couples with unexplained infertility, 34 with mild male infertility and 39 with mild endometriosis (total = 580) were randomized into three arms: expectant management, Clomifene citrate and IUI [22]. Live birth rates of 17% (32/193) and 23% (43/191) were obtained following expectant management and IUI respectively, a difference which did not reach statistical significance (OR 1.46, 95% CI 0.88 – 2.43). The clinical pregnancy rates were also similar in both groups (expectant group 17% vs IUI group 23%) (OR 1.41, 95% CI 0.73 – 2.74). The number needed to treat for benefit (NNB) with IUI was 17 - suggesting that 17 women would need to undergo IUI to achieve one extra live birth.

The Cochrane review by Veltman-Verhulst et al. included this trial by Bhattacharya et al. but excluded data from 73 couples with mild male factor and mild endometriosis [22, 28]. The live birth rate in the IUI group was 23% (38/167) and in the expectant management group 16% (27/167). The difference between the two did not reach statistical significance (OR 1.60, 95% 0.92 – 2.78) (Table 1).

Clomifene + IUI versus expectant management

In the Cochrane review by Hughes et al. data from two trials comparing Clomifene citrate with IUI versus expectant management were pooled [27]. The results were unable to show any clinical benefit associated with treatment with Clomifene and IUI (OR 2.40, 95% CI 0.70 – 8.19).

SO + IUI vs expectant management

Steures et al. conducted a Dutch multicentre randomized controlled trial comparing super ovulation (gonadotrophin or Clomifene) and IUI with expectant management in couples with unexplained infertility and an intermediate prognosis [30]. The live birth rates were comparable in the two groups - 20% (26/127) and 24% (30/126) with SO + IUI and expectant management respectively (OR 0.82; 95% CI 0.45 – 1.49) (Table 1).The difference in multiple pregnancy rates did not reach statistical significance (OR 2.00, 95% CI 0.18 – 22.34).

In a cross over randomized trial which compared super ovulation (Clomifene) and IUI with timed intercourse in a natural cycle, Deaton et al. randomised 67 women with unexplained infertility and surgically corrected endometriosis [31]. Pregnancy rates per patient were 34% (IUI) vs 14% (expectant management). Despite an odds ratio of 3.20 in favour of IUI, the results were not statistically significant and the wide confidence intervals (95% CI 0.82 – 12.50) reflected the imprecision of the estimate.

SO + IUI vs timed intercourse in stimulated cycles

The review of SO + IUI versus timed intercourse by Veltman-Verhulst et al., based on results from 2 trials, suggests comparable live birth rates (OR 1.59, 95% CI 0.88 – 2.88) [28]. There was, however, evidence of significant statistical heterogeneity (I^2 = 72%) between the trials.

The pooled odds ratio for pregnancy based on data from 7 trials was in favour of the SO + IUI group (OR 1.68, 95% CI 1.13 – 2.50). The stimulation protocol reported in the studies included Clomifene, gonadotrophin and a combination of Clomifene and gonadotrophins (Table 1).

Four trials reported multiple pregnancy rates and the pooled odds ratio obtained after combining the trials was 1.46 (95% CI 0.55 – 3.87).

IUI in a natural cycle vs SO + IUI

The largest multicentre trial evaluating IUI was conducted in the United States by Guzick et al. and included 932 couples with unexplained or male factor infertility [32]. Participants were randomized to four treatment arms: intracervical insemination (ICI), IUI, SO (gonadotrophin) with ICI and SO (gonadotrophin) with IUI. Four treatment cycles were planned for each couple. Pregnancy rates per couple were significantly higher for SO + IUI (33%) as compared to the other three groups (ICI = 10%, IUI = 18% and SO + IUI = 19%). Treatment with SO + IUI was three times more likely to lead to pregnancy compared to ICI alone and twice more likely to achieve pregnancy than IUI or SO + ICI.

In the Cochrane review by Veltman-Verhulst et al., pooled data from four trials were used to generate a combined odds ratio for live births in favour of SO + IUI cycles when compared with natural cycle IUI (OR 2.07, 95% CI 1.22 – 3.50) (Table 1) [28].

Veltman-Verhulst et al. could not perform a meta-analysis for multiple pregnancy outcomes due to lack of data from the primary trials [28]. A small randomized controlled trial by Murdoch et al. (n = 39) found multiple pregnancy rates to be similar in both groups (odds ratio of 3.00, 95% CI 0.11 – 78.27) with very wide confidence intervals [33]. Guzick et al. reported a multiple pregnancy rate of 29% in the SO + IUI group and 4% in the IUI group [32].

IUI vs IVF

Goverde et al. in a prospective randomized trial compared IUI, SO + IUI and IVF in couples with unexplained or male factor infertility [34]. The trial included 86 couples in the IUI arm, 85 in the SO + IUI arm and 87 in the IVF arm; a maximum of 6 treatment cycles were planned in each arm. The differences in live birth rates between IVF (41%) and IUI (26%) were not statistically significant with an odds ratio of 1.96 (95% CI 0.88-4.36). The wide confidence levels reflect the relative lack of precision of this estimate due to the small sample size.

SO + IUI vs IVF

A Cochrane review by Pandian et al. identified three trials comparing SO + IUI with IVF [35]. Due to different protocols leading to significant heterogeneity, data from only two of these which compared three cycles of SO + IUI with one cycle of IVF could be aggregated. The pooled odds ratio was 1.09 (95% CI 0.74 – 1.59) suggesting no clear evidence of improved outcomes associated with either treatment (Table 1).

The multiple pregnancy rates were also similar between both the groups with the pooled odds ratio from the three trials being 0.64 (95% CI 0.31 – 1.29) (Table 1).

In the third trial by Reindollar et al. 503 couples with unexplained infertility were randomized into two arms [36]. In the conventional arm women received 3 cycles of Clomifene with IUI followed by 3 cycles of gonadotrophin IUI and then IVF, while those in the second (accelerated) arm received IVF straight after Clomifene with IUI. Higher pregnancy rates were achieved in accelerated arm (hazard ratio 1.25, 95% CI 1.00 – 1.56). The pregnancy rates per cycle were 7.6%, 9.8% and 30.7% for CC + IUI, gonadotrophin with IUI and IVF respectively.

Pandian et al. included the trial by Reindollar et al. in their review but did not combine it with data from the other 2 trials due to statistical heterogeneity [35, 36]. Live birth rates in the IVF group were significantly higher than those in the SO + IUI group with an odds ratio of 2.66 (95% CI 1.94 – 3.63).

IUI: Health economic considerations

IUI vs expectant management

In an economic evaluation of a large multicentre trial, Wordsworth et al. evaluated the cost effectiveness of IUI vs expectant management as a first line treatment option in unexplained infertility [23]. The mean (standard deviation) cost per treatment cycle for expectant management was £0 and £98 (£31) for IUI. The cost per live birth for expectant management was £72 (95% CI £0 - £206) and £1487 (95% CI £1116 - £2155) for IUI. The live birth rates were similar in both groups.

The authors concluded that IUI was expensive and did not result in higher live birth rates as compared to expectant management and are unlikely to be cost effective in a National Health Service setting.

IUI vs IVF and SO IUI vs IVF

Goverde et al. evaluated the cost effectiveness of IUI, SO + IUI and IVF [34]. The treatment costs included hospital costs (personal, materials, equipment, housing, etc) and ambulatory costs (medication, urinary LH kits etc). Costs for infertility work up and antenatal care after 12 weeks were not included.

The cost of a single IUI cycle was 623 Dutch guilders (NLG), NLG 931 for SO + IUI and NLG 3350 for an IVF treatment cycle. The cost per pregnancy which resulted in live birth was NLG 8423 for IUI, NLG 10661 for SO + IUI and NLG 27409 for IVF treatment.

Pashyan et al. used a mathematical model to estimate and compare the cost effectiveness of primary IVF with IUI and IVF as a treatment option [37]. The cost effectiveness ratio for IVF was £12,600. The incremental cost effectiveness ratio for IUI and IVF was £13,100. For 100 couples diagnosed with unexplained or male factor infertility, 6 cycles of IUI will cost an extra £174,200 – providing an opportunity for an additional 54 IVF cycles and 14 live births. The assumed mean live birth rate for IUI was 3.55 per cycle. The authors concluded that a primary strategy of IVF was more cost effective than IUI followed by IVF.

IVF vs expectant management

Hughes et al. conducted a randomised trial in which 139 couples with unexplained infertility or male factor were randomized into two groups – direct IVF or 3 months expectant management [38]. The live birth rates obtained were 29% (20/68) in the IVF group and 1% (1/71) in those managed

expectantly. The authors concluded that the relative probability of live birth was nearly 21 fold higher in the IVF arm than in the expectant group.

Pandian et al., in their Cochrane review, analyzed data from couples with unexplained infertility recruited to the trial by Hughes et al. [35,38]. The live birth rate was 46% (11/24) in the IVF group (single cycle) and 4% (1/27) in the expectant group. The difference was statistically significant in favour of the IVF group (OR 22, 95 % CI 2.56 – 189.37) (Table 1).

In the randomised controlled trial by Soliman et al. pregnancy rates for couples with unexplained infertility were 5 % (1/21) and 14 % (2/12) in the IVF and expectant management group respectively [39]. The odds ratio for pregnancy rate after pooling data from the two trials was also significantly in favour of the IVF group as compared to the expectant management, although the large confidence interval reflects the uncertainty (OR 3.24, 95% CI 1.07 – 9.80).

Contribution of IVF

The contribution of IVF to ongoing pregnancy rates in an unselected subfertile population in a tertiary care centre was evaluated by Brandes et al. [20]. This cohort study included 1391 infertile couples followed up for 5 years. A total of 1001 couples (72%) had ongoing pregnancies, of which almost half of all the pregnancies were spontaneous (45.6%), 19.2% pregnancies occurred after ovulation induction, 14.0% after IUI and 21.2% pregnancies after IVF treatment. Thus, only 13% of all the ongoing pregnancies in couples with unexplained infertility were attributable to IVF, suggesting that the role of IVF is often overestimated.

Summary

The definition of infertility, which is based on the expectation of spontaneous pregnancy over an agreed time horizon, essentially represents a prognostic, rather than a diagnostic approach to this condition. Unexplained infertility represents an inability on the part of clinicians to identify a definite

biological barrier to conception. This uncertainty has traditionally encouraged a degree of permissiveness in terms of using treatments of unproven effectiveness. Recent trials have questioned the clinical and cost effectiveness of empirical Clomifene citrate and unstimulated IUI in the treatment of unexplained infertility. While SO + IUI has been shown to be more effective than unstimulated IUI, use of ovarian stimulation is associated with high rates of multiple birth. This has highlighted the role of expectant management in couples with a short duration of infertility. IVF is used for longstanding unresolved unexplained infertility and judicious use of elective single embryo transfer can minimise the risk of multiples. Data supporting the use of IVF over SO + IUI in the management of treatment of naive couples are inconclusive, but IVF appears to be more effective in couples previously treated unsuccessfully with Clomifene + IUI.

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