Role of assisted hatching in in vitro fertilization: a guideline

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There is good evidence that assisted hatching (AH) slightly improves clinical pregnancy rates, particularly in poor prognosis patients, including those with prior failed in vitro fertilization (IVF) cycles. Due to a limited number of studies, there is insufficient evidence to conclude that AH improves live-birth rates. This document replaces the 2008 American Society for Reproductive Medicine and Society for Assisted Reproductive Technology Practice Committees' document titled, "Assisted hatching in in vitro fertilization: a review of the literature. A committee opinion" (Fertil Steril 2008;90 [Suppl 5]:S196–8). (Fertil Steril® 2014;102:348–51. ©2014 by American Society for Reproductive Medicine.)

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SEARCH STRATEGY

A systematic literature search was performed using the following two search strategies:

1. (Assisted OR zona hatching OR drilling OR thinning) AND (pregnancy OR implantation OR live birth) AND blastocyst
2. Assisted hatching AND IVF (Humans [Mesh] AND English [lang])

The search was restricted to MEDLINE citations published in the English language from 1966 to October 2014. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of the procedure correlated with outcome measure (pregnancy, implantation, or live birth rates), meta-analyses, and relevant articles from bibliographies of identified articles.

The quality of the evidence was evaluated using the following grading system:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The strength of the evidence was evaluated as follows:

Level A: There is good evidence to support the recommendations, either for or against.

Level B: There is fair evidence to support the recommendations, either for or against.

Level C: There is insufficient evidence to support the recommendations, either for or against.

Hatching of the blastocyst is a critical step in the sequence of physiologic events culminating in implantation. Failure to hatch, due to intrinsic abnormalities in either the blastocyst or zona pellucida (ZP), may be one of many factors limiting human reproductive efficiency.

Assisted hatching (AH) involves the artificial thinning or breaching of the ZP and has been proposed as one technique to improve implantation and pregnancy rates following in vitro fertilization (IVF). An increased implantation rate following mechanical opening of the ZP (partial zona dissection [PZD]) was first reported in 1990 (1). A randomized trial of patients who underwent selected assisted hatching 72 hours post-retrieval (zona drilling with acidified Tyrode's solution) suggested an improvement in implantation rates when the procedure was selectively applied to embryos with a "poor prognosis" (based on zona thickness, blastomere number,

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fragmentation rates, maternal age, etc.) (2). Since these early reports, many assisted reproductive technology (ART) programs have incorporated the use of assisted hatching in an effort to improve clinical outcomes.

The assisted hatching procedure is generally performed prior to embryo transfer (ET) on day 3, 5, or 6 after fertilization using various methods. These AH methods include the creation of an opening in the zona either by drilling with acidified Tyrode's solution (3, 4), PZD with a glass microneedle (5), laser photoablation (6), or use of a piezo micromanipulator (7). The ZP also has been artificially thinned without breaching its integrity with proteolytic enzymes, acidified Tyrode's solution, or laser (8, 9).

The assisted hatching procedure may be associated with specific complications independent of the IVF procedure itself, including lethal damage to the embryo and damage to individual blastomeres with reduction of embryo viability. In addition, artificial manipulation of the ZP has been associated with an increased risk of monozygotic (MZ) twin pregnancy (10, 11). Despite limited evidence of the benefits or risks, patients whose embryos undergo assisted hatching are often treated with antibiotics and steroids before and after ET, exposing them to the potential risks and side effects of such treatments.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

Assisted Hatching and Clinical Pregnancy Rates (CPRs)

A Cochrane comprehensive review and a meta-analysis identified 31 randomized, controlled trials (RCTs) involving a total of 5,728 women undergoing IVF or intracytoplasmic sperm injection (ICSI) that compared outcomes from 2,933 women in the assisted hatching group to 2,795 women in the control group (12). The odds ratio for clinical pregnancy per woman randomized was 1.13 (95% confidence interval [CI] 1.01–1.27), slightly but significantly in favor of assisted hatching. However, there was significant heterogeneity among trials, suggesting that combining trials may not be appropriate. The largest trial published demonstrated a CPR of 39% (189/487) in the AH group compared with 37% (173/473) in the no-AH group with no significant benefit to CPR with AH (odds ratio [OR] 1.10 95% CI 0.85–1.43) (13). No additional RCTs were identified in the searches that were not included in the Cochrane review.

Assisted Hatching and Live Birth Rates

Most of the research on AH has examined the success of the procedure by assessing CPRs. Despite the widespread and longtime use of this procedure, there have been few clinical trials assessing the effect of AH on live-birth rates (LBRs). In the previously discussed Cochrane review, only 9 of the 31 trials examined the influence of AH on live-birth rates (12). Overall, only 255 live births have been reported from these trials. There was no evidence of significant differences between the odds of a live birth in women who had AH vs. women who did not OR 1.03, 95% CI 0.85–1.25) (Table 1) (14–17).

Given the limited number of studies, there is insufficient evidence to conclude that AH improves live birth rates.

TABLE 1

Studies reporting live births.

	LBR		
Studies	**Control**	**AH**	**OR (95% CI)**
Cohen et al., 1992 (2)	26/68	34/69	1.57 (0.80, 3.10)
Hellebaut et al., 1996 (5)	20/60	21/60	1.08 (0.51, 2.29)
Hurst et al., 1998 (3)	3/7	2/13	0.24 (0.03, 2.03)
Lazendorf et al., 1998 (4)	15/48	12/41	0.91 (0.37, 2.26)
Sagoskin et al., 2007 (17)	37/82	55/121	1.01 (0.58, 1.78)
Primi et al., 2004 (15)	8/74	3/84	0.31 (0.08, 1.20)
Balakier et al., 2009 (16)	16/39	13/45	0.58 (0.24, 1.45)
Ge et al., 2008 (13)	144/473	156/487	1.08 (0.82, 1.41)
Petersen et al., 2005 (14)	13/75	17/75	1.40 (0.62, 3.13)
Total N	995	926	1.03 (0.85, 1.26)

Note: Adapted from Cochrane Review (12). LBR = live birth rate; AH = assisted hatching; OR = odds ratio; CI = confidence interval.

Practice Committee. Assisted hatching. Fertil Steril 2014.

Assisted Hatching Methods

Several studies have evaluated the effects of different methods of assisted hatching on clinical pregnancy and live birth rates, including chemical methods (acidified Tyrode's solution or thinning with proteolytic enzymes), laser methods, or mechanical dissection. Results have varied and likely reflect, at least in part, variations in the level of experience and hatching methods. Nonetheless, the Cochrane study found that CPRs were significantly higher in patients undergoing chemical AH vs. no AH (11 RCT OR 1.33, 1.08–1.71) but no difference in LBR in 4 trials. No significant differences in CPR or LBR were found when mechanical or laser AH was compared to no AH in a limited number of trials (12).

While chemical methods of AH have been associated with improved CPR, there is insufficient evidence to assess differences in LBR with different AH methods.

Assisted Hatching in Specific Patient Populations

Some studies have found that specific populations may benefit from AH. A subgroup analysis in the Cochrane review found that among women who had previously undergone unsuccessful cycles of IVF/ICSI there was an improvement in CPR with AH (9 trials, OR 1.42, 95% CI 1.11–1.81) but not LBR (1 trial, OR 1.4, 95% CI 0.62–3.13) (12). Further, in women with a poor prognosis there was a significant improvement in CPR (12 trials, OR 1.49, 95% CI 1.19–1.85) but not in women with a good prognosis. However, LBR was no different in women with a poor prognosis who underwent AH compared with those who did not (4 trials, OR 0.94, 95% CI 0.74–1.19). When assessing outcomes with AH in fresh vs. frozen embryo transfer cycles, AH was found to be associated with improved CPR only with fresh (24 trials, OR

1.14 95% CI 1.14, 1.01–1.3) and not frozen embryo transfer cycles (8 trials, OR 1.14, 95% CI 0.9–1.44).

Most studies support the hypothesis that AH improves CPR in patients who have had prior failed IVF cycles or have a poor prognosis. However, there is insufficient evidence that AH improves LBRs in these populations.

Assisted Hatching and Twin Pregnancy

Overall, the risk of multiple pregnancy appears to be higher in women who undergo assisted hatching compared with those who do not. The Cochrane review pooled data from 14 RCTs and found an increased odds of multiple pregnancy OR 1.39 (95% CI 1.09–1.77) (12). Although the majority of ART-related multiple gestations are dizygotic, some studies have reported an increase in MZ twin pregnancy. Compared with dizygotic twin pregnancies, MZ twin pregnancies have unique risks and increased morbidities. Thus, it is particularly important to understand the risk factors. Assisted hatching, which breaches the zona pellucida, has been associated with MZ twin pregnancy. For example, a large case-control study that used data from the Society for Assisted Reproductive Technology (SART) did find an association between AH and MZ twinning. This study included data from 35,503 cycles with ET and compared cases of MZ twin pregnancy with 2 separate control groups: other IVF-ET multiple gestation pregnancies and IVF-ET singleton pregnancies (11). After adjustment for age, number of embryos transferred, prior cycles, infertility diagnosis, ICSI, and surplus embryo cryopreservation, MZ twinning was over 3 times as likely with AH when compared with multiple gestation pregnancies (OR 3.2, 95% CI 1.2–8.0) or singleton pregnancies (OR 3.8, 95% CI 1.8–9.8). This study demonstrated a greater impact of assisted hatching on MZ twinning than previously described. However, several other studies have not shown that AH is significantly associated with MZ twinning. The Cochrane review summarized results from 6 clinical trials (12). The pooled data showed a nonstatistically significant difference in the MZ twin rate of 0.8% for the AH group compared with 0% for the control group (OR 3.23, 95% CI 0.34–31.03). Similarly, other studies have not shown an increase in the rate of MZ twin pregnancy with assisted hatching in patients undergoing either fresh or frozen transfer cycles (18). One study reviewed 8 years of data from their IVF program and identified risk factors for MZ twin pregnancy (19). MZ twin pregnancy rate was found to be highest when the maternal age of oocyte source was <35 years. There was no association found between MZ twinning and AH or ICSI, which also breaches the integrity of the ZP.

There is good evidence that AH is associated with multiple pregnancy, but insufficient evidence that it is associated with an increased risk of MZ twinning. The overall rate of MZ twin pregnancy in IVF with AH is less than 1.0%.

SUMMARY

- Despite its widespread and longtime use, there have been a limited number of studies that have examined the effect of AH on LBR. As a result, there is insufficient evidence that AH improves birth rates (Level C).
- There is good evidence that AH slightly improves CPR in poor prognosis patients, including those with prior failed IVF cycles and who have a poor prognosis (Level A).
- AH appears to be associated with an increased risk of multiple pregnancy (Level A), but there is insufficient evidence that it is associated with an increased risk of MZ twin pregnancy (Level C).
- Until data about LBR are available and in the context of increased risk of multiple pregnancy, it is premature to recommend AH in all patients with poor prognosis.

RECOMMENDATIONS

- AH should not be recommended routinely for all patients undergoing IVF (Level C).

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