

Reappraisal of clinical data supports double IUI for improved pregnancy outcomes

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Abstract

Optimising pregnancy and live birth outcomes for fertility procedures is highly desirable and involves disentangling numerous potentially contributing factors. In IUI procedures would double inseminations within a cycle be beneficial? Despite mistaken belief amongst the fertility practitioners the available evidence including Cochrane review has suggested, there would be beneficial effects of utilising double IUI within a cycle. Here we examine new evidence attempting to clarify the role of double versus single IUI.

Key words: double IUI, infertility, male factor, pregnancy success.

IUI is less stressful, less invasive and less expensive than IVF in our opinion and evidence from some patient populations supports IUI as a first line treatment option over IVF (Bahadur et al., 2016; Tjon-Kon-Fat et al., 2015; Ombelet et al., 2017; Farquhar et al., 2018). Improving IUI outcomes has been disproportionately overlooked compared with more expensive procedures (Heneghan et al., 2016). The value of IUI as first line treatment and ways of optimising outcomes is reported (Bahadur et al., 2017a).

If sperm is available at the right time for insemination then fertilisation is likely to occur and the idea of multiple inseminations during a cycle could help capture the right moment for fertilisation and increase the pregnancy rates. Would doing two IUI's on successive days (double IUI) over single IUI therefore be beneficial? Practitioners have long dismissed the benefits of multiple inseminations within a cycle based on a Cochrane review involving three studies and 386 women, which showed no benefit of double IUI (OR 1.45, 95% CI 0.78-2.70) (Cantineau, 2003a). The updated intervention review in October 2007 incorporated six studies and 1785 women (Cantineau, 2003b). One study was excluded as the data was replicated. The results of five studies that reported pregnancy rate per couple showed a

significant effect of using double insemination (Peto odds ratio 1.8, 95% confidence interval 1.4 to 2.4). In conclusion, double intrauterine insemination resulted in significant benefit over single intrauterine insemination in the treatment of subfertile couples with husband semen.

The validity of a meta-analysis is highly dependent on the quality and inclusion/exclusion criteria, the subjective level of quality assigned to studies and grading being biased toward RCT and the choice of statistical analyses (Alikani et al., 2017). A parallel analysis wrongly promoted IVF over IUI through the NICE guidelines in the absence of evidence (Bahadur et al., 2017b).

Numerous studies post Cochrane review shows the beneficial effects of double IUI over single IUI. In one study, there was a two-fold significant increase in pregnancies after a cycle with a double IUI compared to single IUI (OR: 2.0; 95% CI: 1.07-3.75; $P < 0.03$) but further large and well-designed randomized studies were requested (Zavos et al., 2013). In another report with 865 patients and 1156 cycles, the pregnancy rate/cycle in the two-insemination/-cycle group (14.9% vs. 11.4%), was without statistically significant differences (RR = 1.34; 95% confidence interval 0.90-1.99) (Osuna et al., 2004).

Interestingly, gonadotropin (Gn) stimulated cycles, ovulatory dysfunction and male factor diagnostic categories were favourable for double IUI; between single and double IUI groups (ovulation dysfunction, 12.9% vs 19.5%, $p < 0.048$, and male factor, 7.9% vs. 17.5%, $p < 0.030$) and ovulation protocols (Clomiphene citrate (CC)-Gn-human chorionic gonadotropin (hCG), 13.0% vs. 21.3%, $p < 0.031$, and L-Gn-hCG, 4.2% vs. 25.0%, $p < 0.002$) (Randall and Gantt, 2008).

Male factor patients had significant benefit receiving double IUI over single IUI, 19.8% and 11.06% ($p < 0.05$), respectively, whereas there was no significant difference within idiopathic infertility groups (10.5% vs. 11.9%, $p > 0.05$) (Liu et al., 2006). Double IUI compared with single IUI gave a better PR and the OR for all cycles was 1.9 (0.76-4.7) ($P = 0.22$), but according to etiology, it was 4.7 (0.9-24.13) ($P = 0.06$) in male factor and 1.2 (0.43-3.33) ($P = 0.779$) for non-male factors (Ghanem et al., 2011).

In the unexplained infertility group the LBR was 11.1% (5/45 patients) with single IUI and 18.4% (9/49) with double IUI ($P = 0.393$) (Bagis et al., 2010). Costings issues will prevail but this must be placed in the context of how successfully pregnancy rates are achieved within each clinic. This is nicely demonstrated in that cost effectiveness can be gained with the use of the more expensive gonadotrophins over CC if more pregnancies can be achieved early (Peeraer et al., 2017). No cost analysis of single versus double IUI has been performed yet.

In conclusion, the available evidence including the Cochrane review did support the use of a double IUI practice within a cycle. Newer data further suggests that male factor infertility and gonadotrophin induced cycles may benefit from double IUI and more systematic studies would be desirable.

References

- Alikani M, Fauser BCJM, Anderson R et al. Response from the Editors: time-lapse systems for ART - meta-analyses and the issue of bias. *Reprod Biomed Online*. 2018;36:293. doi: 10.1016/j.rbmo.2017.12.004.
- Bagis T, Haydardedeoglu B, Kilicdag EB et al. Single versus double intrauterine insemination in multi-follicular ovarian hyperstimulation cycles: a randomized trial. *Hum Reprod*. 2010;25:1684-90.
- Bahadur G, Homburg R, Muneer A et al. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. *Hum Reprod*. 2016;31:1141-6.
- Bahadur G, Homburg R, Al-Habib A. A New Dawn for Intrauterine Insemination: Efficient and Prudent Practice will Benefit Patients, the Fertility Industry and the Healthcare Bodies. *J Obstet Gynaecol India*. 2017a;67:79-85.
- Bahadur G, Woodward B, Homburg R et al. Pitfalls of NICE recommendations on fertility treatment. *BMJ*. 2017b;356:j751. doi: 10.1136/bmj.j751.
- Cantineau AE, Heineman MJ, Cohlen BJ. Single versus double intrauterine insemination in stimulated cycles for subfertile couples: a systematic review based on a Cochrane review. *Hum Reprod*. 2003a;18:941-6.
- Cantineau AE, Heineman MJ, Cohlen BJ. Single versus double intrauterine insemination (IUI) in stimulated cycles for subfertile couples. *Cochrane Database Syst Rev*. 2003b;CD003854.
- Farquhar CM, Liu E, Armstrong S et al. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. *Lancet*. 2018; 3;391(10119):441-50.
- Ghanem ME, Bakre NI, Emam MA et al. The effects of timing of intrauterine insemination in relation to ovulation and the number of inseminations on cycle pregnancy rate in common infertility etiologies. *Hum Reprod*. 2011;26:576-83
- Heneghan C, Spencer EA, Bobrovitz N et al. Lack of evidence for interventions offered in UK fertility centres. *BMJ*. 2016 27;355:i6295.
- Liu W, Gong F, Luo K et al. Comparing the pregnancy rates of one versus two intrauterine inseminations (IUIs) in male factor and idiopathic infertility. *J Assist Reprod Genet*. 2006;23:75-9.
- Omelet W. The revival of intrauterine insemination: evidence-based data have changed the picture. *Facts Views Vis ObGyn*. 2017;9:131-2.
- Osuna C, Matorras R, Pijoan JI et al. One versus two inseminations per cycle in intrauterine insemination with sperm from patients' husbands: a systematic review of the literature. *Fertil Steril*. 2004; 82:17-24
- Peeraer K, Luyten J, Tomassetti C et al. Cost-effectiveness of ovarian stimulation with gonadotrophin and clomiphene citrate in an intrauterine insemination programme for subfertile couples. *Reprod Biomed Online*. 2018;36:302-10. doi: 10.1016/j.rbmo.2017.12.007.
- Randall GW, Gantt PA. Double vs. single intrauterine insemination per cycle: use in gonadotropin cycles and in diagnostic categories of ovulatory dysfunction and male factor infertility. *J Reprod Med*. 2008 ;53:196-202.