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INVITED REVIEW ARTICLE

A New Dawn for Intrauterine Insemination: Efficient and Prudent Practice will Benefit Patients, the Fertility Industry and the Healthcare Bodies

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Dr. Gulam Bahadur is a past member of the HFEA. His main involvement is in andrology with special emphasis on diagnostic analyses, male cancer patients, counselling, sperm donor recruitment and sperm freezing, and recovery rates following cryopreservation. Dr Bahadur has produced one of the first reports on ovarian tissue freezing for cancer patients. Current interests relate to optimising pregnancy rates in intrauterine insemination by understanding the factors driving the pregnancies and risks. Recently a new report points towards enhancing male factor using consecutive ejaculates and how this can be used favourably for IUI.

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Abstract This review addresses the misplaced facts about the IUI procedure within a lucrative fertility industry. Evidence suggests IUI must be a first-line treatment option for most couples except in cases of bilateral tubal blockage and severe oligozoospermia. We introduce the concept of using 'consecutive ejaculation' in men with subfertility and one which can radically alter the male infertility definition, thereby providing a new approach to examining and managing male factor infertility. The review also explores various aspects affecting the IUI procedure, its determinants of success, risks and areas for future improvements. Areas such as choice of patients, clinical management of patients, the type of stimulation regime, timing and the management of sperm usage have significant bearing to whether IUI will succeed. The paper asserts that IUI should be the first choice of fertility treatment.

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Keywords IUI · IVF · GnRH · Clomiphene · Cost-effectiveness · Expectant management · Pregnancy rates · Unifollicular · Bifollicular · Male factor

Introduction

There has been a lapse in the progress of intrauterine insemination (IUI) particularly in improving clinical pregnancy rates, as witnessed with IVF/ICSI practices [1, 2]. New evidence strongly supports the IUI procedure as a first-line treatment option [1, 3]. The added costs necessary to achieve one additional healthy child in the IVF-SET group compared with IUI-COH were €43,375 [4]. The Cochrane reviews dismiss multiple birth rate concerns in the IUI procedure [5–7].

IUI procedure increases the chance that maximum number of healthy sperm reaches the site of fertilisation. In couples with abnormal mucus, the rationale might be to bypass a possible cervical factor. First-line treatment using IUI must be attempted in all patients except in women with cervical atresia, cervicitis, endometritis or bilateral tubal obstruction and in most cases of amenorrhoea or severe oligozoospermia. 'Consecutive ejaculate' qualities in subfertile males also support in-depth analyses of subfertile males [8].

IUI Procedures and Insemination Methods

Insemination with unprocessed semen is associated with pelvic infection, and it is necessary to remove seminal plasma to avoid prostaglandin-induced uterine contractions [9]. The most frequently used methods involve centrifuging spermatozoa through culture medium or density gradients followed by re-suspension in suitable culture media otherwise swim up methods. A systematic review of sperm preparation techniques concluded that there were insufficient randomised studies to choose the best method [9]. A total motile sperm count of 10 million may be a useful threshold value for decisions regarding the treatment of a couple with IUI or IVF [10], although 5 million is widely accepted [11].

Mode of Insemination

IUI is performed commonly using 0.2–0.5 ml sperm suspension into the uterus with a catheter, usually without imaging guidance. Increasingly clinics with better success appear to be using 1 mil for IUI to overcome the collective loss of fluid during the various stages of loading the catheter and expulsion. A randomised clinical trial compared immobilisation for 15 min with immediate mobilisation subsequent to IUI and showed higher ongoing pregnancy rates in couples immobilising subsequent to IUI. The persistent significant difference in ongoing pregnancy rates underpins the importance of immobilisation after IUI. There is no valid reason to withhold women from immobilising for 15 min after IUI [12].

To compare pregnancy-related outcomes from women undergoing IUI cycles performed with either soft or firm catheters in subfertile women, no specific conclusion can be made regarding the superiority of one catheter class over another [13].

Timing of Insemination

Timing is a single most important subject which can determine the success of IUI and yet little evidence-based information exists to decipher what is critical for an optimal success rate, so it is rather surprising that few studies were designed to find the optimal time for insemination [14]. The systematic review found no difference in the pregnancy rate per couple with two inseminations compared with one [15]. In the majority of studies, IUI is done 32–36 h following hCG administration, although in one pilot study it appears that optimal time post-hCG trigger for a pregnancy was 30 h [8]. There may also be differences in what is optimal for trigger in Clomid cycles and hMG cycles. Data suggest that the pregnancy-related diameter of the leading follicle in CC cycles is significantly larger than that in gonadotropin cycles and the best time for hCG trigger in the CC cycle is when the leading follicle reaches 20 mm [16], whereas in hMG cycles 18 mm appears optimal.

Premature LH surges also occur in substantial treatment cycles and in 25–30 % of stimulated IUI cycles [17, 18], which may interfere with timing of the IUI leading to treatment failures. The LH surge is required for luteinisation, final maturation of the oocyte and follicle rupture, and using a GnRH antagonist should abolish premature luteinisation [18]. Premature LH may be more frequent in older women since their maximum follicle diameter at the time of ovulation is substantially smaller [19, 20].

IUI and the Endometrium

With regard to endometrial thickness, limited data exist in relation to pregnancies [21]. Mean endometrial thickness in patients stimulated for IVF was significantly higher than in patients stimulated for IUI and normally cycling women ($P < 0.001$), and pregnancy rates (PRs) are significantly

higher in patients with an endometrial thickness >9 mm, while thin endometria, generally measuring <7 mm, are thought to be less able to support implantation and pregnancy [21]. There are strategies to help endometrial conditions to boost pregnancy outcomes. Low-dose aspirin support for thin endometrium (<8 mm) gave significantly better pregnancy rates (18.4 vs. 9.0 %) after aspirin therapy in IUI procedure [22]. Another strategy to neutralise the anti-oestrogenic endometrial effect of CC by co-treatment of CC with ethinyl estradiol (EE2) is documented in many other studies [23–27]. EE2 appears to reverse the deleterious effects of CC on endometrial thickness contributing to a significantly lower miscarriage rate and significantly higher ongoing pregnancy rate in the CC +EE2 group [27] although more studies are required [17]. It would appear therefore that IVF type procedures will have beneficial effects on the endometrium and this should be adopted in IUI procedure.

Ovulation Induction Agents

The Cochrane database [28] reviewed the evidence of oral ovulation-inducing agents versus injectable ovulation-inducing agents in the treatment of unexplained infertility up to 2002 showing that there is insufficient evidence to prefer either of the methods when comparing pregnancy or live birth rates. This Cochrane review identified five studies where anti-oestrogens were compared with gonadotropins for ovulation induction. No study compared either anti-oestrogen or gonadotropins with a combination of both. The report compared clomiphene with human menopausal gonadotropins [29] and that showed no significant difference in live birth rate per couple (OR 0.51, 95 % CI 0.18–1.47). There were three studies which had primary outcome of pregnancy rate per women. There was a significantly higher pregnancy rate in the group which were treated with hMG (OR 0.44, 95 % CI 0.19–0.99). There is a general misconception about the economics of using gonadotropins versus the cheaper clomiphene in that live births cannot be costed to drug charges alone without considering the much wider running costs including scans and consultation.

Clomiphene Citrate

Clomiphene citrate, an anti-oestrogen, is mostly used as first choice for COS in the context of IUI since clomiphene can be administered orally and is cheaper than gonadotropin injections [29–31]. Clomiphene is a selective oestrogen receptor modulator (SERM), a no steroidal oestrogen that binds to the oestrogen receptors at multiple sites throughout the reproductive tract, and can act as an oestrogen agonist or as an antagonist. Clomiphene binds to oestrogen receptors in the hypothalamus, inhibiting negative feedback of oestrogen on gonadotropin release. Subsequent up-regulation of the hypothalamic–pituitary–gonadal axis leads to growth of the ovarian follicle(s). It is unclear to what extent in particular Clomid interferes with the functional properties of sperm given human sperm expresses the oestrogen receptors [32, 33].

Clomiphene is a very commonly used ovulation-inducing agent the effectiveness of the treatment can only be judged by the evidence of randomised controlled trials. The most reliable evidence from a systematic review [34] showed data relating to 1159 participants from seven trials there was no evidence that clomiphene citrate was more effective than no treatment or placebo for live birth (OR 0.79, 95 % CI 0.45–1.38; $P = 0.41$) or for clinical pregnancy per woman randomised both with IUI (OR 2.40, 95 % CI 0.70–8.19; $P = 0.16$), without IUI (OR 1.03, 95 % CI 0.64–1.66; $P = 0.91$) and without IUI but using hCG (OR 1.66, 95 % CI 0.56–4.80; $P = 0.35$). It should be noted that heterogeneity between studies ranged from 34 to 58 %.

Gonadotropins

Gonadotropins are glycoprotein hormones that can be extracted from urine of menopausal women or can be manufactured in recombinant variants. They stimulate follicular growth by acting directly on ovarian FSH receptors and have no anti-oestrogenic effect on cervical mucus or endometrium such as clomiphene. A recent report confirms that ovarian stimulation with low-dose hMG was superior to CC in IUI cycles with respect to clinical pregnancy rate [5].

Thirteen studies identified systematically and involving 3081 patients demonstrated that expectant management may be comparable to treatment with CC and timed intercourse or IUI, while CC may be more effective than letrozole. However, gonadotropins seem more effective both oral agents and care was essential in managing potential multiple births. More importantly, gonadotropins with IUI for unexplained infertility were as effective as IVF and ICSI [26]. However, adequately powered, randomised controlled trials that compare all of the available treatments for unexplained infertility were needed. Therefore, despite its wide utilisation, IVF is no more effective than IUI with gonadotropin.

Aromatase Inhibitors

Aromatase inhibitors suppress oestrogen production but do not have the anti-oestrogenic effect of clomiphene citrate in the late follicular phase and they may have fewer side

effects than clomiphene [35]. A meta-analysis and systematic review [36] compared the efficacy of aromatase inhibitors (letrozole, anastrozole) versus clomiphene citrate for unexplained infertility, and the five trials support the role of aromatase inhibitors in unexplained infertility [36–38]. There was no significant difference between compared arms according to pregnancy rate, pooled OR 0.87 (95 %CI 0.46–1.65, $P = 0.666$). The available data are limited to unexplained infertility.

The Cochrane review [39] of 26 RCTs ($n = 5560$) of aromatase inhibitors in women with anovulatory polycystic ovary syndrome and infertility indicated letrozole significantly increased live birth rate compared with clomiphene citrate (OR 1.64) with no difference in rates of ovarian hyperstimulation syndrome (OHSS; RR 0.00) and lower rates of multiple pregnancy. In another study, women with unexplained infertility, ovarian stimulation with letrozole, resulted in a significantly lower frequency of multiple gestations but also a lower frequency of live birth, as compared with gonadotropin but not as compared with clomiphene. After treatment with gonadotropin, clomiphene or letrozole, clinical pregnancies occurred in 35.5, 28.3 and 22.4 % of cycles, and live birth in 32.2, 23.3 and 18.7 %, respectively; pregnancy rates with letrozole were significantly lower than the rates with standard therapy (gonadotropin or clomiphene) ($P = 0.003$) or gonadotropin alone ($P < 0.001$) but not with clomiphene alone ($P = 0.10$). However, the number of follicles prior to insemination remains unknown, or having an established strict cancellation policy prior to insemination to obviate the risks of multiple births [40].

Intra Uterine Insemination (IUI)

The data which exist on IUI need to be interpreted with caution given the biases in promoting more expensive IVF treatments [1, 2]. Clearly the average pregnancy rate of around 13 % per cycle, translating to around 25 % of the women, is almost double than what most trials and published data on IUI exist. Clearly optimising each IUI cycle outcome begins to benefit women most of whom will wish for the least intrusive and least stressful procedures [1, 2], although the IVF industry appears to rely on 25–50 % overuse of IVF procedures. Therefore, the key message for IUI is to be able to identify all contributing factors to construct a realistic strategy in optimising pregnancy rates, while credibility can only occur if risks of higher-order multiple births and OHSS can be minimised. The use of clomiphene citrate and IUI, over IUI alone, has not proved to be effective [34]. Clearly the development of bifollicular IUI cycles potentially increases the chance of achieving an IUI pregnancy by 3.4-fold compared with unifollicular cycles [44]. This receives support from the French prospective study where the pregnancy rates alongside the number of mature recruited follicles were significant (9.4 % for one vs. 15.2 % for two) [45].

Problems in Presenting Evidence for and Against IUI

Our basic understanding of infertility and definitions remains inconsistent, and the literature is laden with heterogeneous interpretations and practices of patient treatment and data interpretation. In the general population, of couples attempting conception, 84 % will conceive after 1 year and 92 % will conceive after 2 years. There is enormous variation in suggested definitions for infertility ranging from 2 years to 1 year [1, 2]. Currently, infertility is 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycle failure to conceive after six cycles of unprotected intercourse irrespective of age. IVF protocols are operating optimally because of the commercial pressures, whereas IUI not. Expectant management [41] is erroneously interpreted against suboptimal stimulation protocols for IUI and against overuse of IVF procedures, thereby distorting interpretations of efficacy.

In Cochran review [6], stimulated cycle IUI comparing with IUI in a natural cycle, a significant increase was found in pregnancy rate per couple [42] (415 women; OR 2.33, 95 %CI 1.46–3.71) in favour of stimulated cycle. These trials did not provide enough data regarding the adverse outcomes such as multiple pregnancy, ovarian hyperstimulation or miscarriage rate. If expectant management (EM) is occurring alongside IUI, then the same is expected alongside IVF treatments and there is no merit in fast tracking IUI patients onto IVF. The randomised trial comparing IUI with EM cannot be relied upon as a useful comparator as their cohort included people with tubal pathology (e.g. one-sided tubal occlusion and hence did not have unexplained infertility) and some were treated with clomiphene citrate [2, 43], while their PR per cycle started was 6.5 % with an ongoing PR of 4.1 %, one of the lowest ever published success rates.

A live birth rate (LBR) of 11.0 % (14/127) for stimulated IUI compared to 2.2 % (4/184) for EM was recorded in one study [2], giving an odds ratio of 5.6 (95 % confidence interval 1.8–17.4) in favour of superovulation and IUI. A pregnancy rate (PR) per cycle of 8.7 % was recorded for the IUI group ($n = 85$), which was lower than for the IVF group at 12.2 % ($n = 87$) [42]. However, the cumulative PR for IVF was not significantly better than for IUI and couples in the IVF group were significantly more likely than those in the IUI group to give up rather than embark upon repeat treatments. They concluded that for couples treated, IUI offered the same likelihood of

successful pregnancy as IVF and was a more cost-effective approach. According to this study, costs per pregnancy resulting in at least one live birth were three times higher following IVF compared to IUI [2].

Financial considerations make references to more expensive hMG against CC usage is entirely misleading. We cannot cost a pregnancy against the cost of drugs alone without taking into account the whole infrastructure related to the treatment cycle, for example consultation, baseline examinations, multiple visits for ovulation monitoring, scans, associated embryo freezing procedure, cost of multiple births, cost of abnormalities and the cost of failure apart from the sheer human emotional investment.

Risks

Multiple births have been a single reason pitched against IUI, but there is no evidence whatsoever regarding this in the Cochrane reviews [1, 46, 47]. Careful monitoring of follicles has reduced the absolute rate of multiple pregnancies to 0.3 % after monofollicular growth and 2.8 % after multifollicular growth [48]. The risk of multiple pregnancies is estimated to increase by 6, 14 and 10 % according to whether 2, 3 or 4 follicles are stimulated, respectively [48].

The contribution of multiple pregnancies made by IUI in the Netherlands was much smaller than the contribution made by IVF [49]. Along with crucial monitoring to minimise higher-order births, IUI can become an even stronger basis for first-line treatment.

Preliminary unpublished results from one of our clinics using 150 hMG GnRH in 170 cycles led to 31.6 % of cycles with I follicle (pregnancy rate of 18 %/cycle), 46 % had 2 follicles (pregnancy rate of 18 %/cycle; 2 sets of twins), while 22.5 % had 3 follicles (pregnancy rate of 26 % per cycle; no multiple births). Multifollicular response will also be dependent on patient types, age, BMI and variability in follicular responses can be expected. While these risks need to be vigorously reviewed on a case-by-case basis, it is clear that benefits can be derived in a multifollicular environment and IUI.

Determinants of Success for IUI Cases

A major drawback in deciphering determinants of success for IUI is that the procedure has been non-optimally practised against the bias of expensive IVF treatments. Clearly ovulation induction and a need for multifollicular environment are beneficial [45]. Despite several leads on the contributing factors for IUI such as women's age, duration of infertility, follicle numbers, endometrial thickness, ovulation induction and timing of insemination, none of the information has so far been presented in a way to serve as guidance on improving IUI pregnancy rates. Male factor influences seem confined to the availability of at least 3 million motile progressive sperm for IUI, and this limitation can be overcome with the use of a 'consecutive ejaculate' provided adequate profiling is performed beforehand on subfertile males. Factors such as timing of insemination, endometrial thickness, BMI, number of cycles of IUI and catheter types, post-insemination resting, need to be recognised. Incorporating AMH tests to tailor the ovulation induction regimes may help outcomes. Clinics will recognise a significant numbers of pregnancies will occur an alternative rest cycles without treatment but with sexual timed intercourse. It may be the previous months' gonadotropin effects may be beneficial, but a properly conducted study needs to be performed to confirm this observation, apart from providing an insight into unexplained infertility. Clearly more research is required to find optimal IUI conditions before resorting to IVF procedures.

What is Effective?

Much depends on having a strict cancellation policy to minimise risks and having informed choices for patients [5]. Reports with pregnancy rates of 13–20 % per cycle [1, 2] had in common the usage of 75–150 iu hMG. The reasons for the treatment were unexplained, male factor, endometriosis, female factor, cervical factor, mixed. Common to all these was the use of ovulation triggering dose of 10,000 iu hCG. In contrast, the same studies reported pregnancy outcomes of 4–7 % per cycle for the CC stimulated cycles. A French prospective study indicated that the use of GnRH antagonists has a positive effect on the delivery rate, especially in the multifollicular stimulations. The overall live birth rate was 11.4 % per cycle, varying from 8.4 to 17.6 % between centres. The main differences in practice that had a statistically significant impact on the delivery rate were the use of GnRH antagonists (15.2 % with vs. 9.4 % without) and the number of mature recruited follicles (9.4 % for one vs. 15.2 % for two) [45].

Summary

IUI has been a poorly practised at the expense of more expensive IVF treatment, with greater associated risks and complexity. It is becoming more apparent that IUI if practised efficiently can provide equally good pregnancy rates for over 74 million couples worldwide who may not have access to complex IVF facilities. Furthermore, the CC-induced IUI cycles were never analysed for the optimal trigger time and

only recently have the differences in follicle sizes been noted for hMG and CC cycles. More women getting pregnant with low-cost IUI will also help funding bodies to be able to pay for 3 IVF cycles in women who absolutely need more IVF cycles. Clinics need a database to allow a real-time monitoring of their progress and our clinics have made progressive improvements over the years to shift pregnancy rates from around 7 % per cycle to around 20 % per cycle with almost 25–33 % of the cohort becoming pregnant. It appears the biggest determinant in the success of IUI is the clinical management of the patient. Numerous publications exist with good pregnancy rates and the methods need to be emulated. It appears that 150 iu hMG and 10,000 iu hCG appear to provide pregnancy rates at the upper levels of 13–20 % per cycle and CC cycles appear to lag considerably in pregnancy rates probably because optimisation of CC cycles never occurred. In future, AMH profiles need to be applied to IUI patients in order to tailor the dose of the gonadotropin. Unlike IUI, IVF constitutes a more invasive treatment process involving higher dosage of controlled ovarian hyperstimulation, anaesthesia and oocyte aspiration medical procedures, while there appear issues of possible increased risk in imprinting disorders for subsequent generations suggested to be caused by the embryo culture in vitro [50].

Conclusion

The future of IUI is promising if every IUI cycle is optimised and the pregnancy rates can be even higher if most cycles were performed with 2 follicles using hMG which also allows for a greater thickness in the endometrium compared to CC cycles. Whatever option is used there needs to be a strict cancellation policy if $\geq$3 mature follicles are present to minimise multiple births. The use of 'consecutive ejaculate' is a new concept in overcoming male factor problems in IUI. For patients, the largest benefit is the least intrusive and least psychologically demanding procedure and one which can benefit a much bigger sub fertile global population.

Compliance with Ethical Standards

Conflict of interest None.

Ethical approval No additional approval was needed to construct this review.

References

1. Bahadur G, Homburg R, Muneer A, et al. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016;31(6):1141–6. doi:10.1093/humrep/dew075.
2. Woodward B, Tomlinson M, Kirkman-Brown J. Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is cause for concern. Hum Fertil. 2016;. doi:10.1080/14647273.2016.1182220.
3. Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PMM, et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with IUI with controlled ovarian hyperstimulation. Br Med J. 2015;2015(350):g7771. doi:10.1136/bmj.g7771.
4. Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PM, et al. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod. 2015;30:2331–9.
5. Peeraer K, Debrock S, De Loecker P, et al. Low-dose human menopausal gonadotrophin versus clomiphene citrate in subfertile couples treated with IUI: a randomized controlled trial. Hum Reprod. 2015;30:1079–88.
6. Veltman-Verhulst SM, Hughes E, Ayeleke RO, et al. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2016;2:CD001838.
7. ESHRE Capri Workshop Group. IUI. Hum Reprod Update. 2009;15(3):265–77. doi:10.1093/humupd/dmp003.
8. Bahadur G, Almossawi O, Illahibuccus A, Al-Habib A, Okolo S. Factors leading to pregnancies in stimulated IUI cycles and the use of consecutive ejaculations within a small clinic environment. JOGI. 2016 (in press).
9. Boomsma CM, Heineman MJ, Cohlen BJ, et al. Semen preparation techniques for IUI (review). Cochrane Database Syst Rev. 2007. doi:10.1002/14651858,CD004507.pub3.
10. Van Voorhis BJ, Barnett M, Sparks AE, et al. Effect of the total motile sperm count on the efficacy and cost-effectiveness of IUI and in vitro fertilization. Fertil Steril. 2001;75:661–8.
11. Khalil MR, Rasmussen PE, Erb K, et al. Homologous IUI. An evaluation of prognostic factors based on a review of 2473 cycles. Acta Obstet Gynecol Scand. 2001;80:74–81.
12. Scholten I, Custers IM, Moolenaar LM, et al. Long-term follow up of couples initially randomized between immobilization and immediate mobilization subsequent to IUI. Reprod Biomed Online. 2014;29(1):125–30. doi:10.1016/j.rbmo.2014.03.012.
13. Van der Poel N, Farquhar C, Abou-Setta AM, et al. Soft versus firm catheters for IUI. Cochrane Database Syst Rev. 2010;11:CD006225.
14. Ragni G, Somigliana E, Vegetti W. Timing of IUI: where are we? Fertil Steril. 2004;82:25–6.
15. Cantineau AEP, Heineman MJ, Cohlen BJ. Single versus double IUI (IUI) in stimulated cycles for subfertile couples. Cochrane Database Syst Rev. 2003. doi:10.1002/14651858.CD003854.
16. Shalom-Paz E, Marzal A, Wiser A, et al. Does optimal follicular size in IUI cycles vary between clomiphene citrate and gonadotrophins treatments? Gynecol Endocrinol. 2014;30(2):107–10.
17. Cantineau AE, Cohlen BJ, Dutch IUI Study Group. The prevalence and influence of luteinizing hormone surges in stimulated cycles combined with IUI during a prospective cohort study. Fertil Steril. 2007;88:107–12.
18. Lambalk CB, Leader A, Olivennes F, et al. Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinisation in stimulated IUI: results of a double-blind, placebo-controlled, multicentre trial. Hum Reprod. 2006;21:632–9.
19. Klein NA, Harper AJ, Houmard BS, et al. Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? J Clin Endocrinol Metab. 2002;87:5746–50.
20. de Koning J, Lambalk CB, Helmerhorst FM, et al. Is GnRH self-priming an obligatory feature of the reproductive cycle? Hum Reprod. 2001;16:209–14.

21. Wolff EF, Vahidi N, Alford C, et al. Widra E Influences on endometrial development during IUI: clinical experience of 2,929 patients with unexplained infertility. Fertil Steril. 2013;100(1): 194–9.
22. Hsieh YY, Tsai HD, Chang CC, et al. Low-dose aspirin for infertile women with thin endometrium receiving IUI: a prospective, randomized study. J Assist Reprod Genet. 2000;17(3): 174–7.
23. Unfer V, Costabile L, Gerli S, et al. Low dose of ethinyl estradiol can reverse the antiestrogenic effects of clomiphene citrate on endometrium. Gynecol Obstet Invest. 2001;51:120–3.
24. Dehbashi S, Parsanezhad ME, Alborzi S, et al. Effect of clomiphene citrate on endometrium thickness and echogenic patterns. Int J Gynaecol Obstet. 2003;80:49–53.
25. Haritha S, Rajagopalan G. Follicular growth, endometrial thickness, and serum estradiol levels in spontaneous and clomiphene citrate-induced cycles. Int J Gynaecol Obstet. 2003;81:287–92.
26. Gunn DD, Bates GW. Evidence-based approach to unexplained infertility: a systematic review. Fertil Steril. 2016;105(6): 1566–74. doi:10.1016/j.fertnstert.2016.02.001.
27. Gerli S, Gholami H, Manna C, et al. Use of ethinyl estradiol to reverse the antiestrogenic effects of clomiphene citrate in patients undergoing IUI: a comparative, randomized study. Fertil Steril. 2000;73:85–9.
28. Athaullah N, Proctor M, Johnson NP. Oral and injectable ovulation induction agents for unexplained subfertility. Cochrane Database Syst Rev. 2002;3:CD003052.
29. Ecochard R, Mathieu C, Royere D, et al. A randomized prospective study comparing pregnancy rates after clomiphene citrate and human menopausal gonadotropin before IUI. Fertil Steril. 2000;73:90–3.
30. Dankert T, Kremer JA, Cohlen BJ, et al. A randomized clinical trial of clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimulation inIUI cycles for unexplained and male subfertility. Hum Reprod. 2007;22:792–7.
31. Berker B, Kahraman K, Taskin S, et al. Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing IUI: a randomized trial. Arch Gynecol Obstet. 2011;284:1561–6.
32. Aquila S, De Amicis F. Steroid receptors and their ligands: effects on male gamete functions. Exp Cell Res. 2014;328(2):303–13. doi:10.1016/j.yexcr.2014.07.015.
33. Guido C, Perrotta I, Panza S, Middea E, Avena P, Santoro M, Marsico S, Imbrogno P, Andò S, Aquila S. Human sperm physiology: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) influence sperm metabolism and may be involved in the pathophysiology of varicocele-associated male infertility. J Cell Physiol. 2011;226(12):3403–12. doi:10.1002/jcp.22703.
34. Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev. 2010. doi:10.1002/14651858.CD000057.
35. Casper RF, Mitwally MF. Review; aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab. 2006;91:760–71.
36. Polyzos NP, Tzioras S, Mauri D, et al. Treatment of unexplained infertility with aromatase inhibitors or clomiphene citrate. A systematic review and meta-analysis. Obstet Gynecol Surv. 2008;63(7):472–9.
37. Al-Fozan H, Al-Khadouri M, Tan SL, et al. A randomized trial of letrozole versus clomiphene citrate in women undergoing super ovulation. Fertil Steril. 2004;82:1561–3.
38. Fatemi HM, Kolibianakis E, Tournaye H, et al. Clomiphene citrate versus letrozole for ovarian stimulation: a pilot study. Reprod Biomed Online. 2003;7:543–6.
39. Franik S, Kremer JA, Nelen WL, et al. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014;2:CD010287.
40. Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med. 2015;373(13):1230–40. doi:10.1056/NEJMoa1414827.
41. Bhattacharya S, Harrild K, Mollison J, et al. Clomifene citrate or unstimulated IUI compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. BMJ. 2008;337:a716. doi:10.1136/bmj.a716.
42. Goverde AJ, McDonnell J, Vermeiden JP, et al. IUI or in vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost effectiveness analysis. Lancet. 2000;355:13–8. doi:10.1016/S0140-6736(99),04002-7.
43. Steures P, van der Steeg JW, Hompes PG, et al. IUI with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. Lancet. 2006;368:216–21. doi:10.1016/S0140-6736(06),69042-9.
44. Tomlinson MJ, Amissah-Arthur JB, Thompson KA, et al. Prognostic indicators for IUI (IUI): statistical model for IUI success. Hum Reprod. 1996;11:1892–6.
45. Monraisin O, Chansel-Debordeaux L, Chiron A, et al. Evaluation of intrauterine insemination practices: a 1-year prospective study in seven French assisted reproduction technology centers. Fertil Steril. 2016;105(6):1589–93. doi:10.1016/j.fertnstert.2016.01.039.
46. Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev. 2012;4: CD003357.
47. Dickey RP, Taylor SN, Lu PY, et al. Risk factors for high-order multiple pregnancy and multiple birth after controlled ovarian hyperstimulation: results of 4,062 IUI cycles. Fertil Steril. 2005;83:671–83.
48. van Rumste MME, Custers IM, van der Veen F, et al. The influence of the number of follicles on pregnancy rates in IUI with ovarian stimulation: a meta-analysis. Hum Reprod Update. 2008;14:563–70.
49. Steures P, van der Steeg JW, Hompes PG, et al. IUI in The Netherlands. Reprod Biomed Online. 2007;14:110–6.
50. Lazaraviciute G, Kauser M, Bhattacharya S, et al. A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. Hum Reprod Update. 2014;20:840–52. doi:10.1093/humupd/dmu033.