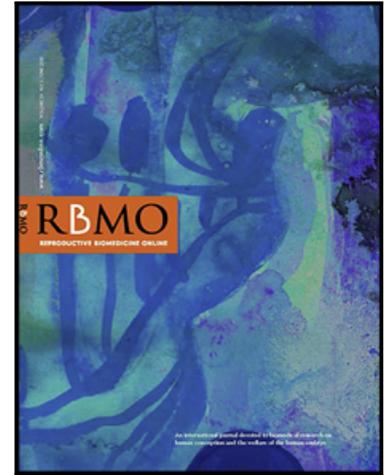


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IUI is a better alternative than IVF as the first-line treatment of unexplained infertility

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Abstract

The treatment of a condition with no known cause such as unexplained infertility is unsurprisingly controversial. The alternatives that have been suggested for the first-line treatment are expectant management, ovarian stimulation, intra-uterine insemination (IUI) with or without ovarian stimulation or IVF. As far as live births are concerned, the choice has realistically been narrowed down to IUI with ovarian stimulation by low-dose gonadotrophins using strict cancellation criteria versus IVF. In several well-designed studies, three cycles of the former have proved as successful as one cycle of IVF. As IUI is less invasive, more comfortable for the patient, markedly less expensive and safe with a high compliance rate, it should be recommended for the first-line treatment of unexplained infertility for couples in whom the female age is not more than 38 years.

The choice of treatment for unexplained infertility is made all the more difficult and controversial by the fact that we have no idea what causes the condition, no agreed definition and that not a few cases will spontaneously resolve. The debate has mainly centered on the merits of intra-uterine insemination (IUI), mostly with ovarian stimulation, compared with IVF/ICSI as first-line treatment. The argument was brought to a head by the National Institute for Health and Care Excellence (NICE) in the UK who published guidelines in 2013 stating that after two years of unexplained infertility, IVF should be offered, with the complete exclusion of IUI. The public funding authorities gleefully jumped on the bandwagon and refused funding for IUI. It is a tribute to the integrity of practitioners in the UK that the majority completely ignored these guidelines. This recommendation brings to mind the award to Qatar to host the next football world cup. There is no evidence whatsoever to justify these two inexplicable decisions as IUI has many advantages over IVF and Qatar is not exactly one of the world's leading football nations and the original dates accepted were to play at the height of summer in temperatures topping 40 degrees.. I am ignoring here the rumoured whiffs of commercialism and will concentrate on the hard data.

Comparisons of treatment options are only really relevant when optimal protocols are employed to produce the best and safest results. As regards IUI for the treatment of unexplained infertility, it has become obvious that its combination with ovarian stimulation by gonadotrophins is superior to its use in a natural cycle or with clomifene or letrozole (Cantineau et al, 2021).

Gonadotrophins used for this purpose should be given in a low-dose regimen while observing strict cancellation criteria when, for example, more than three follicles greater than 14mm diameter are produced. Over the female age of 38 years, IUI should probably not be the first-line treatment.

Ideally, when IVF is used to treat unexplained infertility, elective single embryo transfer should be employed. Both this and the use of a low-dose gonadotrophin protocol in IUI are, of course, employed for the prevention of multiple pregnancies.

In a 1 to 1 cycle comparison of results between IVF and IUI for the first line treatment of unexplained infertility, IVF has a superior live birth rate. Three cycles of IUI have mostly been compared to one cycle of IVF and this comparison evens up the results. Numerous well-constructed evidence-based studies support IUI as first-line treatment. Three randomized controlled trials (RCT's) have compared IUI and IVF (Custers *et al.*, 2011; Bensdorp *et al.*, 2015; Nandi *et al.*, 2017). Each of these studies used ovarian stimulation with IUI and reported similar live birth outcomes for three to six IUI cycles as for one to two IVF cycles.

In a Cochrane analysis of women who were treatment-naïve there was no conclusive evidence of a difference in live birth rates between IVF and IUI with ovarian stimulation by gonadotrophins (Pandian et al, 2015). In the latest collection of data including eight RCT's (Nandi et al, 2021), a sensitivity analysis based on women's age and a history of previous IUI or IVF treatment showed no significant difference in the live birth rates (RR 1.01, 95% CI 0.88–1.15) in treatment-naïve women younger than 38 years. Importantly, there was also no difference in multiple pregnancy rates.

No special infrastructure is involved for IUI which is much less expensive than IVF. IUI with ovarian stimulation has repeatedly been shown to be cheaper per live birth than IVF (Tjon-Kon-Fat et al, 2015; van Rumste et al, 2014). In an enormous study utilizing the Human Embryo and Embryology Authority (HFEA) database in the UK, Bahadur et al, (2020) showed that not only is IUI safer than IVF for the treatment of unexplained infertility but also considerably more cost-

effective per live birth. Despite there being no evidence of an improvement in pregnancy rates by employing ICSI for couples with a diagnosis of unexplained infertility rather than standard IVF, many units use this procedure routinely making the treatment even more expensive and labour intensive.

In countries with limited resources and where IVF is not available or very expensive, IUI is often the only treatment for unexplained infertility. Conversely, in other countries where private IVF clinics rule the roost, there is often no incentive to perform IUI when IVF is a much more lucrative alternative.

The procedure of IUI still has room for improvement. Stricter adherence to cancellation criteria using a low-dose gonadotrophin ovarian stimulation will further reduce the multiple pregnancy rate. In addition, the use of slow release insemination, rather than a bolus, has been showing some promise in improving results (Marschalek et al, 2020). The hypothesis behind this is that a persistent low concentration of spermatozoa might prolong the period of potential fertilization matching more closely the physiological course of events as compared with a bolus insemination.

From the patients' point of view, IUI is less invasive, carries minimal risks and has a much higher compliance than IVF with its high drop-out rate. Once in an IVF programme, there is no resorting back to IUI. One year after the 'diagnosis' of unexplained infertility is made the spontaneous pregnancy rate is high and even after two years, spontaneous pregnancies occur. If deciding to treat during these time periods, then surely it is much more logical to use IUI with a reasonable chance of a spontaneous or induced pregnancy and leave the more difficult, invasive and expensive option of IVF still open for those who fail to conceive.

Even the Americans, not usually well known for adopting a conservative approach, have been advised by the Practice Committee of the ASRM in 2020 that the best initial therapy is a course (typically 3 or 4 cycles) of ovarian stimulation with oral medications and intrauterine insemination (OS-IUI) followed by in vitro fertilization for those unsuccessful with OS-IUI treatments.

Now that common sense has prevailed and the dates of the football world cup have been changed to the winter months in Qatar, surely, also using common sense, we can adopt IUI as the first-line treatment for unexplained infertility for eligible couples rather than IVF.

References

Bahadur, G., Homburg, R., Bosmans, J.E., Huirne, J., Hinstridge, P., Jayaprakasan, K., Racich, P., Alam, R., Karapanos, I., Illahibuccus, A., Al-Habib, A., Jauniaux, E. Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles. *BMJ Open*. 2020 Mar 16;10(3):e034566. doi: 10.1136/bmjopen-2019-034566.

Bensdorp, A.J., Tjon-Kon-Fat, R.I., Bossuyt, P.M., Koks, C.A., Oosterhuis, G.J., Hoek, A., Hompes, P.G., Broekmans, F.J., Verhoeve, H.R., de Bruin, J.P., van Golde, R., Repping, S., Cohlen, B.J., Lambers, M.D., van Bommel, P.F., Slappendel, E., Perquin, D., Smeenk, J.M., Pelinck, M.J., Gianotten, J., Hoozemans, D.A., Maas, J.W., Eijkemans, M.J., van der Veen, F., Mol, B.W., van Wely, M. 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 intrauterine insemination with controlled ovarian hyperstimulation. *BMJ*. 2015 Jan 9;350:g7771. doi: 10.1136/bmj.g7771.

Cantineau, A., Rutten, A., Cohlen, B.J. Agents for ovarian stimulation for intrauterine insemination (IUI) in ovulatory women with infertility. *Cochrane Database Syst. Rev* 2021 Nov 5;11:CD005356 doi: 10.1002/14651858.CD005356.pub3.

Custers, I.M., König, T.E., Broekmans, F.J., Hompes, P.G., Kaaijk, E., Oosterhuis, J., Mochtar, M.H., Repping, S., van Wely, M., Steures, P., van der Veen, F., Mol, B.W.

Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. *Fertil. Steril*. 2011

Nov;96(5):1107-11.e1. doi: 10.1016/j.fertnstert.2011.08.005. Epub 2011 Sep

3.PMID: 21890134

Marschalek, J., Egarter, C., Vytiska-Binsdorfer, E., Obruca, A., Campbell, J., Harris, P., van Santen, M., Lesoine, B., Ott, J., Franz, M. Pregnancy rates after slow-release insemination (SRI) and standard bolus intrauterine insemination (IUI) - A multicentre randomised, controlled trial. *Sci. Rep.* 2020 May 7;10(1):7719. doi: 10.1038/s41598-020-64164-4.

Nandi, A., Bhide, P., Gudi, A., Shah, A., Hooper, R., Khan, K., Homburg, R. Intra Uterine Insemination with gonadotropin stimulation or In-Vitro Fertilization for the treatment of unexplained subfertility - A randomized controlled trial. *Fertil. Steril.* 2017;107:1329–35.

Nandi, A., Raja, G., White, D., Tarek, E.T. Intrauterine insemination + controlled ovarian hyperstimulation versus in vitro fertilisation in unexplained infertility: a systematic review and meta-analysis. *Archives of Gynecology and Obstetrics* (2021) Oct 12. doi: 10.1007/s00404-021-06277-3. Online ahead of print.

Pandian, Z., Gibreel, A., Bhattacharya, S. In vitro fertilisation for unexplained subfertility. *Cochrane Database Syst. Rev.* 2015 Nov 19;2015(11):CD003357. doi: 10.1002/14651858.CD003357.pub4. PMID: 26583517; PMCID: PMC7154339.

Tjon-Kon-Fat, R.I., Bendsorp, A.J., Bossuyt, P.M., Koks, C., Oosterhuis, G.J., Hoek, A., Hompes, P., Broekmans, F.J., Verhoeve, H.R., de Bruin, J.P., van Golde, R., Repping, S., Cohlen, B.J., Lambers, M.D., van Bommel, P.F., Slappendel, E., Perquin, D., Smeenk, J., Pelinck, M.J., Gianotten, J., Hoozemans, D.A., Maas, J.W., Groen, H., Eijkemans, M.J., van der Veen, F., Mol, B.W., van Wely, M. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation? *Hum. Reprod.* 2015 Oct;30(10):2331-9. doi: 10.1093/humrep/dev193. Epub 2015 Aug 12. PMID: 26269539.

van Rumste, M.M., Custers, I.M., van Wely, M., Koks, C.A., van Weering, H.G., Beckers, N.G., Scheffer, G.J., Broekmans, F.J., Hompes, P.G., Mochtar, M.H., van der Veen, F., Mol, B.W. IVF with planned single-embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility: an economic analysis. *Reprod. Biomed. Online.* 2014 Mar;28(3):336-42. doi: 10.1016/j.rbmo.2013.10.021. Epub 2013 Dec 1. PMID: 24456703.