Should couples with unexplained infertility have three to six cycles of intrauterine insemination with ovarian stimulation or in vitro fertilization as first-line treatment?

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PRO (IUI): Couples with unexplained infertility should be recommended to have three to six cycles of IUI with ovarian stimulation as first-line treatment

Pro 1. Willem Ombelet, M.D., Ph.D.

The most acceptable definition of "unexplained infertility" is 1 to 3 years of attempting conception unsuccessfully when routine tests for tubal patency, ovulatory disorders, and sperm quality are normal. According to the literature, between 15% to 30% of all couples presenting with infertility after 1 year receive a diagnosis of unexplained infertility. Possible interventions in case of unexplained infertility consist of three options: expectant management, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) or intrauterine insemination (IUI) with mild gonadotropin, letrozole, or clomiphene citrate (CC) ovarian stimulation.

Increasing success rates after IVF-ICSI with better implantation rates per embryo have been reported in recent



Pro 1. Aine McNally, M.R.C.O.G.



William Ledger, M.D.

PRO (IVF): Couples with unexplained infertility should be recommended to have IVF as first-line treatment

For many years, IVF has been viewed as the last resort for couples presenting with infertility, rather than as the first-line treatment. Although some conditions present a clear indication for first-line IVF—for example, severe male factor infertility or tubal disease—for those couples with unexplained or mild male factor infertility, IUI has often been favored as a more tolerable and cost effective option. However, this concept has been challenged in recent years because the increasing success rates and decreasing complications recorded for IVF have closed the gap. With the U.K. National

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years, partly because of better air quality and quality control programs in IVF laboratories and technical changes in the procedures itself, such as the use of soft catheters and ultrasound-guided embryo transfers (1, 2). High-order multiple births, the main complication associated with IVF, have declined substantially in many countries because fewer embryos are transferred. These changes have made conventional IVF a more attractive option from a cost-effective point of view when compared with IUI.

The rationale behind IUI with or without ovarian stimulation (OS) is to increase the gamete density at the site of fertilization. Compared with IVF, IUI can be done without expensive infrastructure and is less invasive, is less expensive, and requires only limited training. Moreover, IUI can be performed with minimal risks and monitoring, resulting in a high couple compliance (3). Three to six cycles of IUI have become common practice worldwide and at least three consecutive IUI cycles are recommended before resorting to IVF (4).

Compared with IVF, a similar increase in pregnancy rates with IUI has not been reported. For IUI to remain the best firstline option in unexplained infertility, we need to increase the delivery rate per cycle without increasing the multiple pregnancy rate. Different strategies to increase IUI success rates—such as different ovarian stimulation protocols, better timing of IUI, and various sperm processing techniques have been investigated, with limited success.

Previous reports had shown that a slow-release IUI might improve the pregnancy rate compared with bolus IUI (5, 6). We compared ongoing pregnancy rates after bolus IUI versus patient-friendly slow-release IUI. By using cluster-weighted generalized estimating equations we found a statistically significant increase (4.5%) in ongoing pregnancy rates in the slow-release group (7).

Better patient selection is also important. In patients with mid-distal or distal unilateral tubal occlusion, a statistically significant decrease in IUI success rate has been found. These patients should be referred for laparoscopic assessment and IVF instead of IUI should be the first-choice treatment (8).

Recent reports have described a statistically significant negative effect of human papilloma virus (HPV) positivity in men and women on clinical pregnancy rates after IUI (9, 10). Therefore, HPV-positive women and men should not receive IUI as a first-line treatment although it is unknown yet whether HPV positivity has an effect on IVF-ICSI pregnancy rates.

During the last 5 years, a number of well-organized studies in different patient populations have shown that IUI should be the first-line treatment option over IVF in selected cases of unexplained infertility (11–13). In a multicenter, randomized, noninferiority INeS trial, Bensdorp et al. (14) showed that IUI-OS was noninferior compared with IVF with single-embryo transfer or IVF in a modified natural cycle, with a reasonably low multiple birth rate for couples with

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Institute for Health and Care Excellence (NICE) guidelines (37) now recommending IVF as the first-line treatment for couples with unexplained infertility, the debate continues on how to best serve these patients.

In its infancy, the success rates for IVF were reported in single digits (38). However, across the world we see consistently rising success rates year after year. For example, the Australia and New Zealand Assisted Reproduction Database (ANZARD) most recent report from 2017 quotes a 26.8% live-birth rate (LBR) per autologous embryo transfer (39). The HFEA data from the same year in the United Kingdom quotes a 22% live-birth rate (40).

Although pregnancy rates from IVF continue to improve, they remain relatively static with IUI (41). A paucity of recent data concerning pregnancy and live-birth rates after IUI was acknowledged in a recent Cochrane review (42), but pregnancy rates are commonly quoted as 10% to 20% (4, 43). A study by Chambers et al. (43) in 2010 reported a pregnancy rate for IUI at 15% for couples with unexplained infertility undergoing their first cycle of IUI, dropping to 7% with the second cycle.

Chambers et al. (43) also showed that increasing IVF success rates translated into a shorter time to pregnancy. There are many studies that consistently show that women and men are waiting until later in life before starting their families. For example, the average age of women giving birth in the United Kingdom has increased from 26.4 years in 1975 to 30.5 in 2017 (44), and the average age of women using assisted reproduction technology (ART) in Australia is 35.9 years (39). This global trend is important for both doctors and patients: rates of embryonic aneuploidy resulting in implantation failure and miscarriage increase with increasing maternal age (45) and treatment success rates steadily decrease. The older patient population now seen in fertility clinics is more at risk of these complications, so time spent on unsuccessful treatment cycles can have a substantial detrimental effect on a couple's chances of ever having a child.

Multiple pregnancies have long been one of the most significant complications of assisted conception. The risks of multiple pregnancy to both mother and fetus are well established, with increasing maternal complications including preeclampsia, gestational diabetes, and a host of other medical problems, and also increased rates of preterm birth and cerebral palsy in the neonate (46). A recent American study has suggested a multiple pregnancy can incur 5 to 20 times the cost to the health care system compared with a singleton (47). Additionally, IVF has seen a striking reduction in rates of multiple pregnancy across many jurisdictions as a result of the trend toward SET. For example, ANZARD has reported that 89% of cycles undertaken in Australia and New Zealand in 2017 were SET, with an overall multiple pregnancy rate of 3.7% (39). The multiple pregnancy rate after IUI is more difficult to ascertain because mandatory reporting of cycle out-

mild male factor or unexplained infertility and a poor prognosis of becoming pregnant naturally. Farquhar et al. (13) randomized 201 patients with unexplained infertility to IUI with CC or expectant management, showing that the former was associated with a threefold greater live-birth rate than the latter (31% vs. 9%). In a large randomized multicentre study in the Netherlands including 738 couples with an unfavorable prognosis, four cycles of IUI + FSH were not superior to four cycles of IUI + CC, with 31% and 26% ongoing pregnancies, respectively, and no difference in the multiple pregnancy rate (12).

Gonadotropins seem to improve live-birth/ongoing pregnancy rates compared with CC within a protocol adhering to strict cancellation criteria, not taking into account costs and patients preference (15). Female age should also be considered as an important factor. According to the 2017 Belgian Register for Assisted Procreation (BELRAP) data the delivery rate per cycle for patients older than 40 years was 1.7% for IUI and 9.5 % for IVF-ICSI (16).

As costs linked to fertility care are not covered by government or insurance companies in most countries, the relative cost-effectiveness of fertility treatments is very important. In an investigation of direct health care costs in the cohort of patients of the INeS-trial, IUI-OS turned out to be the most cost-effective strategy and up to six cycles of IUI-OS was still cost-effective when compared with direct IVF (11). Making use of a computer-simulated cohort of infertile women, Moolenaar et al. (17) showed that above a prewash total motile sperm count (TMSC) of 3 million, IUI is less costly than conventional IVF, but below 3 million IVF-ICSI is less costly. In a cost-effectiveness analysis alongside the randomized controlled trial of Danhof et al. (18), it was concluded that gonadotropin-IUI were more expensive compared with CC-IUI without being statistically significantly more effective. The U.K. data from a Human Fertilisation and Embryology Authority (HFEA) freedom of information request for 2012-2016 show that IUI is safer and more cost-effective than IVF treatment (19).

Intrauterine insemination is publicly funded in 14 out of 42 European countries (20), and this will surely increase the number of IUIs performed. On the other hand, IUI is the only available method for unexplained infertility in many resource-poor countries where IVF-ICSI is not accessible for the large majority of the population due to limited availability of IVF centers and high costs (21, 22).

To conclude, for women younger than 40 years with unexplained infertility, three to six cycles of IUI with ovarian stimulation should be recommended as a first-line therapy, provided a strict cancellation strategy is followed to avoid

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comes is not applicable to IUI; however, it is often quoted at around 10% (48, 49). Close monitoring of ovarian response to gonadotropin stimulation and responsible practice can mitigate this somewhat, but it is undoubtably harder to achieve equivalently low multiple pregnancy rates in an IUI program than in an IVF program with SET.

Another key advantage when recommending IVF over IUI is the potential for family building. Intrauterine insemination can only create one pregnancy per cycle (accepting that 10% may be multiple) whereas with the increasing efficacy of embryo cryopreservation there is the realistic potential to achieve several healthily spaced pregnancies over several years from a single stimulated IVF cycle. Global studies now confirm that the live-birth rate after transfer of a cryopreserved blastocyst is at least equivalent to what is achieved after fresh embryo transfer (39, 40). A 2019 study showed that over a 7-year period, 43% of patients with a baby conceived by ART returned for a second treatment. Cumulative livebirth rates were very promising for these patients, reported at 60% to 88% from frozen embryos, and 50% to 69% from fresh cycles (50).

Although IVF is without question an emotionally and physically draining process, changes to practices and regimens have seen a reduction in complications and improvement in patient acceptability (51). A move toward gonadotropin-releasing hormone (GnRH) antagonist controlled IVF cycles, which are of shorter duration and involve fewer injections, has made modern IVF superovulation less strenuous for patients to perform. This approach to superovulation coupled with use of a GnRH-agonist trigger to induce final oocyte maturation followed by fertilization and blastocyst cryopreservation has brought considerable reduction in risk of moderate and severe ovarian hyperstimulation (quoted at 0.4% in the most recent ANZARD review) (39).

Preimplantation genetic testing (PGT) provides further impetus in favor of IVF. Preimplantation testing obviously requires access to the embryo to perform a biopsy and is hence not applicable in IUI cycles. For families who are known to be afflicted by heritable conditions, PGT is clearly advantageous; it also allows older patients to opt for aneuploidy screening and enables couples to select for gender in parts of the World where this is permitted.

Evidence suggests cultural normative factors play a role in what patients deem socially and morally acceptable (52). With the use of ART increasing by 5% to 10% per year (53) and 1 in 24 babies born in Australia in 2017 being conceived after IVF (39), ART has undoubtably became more acceptable in many societies in recent years. This acceptability removes

multiple pregnancies. The results from IUI have to improve by optimizing patient selection and refining the techniques and treatment strategies.



Pro 2: Rik van Eekelen, Ph.D.

When I talk to laypeople about fertility, they are always surprised to discover how little we truly understand of conception and implantation. Perhaps the best example of this is unexplained infertility, the enigma of reproductive medicine. Why are these couples unable to conceive? We do not know. We do know that some of them are not diseased at

all: conceiving is, after all, very much like throwing a die (23). Sometimes you throw a six, but you will not be surprised if you get anything else. Some patients will not throw a six many times in a row. These "unlucky" patients—who are perfectly healthy—are very likely to conceive naturally, despite their diagnosis after (at least) 1 year of trying. Approximately 30% of unexplained infertile couples conceive in the year following diagnosis (24–26).

On the other side of the spectrum are the couples with unexplained infertility who seem to be unable to conceive no matter what we try, even after IVF. This can be considered sterility (27). With a perspective that covers many years—the entire reproductive life span of a woman—it will not matter what treatment options are presented to sterile couples. All other subtypes of unexplained infertility, with biological mechanisms we are currently unaware of, lie somewhere in between: lower than average fertility but not sterile. This

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another obstacle that may have influenced patient choice in past times. In vitro fertilization has also become more acceptable to patients who have ethical concerns over the creation of "surplus" cryopreserved embryos that they may be reluctant to discard. Modern low-stimulation approaches that aim to create one or a small number of embryos per cycle show promising results and avoid this dilemma (54, 55).

Finally, "unexplained infertility" is a frustrating nondiagnosis, and patients frequently struggle to accept the nature of their problem and seek a reason for their inability to conceive. In vitro fertilization offers significant diagnostic possibilities which may emerge during the course of a treatment cycle. Technological improvements—including highmagnification selection of sperm for ICSI, video time-lapse imaging of embryo development, and PGT—offer the potential to identify issues with egg or sperm quality, fertilization, and embryo development, something which IUI cannot offer. Although these issues may not be amenable to intervention, the additional knowledge gained from an IVF cycle may be of paramount importance to the couple in coming to terms with their diagnosis and, in some cases, discontinuing futile treatment.



Pro 2. Kevin Doody, M.D.

Unexplained infertility can resolve spontaneously or in some cases can be cured with IUI treatments or through IVF, and this discussion will be limited to these two treatment options. Infertility is a disease. The goal of treatment of any disease is to cure without producing harm. Treatments rarely cure 100% of all patients or are without side effects. Decisions between alternative treat-

ments must be made via comparisons of efficacy and safety. Economic considerations and other patient burdens should also be considered, especially when treatment outcomes are similar or data are lacking to compare outcomes. Although economics should be considered, these concerns should not drive treatment decisions when treatments are affordable. Consider as an example a chemotherapeutic regimen at a cost of \$2,000 that cures only 10% of patient cancers. Contrast this with an alternative treatment that costs \$20,000 but cures 50%. In most economic environments, it would not be ethically justifiable to choose the cheaper alternative simply because the calculated cost per life saved is lower.

The value associated with a given fertility treatment's outcomes cannot be easily measured in dollars and cents. Economic measurements are further complicated by the

can be referred to as subfertility, which includes age-related fertility decline (25, 28).

Our current inability to accurately distinguish among these types of patients is the core of this dilemma. The logical conclusion is that we are dependent on the factor of time. As time passes, selection takes place, during which couples with the best prognoses conceive; this filters out the healthy-butunlucky and subfertile patients who do not necessarily require IUI, let alone IVF (26, 29). I believe that, from this principle, it follows that several cycles of IUI (ideally in combination with ovarian stimulation) should be the first-line treatment for couples with unexplained infertility.

There are four reasons to choose IUI. The most important argument is invasiveness: IVF is generally considered a stressful and painful procedure, and IUI much less so. Especially for women with unexplained infertility of whom many do not require IVF, the primum non nocere oath should be adhered to. A second argument concerns improving the mental health of patients: they may feel their issue is acknowledged when their trajectory now involves active treatment, without resorting to the most invasive and stressful option. A third argument is that the effectiveness of IVF versus IUI in terms of increasing the chance of a live birth has a poor evidence base; there are no trials that compare IVF with both IUI and expectant management (30-32). Even if observational data suggest that the per-cycle chance of IVF is the highest, it is much less clear if this is the case over a longer period of follow up, or when receiving IUI first and then IVF (14, 33). The fourth and last argument is stalling for time allows selection to take place: couples rarely receive consecutive IUI cycles, such that their IUI trajectory also serves as a postponement of IVF during which they might even conceive naturally. Again, this selection could filter out the last healthy-but-unlucky or subfertile patients in particular, without harming the sterile patients.

As for not offering IUI as a first-line treatment, there are a couple of exceptions to consider. Shorter time to pregnancy is a more important argument for couples that wish to have multiple children, although the clinician should prepare the couple for the fact that this might be unattainable. This is especially true when the woman is of a more advanced age (i.e., 38 years or above), although the higher the female age, the less certain it is that IVF offers much benefit compared with expectant management (34, 35). If a multiple pregnancy has to be avoided at all costs (e.g., due to a high risk of complications), this can be achieved with IUI without ovarian stimulation or, generally considered more effective, IVF using single-embryo transfer (SET).

Albeit costs depend on the country and reimbursement system, the general consensus (with current limited evidence) is as follows: IUI-OS seems more expensive and more effective than expectant management, and IVF seems more expensive and more effective than IUI-OS (32, 33). When

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second-order consequences of treatments (e.g., the impact of treatment on productivity, including the productivity of offspring) and the financial costs of side effects or complications of treatments. Attempts to estimate the totality of economic cost will require complex models which are often based on unproven or incomplete assumptions. Any model that has not been tested and validated is not a useful tool for clinical decision-making.

The mechanisms by which IUI and IVF treatments overcome infertility may be similar for some couples. It should be remembered that unexplained infertility always does have an etiology, but the cause(s) may be varied and difficult or impossible to determine using our generally accepted and available diagnostic tests. Intrauterine insemination may work in situations where an occult cervical factor or mild fertilization dysfunction is present, but it would not be expected to benefit infertility related to tubal dysfunction or severely impaired sperm–egg interaction. These causes would be well suited for treatment with IVF or its variants, including ICSI.

Unexplained infertility may, in some cases, be due to high proportions of abnormal gametes. In vitro fertilization is often times a treatment marked by attrition. Large numbers of eggs may be required to obtain a relatively few—or even one—healthy embryos. A similar strategy can be employed with IUI. To achieve this with IUI, however, requires multiple treatment cycles performed with superovulation. Superovulation with gonadotropins, a previous strategy to improve rates with IUI, is rarely performed due the frequent occurrence of complications including ovarian hyperstimulation syndrome and high-order multiple gestation. It has been argued that CC or letrozole superovulation performed in conjunction with IUI strikes a balance. This strategy is low tech and low cost compared with IVF with a multiple gestation rate of less than 10%.

Multiple gestation is the principal source of safety concerns with both IUI and IVF. Both techniques can be performed in natural cycles without an increase in this risk, but success rates are unacceptably diminished. In vitro fertilization has procedural and anesthetic risks that IUI avoids. Egg retrieval is invasive, painful without anesthesia, and has known risks of harm to pelvic structures and bleeding, although these injuries are thankfully rare. The risks with IVF are quite small compared with the risks of pregnancy (thrombosis, hemorrhage, and even death). Multiple gestation occurring through IUI or IVF treatments has a far greater risk of harm than the fertility treatments themselves. Multiple gestation can be largely avoided with IVF though the use of SET. According to the most recent data, 25 percent of Society for Assisted Reproductive Technology (SART) programs have lower than a 5% incidence of twins in women younger than 38 years and virtually no triplets or high-order gestations.

Spontaneous abortion is another complication of fertility treatment although the data regarding the incidence of this after conception by IUI are sparse. Although the miscarriage

multiple options are available to solve the same problem, the major decision-making problem is which to give first (36). If the couple must pay for their own treatment, depending on their budget, IVF might be chosen to avoid incurring costs for two treatment trajectories.

The evidence so far supports that treating later-allowing selection to take place over time, be it via expectant management or an IUI trajectory-avoids costly and invasive IVF treatment without decreasing the cumulative chance of live birth. Not only has this been shown in a recent costeffectiveness analysis that combined the current body of evidence on unexplained infertility (32, 33), this was also shown in the most recent trial that compared IUI-OS with IVF, the Dutch INeS trial (14). In this trial, the primary analysis followed the intention-to-treat principle, meaning that patients allocated to IUI-OS were analyzed as IUI-OS regardless of what they actually received. The investigators showed that a considerable fraction of the couples allocated to IUI-OS who did not conceive at first then switched to IVF SET. This yielded a less expensive strategy, in which the cumulative chance of live birth was similar to the strategy in which everyone started with IVF SET.

To summarize, IUI as first-line treatment spares many women with unexplained infertility from an invasive, stressful treatment. This approach also seems to be cost-effective without decreasing the cumulative chance of a live birth.

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rate after IUI treatments may not be different compared with pregnancies achieved naturally, screening of embryos with PGT has been shown to greatly reduce this risk for patients undergoing IVF.

Differences in efficacy between the two treatment options are generally held to be substantial despite a relative lack of good data for IUI. Organized registry groups do not track IUI treatments consistently as they do IVF cycles. The rates provided in the literature generally reflect relatively small numbers and/or are based on single-center experience. Pregnancy rates per treatment attempt in the high single digits have commonly been reported. Live-birth data are lacking, but it must be assumed that the live-birth rates are substantially lower. On the other hand, success with IVF has been much more consistent. In the 2017 SART national summary report, the live-birth rate per start of egg retrieval cycle averaged 54.7% in women up to age 35. Although the success rates decline with age, the IVF live-birth rates exceed 25% even in women aged 38-40 years. The differences in efficacy are accentuated when one considers that a single IVF cycle can produce more than one healthy embryo, thus frequently allowing additional pregnancies for couples desiring a larger family. By contrast, attempts to conceive after successful IUI will likely have lower success rates due to reproductive aging.

In summary, IVF does not have demonstrable safety concerns compared with stimulated IUI but has clear and substantial benefits regarding efficacy (rate of cure) of unexplained infertility. From a strictly medical standpoint this is the desired first-line treatment option. It has been argued that IUI can be used as a first-line treatment in younger women and IVF can be employed after failure for the vast majority of treated couples. This strategy ignores the fact that infertility has a significant impact on emotional health. Failed treatments often lead to enhanced anxiety and depression, and are a cause of marital stress and treatment discontinuation for many couples.

This discussion does not lead to a conclusion that there is absolutely no role for IUI treatments for unexplained infertility. For some patients, IUI might be preferred because it may be perceived as a "more natural" means of achieving pregnancy. For these individuals, intravaginal culture for fertilization and embryo development may also be preferred over conventional laboratory IVF techniques. Finally, IVF may represent too much of a financial burden for patients who have constrained resources. Access to IVF treatments should improve as thirdparty payors increasingly recognize that infertility deserves adequate treatment as does any disease that has such a major impact on quality of life for our patients.

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