ratio itself. The effect of this last choice also becomes visible, if you should try to extract a number-needed-to-treat (NNT) from each of the meta-analyses: Gelbaya NNT = 26.5 and Ruopp NNT = 23.5. All together, these choices affect the quality of a meta-analysis. Even Cochrane reviews that are held to a strict protocol to help preserve this high quality standard display in 11% of their systematic reviews a non-properly conducted meta-analysis (Jorgensen et al., 2006).

This series of meta-analyses illustrates that meta-analyses are the result of the choices made by the authors and therefore are a reflection of their opinion on the best available evidence. When reading meta-analyses, one should be aware of the fact that these choices were made along the way. One should consider whether these choices are agreeable and acceptable. It may be that meta-analyses are not as objective as one would hope.

References


Letrozole in ovulation induction: time to make decisions

Sir,

Over the last 5 years, numerous trials have been conducted investigating the use of letrozole as an ovulation induction regimen. Investigators have tested the effect of letrozole in women with anovulatory or unexplained infertility, as a co-treatment in IVF/ICSI cycles, alone or in combination with other ovulation induction agents and in different treatment schedules or doses. Nonetheless, regardless of the amount of information provided the picture is still ambiguous.

First, in women with polycystic ovary syndrome, the superiority of letrozole over clomiphene citrate has been questioned. Whereas early data showed that aromatase inhibitors might result in significantly higher clinical pregnancy and live birth rates (Polyzos et al., 2008a), more recent randomized evidence seems to reverse this initial observation (Badawy et al., 2007a).

Secondly, in women with unexplained infertility no clear benefit was observed with the use of letrozole or anastrozole from randomized trials and meta-analysis (Polyzos et al., 2008b). Moreover, the ideal dose of letrozole in controlled ovarian hyperstimulation is rather unclear; early randomized data supported that higher doses of letrozole may result in higher pregnancy rates (Al-Fadhli et al., 2006) whereas a more recent randomized trial revealed that higher doses do not offer any advantage compared with lower 2.5 mg daily dose (Badawy et al., 2007b).

Thirdly, in IVF/ICSI cycles, letrozole resulted in significantly higher number of oocytes retrieved (Garcia-Velasco et al., 2005; Verpoest et al., 2006). However, this was not reflected in terms of clinical pregnancy rates in all of the trials; the pregnancy rate per cycle was significantly higher in the letrozole co-treatment group only in one randomized trial (Verpoest et al., 2006), higher but not statistically significant in a prospective cohort (Garcia-Velasco et al., 2005) and comparable among investigational arms in another randomized trial (Goswami et al., 2004).

Finally, results regarding the safety of letrozole for fetuses are also contradictory. Preliminary data suggested an increased risk of congenital anomalies in letrozole treated babies (Biljan et al., 2005), whereas recent data from retrospective (Tulandi et al., 2006) and randomized (Badawy et al., 2008) trials have capsized these initial findings and supported the safety of letrozole compared to traditional ovulation induction treatment.

It is worth mentioning that all previously published trials pioneered and provided insightful directions. Nonetheless, the number of patients enrolled in most of the trials was comparatively small and therefore underpowered to provide clear evidence. In addition statistical design, randomization mode, allocation concealment or blinding were not adequately reported. Taking into account that the more recent published trials have erased doubts regarding the safety of letrozole for newborns (Badawy et al., in press; Tulandi et al., 2006), we believe that a more systematic research approach should be adopted. A large multicenter, properly designed and adequately powered trial is required if a clear conclusion is to be made on the role of letrozole in ovulation induction. Clinical investigators, journals editors, public health institutions and letrozole providers should work towards this direction to reach a safe conclusion. If not, then small randomized trials will keep being published resulting in dubious conclusions which may eventually halt rather than progress the use of letrozole in clinical practice.

In the meantime, and until such a trial has been completed, an individual patient data meta-analysis might provide preliminary evidence of whether the use of letrozole over clomiphene may result in higher pregnancy rate.

Letrozole is a new promising weapon in the arsenal of drugs in ovulation induction. At the moment any attempt to introduce it into clinical practice is questionable since the available evidence neither has the power nor the consistency to lead to such a decision. Consequently, a large randomized multicentre trial with proper design, systematic approach and adequate reporting is mandatory.
References


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