To assist or not to assist embryo hatching

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At early stages of development, the human embryo is protected by a surrounding two-layer coating—the zona pellucida. As the embryo develops further, this coating becomes thinner and, at the blastocyst stage, the thin coating is broken off and the embryo ‘hatches’ such that it can implant into the uterine wall.

Following in vitro fertilization and in vitro growth, many embryos do not implant after embryo transfer. Cultured embryos are known to hatch and implant at a lower rate than naturally developed embryos in vivo. This lower hatching rate could be attributed to a thicker zona pellucida. A thicker zona has, for instance, been seen in older women and women with high basal FSH levels. It was therefore suggested that making a hole in or thinning of this outer layer may help embryos to ‘hatch’, thus increasing the implantation rates. In 1990 such an assisted hatching procedure was developed (Cohen, 1991).

In 2009 a Cochrane review was published on assisted hatching in ART cycles (Das et al., 2009). This Cochrane review reported 28 trials that were described in 25 publications (16 full papers and 9 abstracts), including 3646 couples. There was no evidence for a difference in live birth rate (7 trials; OR: 1.1, 95% CI: 0.83–1.55). Only the clinical pregnancy rate was higher after assisted hatching versus no assisted hatching (28 trials, OR: 1.3, 95% CI: 1.12–1.49).

A new systematic review and meta-analysis on assisted hatching is published in this edition of Human Reproduction Update (Martins et al., 2011). This review reports on 33 trials that were described in 28 full publications, including 5507 couples. The reviewers did not find any evidence for a difference in ongoing pregnancy or live birth [risk rate (RR): 1.03, 95% CI: 0.91–1.16], but, again, they did find borderline evidence for a difference in clinical pregnancy in favor of assisted hatching (RR: 1.1, 95% CI: 1.00–1.24).

There are some differences between the Cochrane review and the Martins review. Recently, several new randomized trials on assisted hatching have been published and therefore more full papers could be included in the Martins review. The Cochrane review, on the other hand, included several abstracts, while no abstracts were included in the present review. The Cochrane review summarized data using a fixed effects odds ratio, while the Martins et al. calculated a random effect RR. Recalculating the clinical pregnancy data of the 18 trials that were included in the Cochrane review into a risk ratio using a random effect model gives an RR of 1.2 (95% CI: 1.04–1.29), compared with the RR of 1.1 (95% CI: 1.00–1.25) in the Martins review. The difference in overall pooled effect measure was thus fairly comparable for both reviews.

The Cochrane reviews and the Martins review both included data according to intention-to-treat (ITT) principles. The basic ITT principle is that participants in the trials are analyzed in the groups to which they were randomly allocated, regardless of whether they received or adhered to the allocated intervention. Authors often prefer per protocol analyses above ITT analyses. In meta-analysis of trials with pregnancy as outcome we favor ITT analysis because it avoids the bias associated with non-random loss of the participants. The ITT analysis can also be seen as a pragmatic presentation of reality as also in normal practice patients that start treatment adhere to the treatment or not, while some patients may drop-out because of treatment related or personal problems.

Both the Cochrane and the Martins meta-analysis found statistically significantly more clinical pregnancies after assisted hatching compared with no assisted hatching, but neither one of the reviews found evidence for a difference in ongoing pregnancies or live births, which is the ultimate goal of any fertility treatment. Only when, in a subgroup analysis, trials were pooled that had included women with multiple treatment failure, more live births/ongoing pregnancies were observed in the assisted hatching group (2 trials, N = 250; RR: 2.5, 95% CI: 1.06–5.96).

Let us try to put this difference into perspective. At several instances in the history of IVF, we thought we had found the Golden grail. For instance, a meta-analysis in 2001 showed that recombinant FSH resulted in more pregnancies than urinary-derived purified FSH (Daya and Gunby, 2000). Figure 1 shows a cumulative meta-analysis including all trials that compared rFSH with urinary-derived purified FSH products. We can see that from 1995 up to 2001, it was indeed clear that the chance of a live birth was higher when using rFSH. From 2002 and onwards however this obvious difference faded. Apparent effects are not always true effects. Now, after many years of research, we have to conclude that for the ultimate outcome, i.e. a healthy baby, it does not matter that much if one stimulates the ovary with rFSH or a urinary-derived FSH product. This is true for various types of gonadotrophins, but also...
for adding recombinant LH or not and the use of GnRH antagonists or agonists, since large meta-analyses have addressed these comparisons and found no or only very small differences (Al-Inany et al., 2006; Mochtar et al., 2007; van Wely et al., 2011). Now the concept of assisted hatching has been evaluated and it would seem the same story is ongoing here. The extra procedure—like all extra procedures—is not without risk. Is it worth the effort? Should more research be done in this area?

There are—33 years after the birth of Louise Brown—still many questions: Should we do IVF at all for indications where couples may have a comparable of even higher chance of conceiving spontaneously than with IVF? What is the optimum number of cycles?

We believe it is time to consider these and other fundamental issues, instead of focusing on minor technical variants of IVF which are unable to overcome the overriding impact of patient characteristics and therefore may not improve the outcome for our patients.

### References


