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The ART Lab of the future

Assisted hatching

Patient centered or evidence based?

Max Curfs, Clinical Embryologist

Fertility Centre Isala

Zwolle

KLEM Wetenschapsmiddag 12 januari 2012

Future?

Assisted Hatching in the clinical setting was first described in 1988
Cohen, Lancet 332: 162

Assisted Hatching can be performed:
- mechanically by using microtools
- chemically with acidic Tyrode's solution
- enzymatically with proteases
- microsurgically with non-contact infrared laser or Piezo technology

The efficacy of Assisted Hatching is still under debate

Dutch Healthcare Insurance Board (CVZ): IVF or ICSI cycles in which AH has been applied, is not to be regarded as evidence based medical care and should not be reimbursed, 2007).

Cross border fertility tourism, especially to Belgium and in lesser extent Germany

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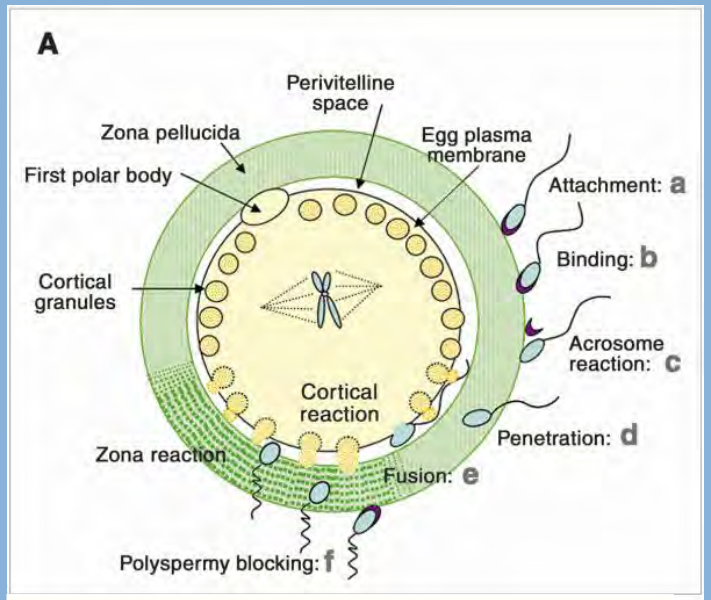
Zona pellucida and hatching *in vivo*



Koyama, J. Reprod. Med. Endocr. 2006

Fertilization

- Sperm binding
- Induction of acrosome reaction
- Induction of hyperactivation
- Induction of cortical reaction
- Prevention of polyspermia

Early embryology

- Isolation of blastomeres from other cells
- Maintaining close contact between blastomeres

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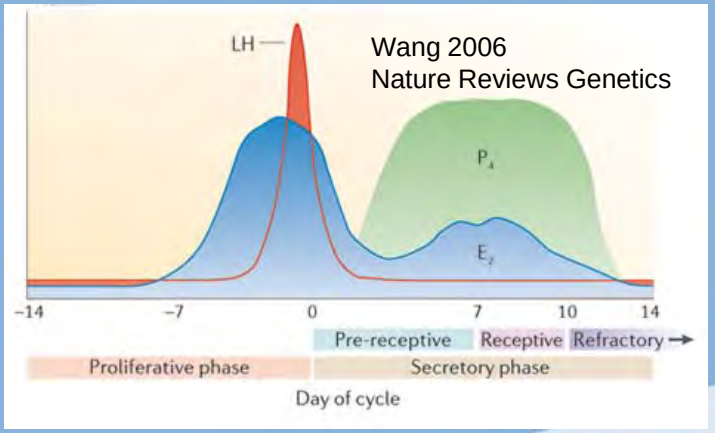
Zona pellucida and hatching *in vivo*

- Expansion
- Breathing (repeatedly collapsing and expanding)
- Proteolytic enzymes (proteases / lysins)

- Hatching in receptive secretory (luteal) phase of the endometrium (implantation window
- Implantation



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Rationale for assisted hatching

Unphysiological zona hardening:

- Suboptimal laboratory conditions

Cohen, J. In Vitro Fertil. Embryo Transf. 1991; DeMeestere, Int. J. Fertil. Womens Med. 1997; Carroll, J. Reprod. Fertil. 1990

- The use of gonadotrophins in ovarian stimulation

Nikas, Hum. Reprod. 1999

Decreased production of lysins by the embryo

Schiewe, Fertil. Steril. 1995

Cultured embryos develop more slowly than *in vivo*

Harlow, Australian Journal of Biology and Science 1982; Hsu, Fertil. Steril. 1999; Mercader, J. Assist. Reprod. Genet. 2001

Increased zona thickness as a result of increased female age, increased ovarian age, smoking and cause of infertility

Loret de Mola, J. Assist. Reprod. Genet. 1997

All of the above can lead to a shift in hatching and implantation towards a less receptive endometrium

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Is Assisted Hatching effective?

Das S, Blake D, Farquhar C and Seif MMW, Assisted hatching on assisted conception (IVF and ICSI) (Review), The Cochrane Library (2009) 4.

Martins WP, Rocha IA, Ferriani RA and Nastri CO, Assisted hatching of human embryos: a systematic review and meta-analysis of randomized controlled trials, Hum Reprod Update (2011) 17: 438-453.

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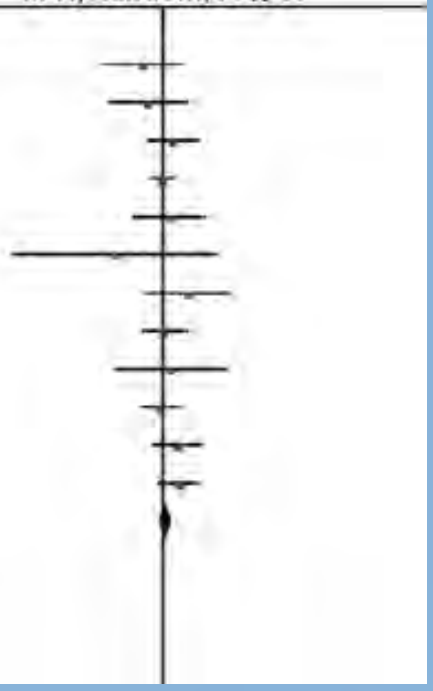
Is Assisted Hatching effective?

Clinical pregnancy

Study or Subgroup	AH Events	AH Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Fresh embryos transferred to unselected or non poor prognosis women						
Balakier et al. 2009	16	45	18	39	2.7%	0.77 [0.46, 1.29]
Baruffi et al. 2000	17	51	21	52	2.8%	0.83 [0.50, 1.37]
Cohen et al. 1992b (I)	37	69	32	68	4.3%	1.14 [0.82, 1.59]
Ge et al. 2008 (I)	164	387	159	373	6.3%	0.99 [0.84, 1.17]
Hellebaut et al. 1996	23	60	21	60	3.1%	1.10 [0.68, 1.75]
Hurst et al. 1998	3	13	3	7	0.6%	0.54 [0.15, 2.00]
Isik et al. 2000	15	24	10	22	2.5%	1.38 [0.79, 2.39]
Kutlu et al. 2010 (I)	42	73	37	66	4.8%	1.03 [0.77, 1.37]
Petersen et al. 2005 (I)	11	35	10	35	1.7%	1.10 [0.54, 2.25]
Sagoskin et al. 2007	63	121	44	82	5.1%	0.97 [0.75, 1.26]
Tucker et al. 1993	49	110	40	108	4.4%	1.20 [0.87, 1.66]
Urman et al. 2002	65	121	52	119	5.1%	1.23 [0.95, 1.60]
Subtotal (95% CI)		**1109**		**1031**	**43.4%**	**1.05 [0.95, 1.15]**
Total events	505		447			

Heterogeneity: Tau² = 0.00; Chi² = 7.26, df = 11 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.95 (P = 0.34)



45,5% vs 43,3%

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Is Assisted Hatching effective?

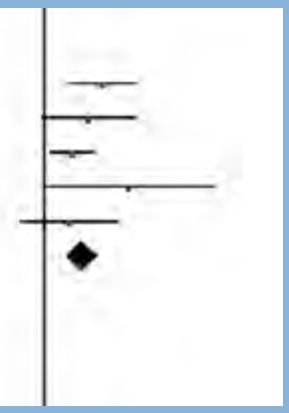
Fresh embryos transferred to women with previous repeated failure

Antinori et al. 1996b	32	72	19	98	3.0%	2.29 [1.42, 3.70]
Chao et al. 1997	18	49	10	51	1.9%	1.87 [0.96, 3.65]
Jelinkova et al. 2003	59	128	40	129	4.5%	1.49 [1.08, 2.04]
Petersen et al. 2005 (II)	10	40	3	40	0.7%	3.33 [0.99, 11.22]
Stein et al. 1995	15	72	12	82	1.8%	1.42 [0.71, 2.84]
Subtotal (95% CI)		**361**		**400**	**11.9%**	**1.73 [1.37, 2.17]**
Total events	134		84			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.70$, df = 4 (P = 0.45); $I^2 = 0\%$

Test for overall effect: Z = 4.69 (P < 0.00001)

37,1% vs 21,0%



Comparison: 2 Clinical pregnancy

Outcome: 5 Clinical pregnancy rate: grouped by prognosis

Study or subgroup	Assisted hatching n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Poor prognosis					
Antinori 1999a	19/73	11/69		2.5 %	1.86 [0.81, 4.25]
Cohen 1992c	7/15	2/15		0.3 %	5.69 [0.94, 34.46]
Elhelw 2005	8/37	5/37		1.2 %	1.77 [0.52, 6.01]
Jelinkova 2002	59/128	40/127		6.5 %	1.86 [1.12, 3.10]
Lanzendorf 1998	16/41	20/48		3.4 %	0.90 [0.38, 2.10]
Petersen 2005a	11/35	10/35		2.1 %	1.15 [0.41, 3.19]
Petersen 2005b	10/40	3/40		0.7 %	4.11 [1.04, 16.29]
Rufas-Sapir 2004	22/104	28/103		6.7 %	0.72 [0.38, 1.36]
Stein 1995	15/72	12/82		2.7 %	1.54 [0.67, 3.54]
Utsunomiya 1998	5/27	4/28		1.0 %	1.36 [0.32, 5.73]
Subtotal (95% CI)	**572**	**584**		**26.9 %**	**1.45 [1.11, 1.89]**

Total events: 172 (Assisted hatching), 135 (Control)

Heterogeneity: $Chi^2 = 11.84$, df = 9 (P = 0.22); $I^2 = 24\%$

Test for overall effect: Z = 2.72 (P = 0.0065)

30,1% vs 23,1%

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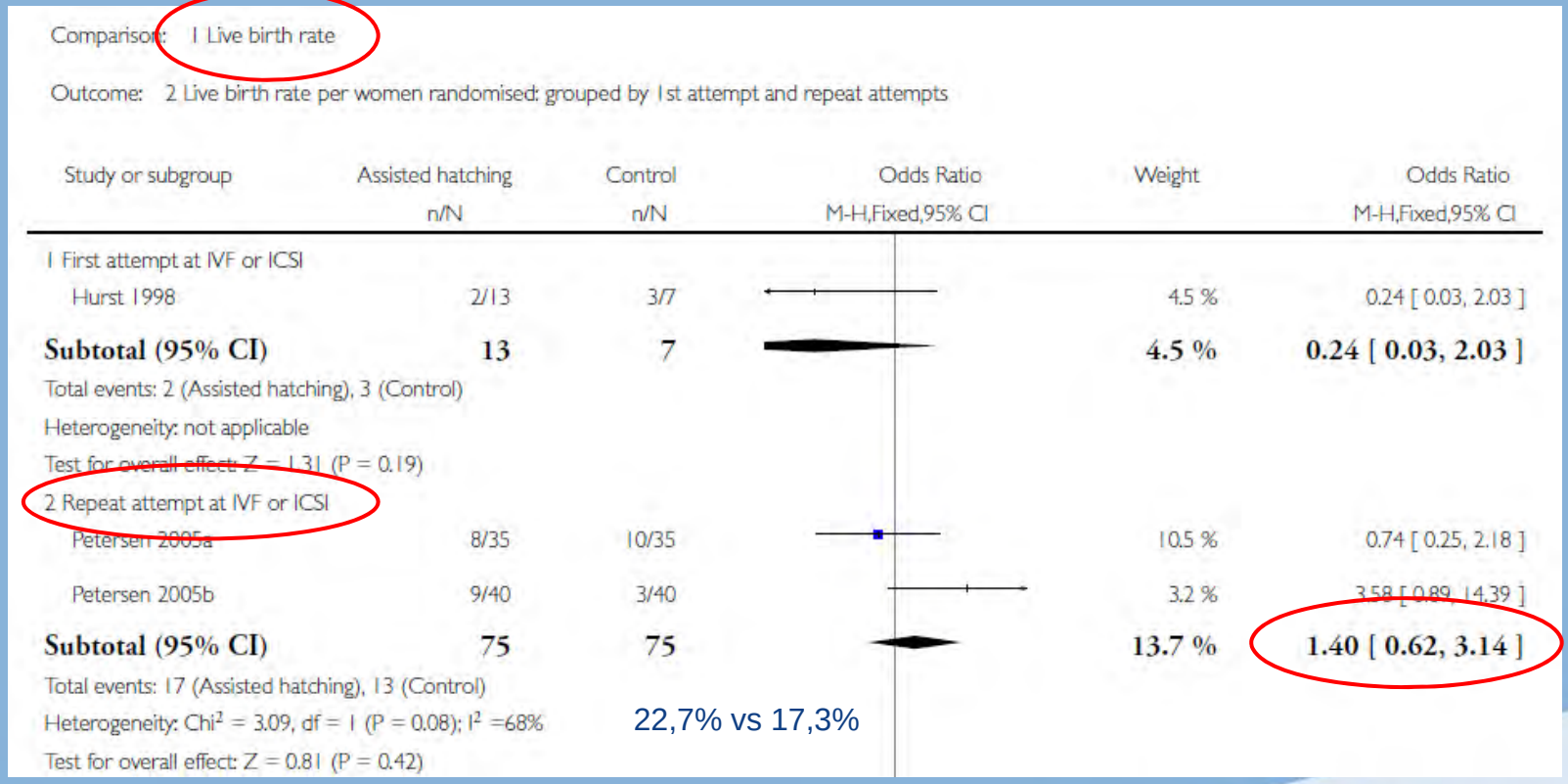
Is Assisted Hatching effective?

What are the results in live birth rate, per started cycle, based on intention tot treat?



Comparison: 1 Live birth rate

Outcome: 2 Live birth rate per women randomised: grouped by 1st attempt and repeat attempts

Study or subgroup	Assisted hatching n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 First attempt at IVF or ICSI					
Hurst 1998	2/13	3/7		4.5 %	0.24 [0.03, 2.03]
Subtotal (95% CI)	**13**	**7**		**4.5 %**	**0.24 [0.03, 2.03]**
Total events: 2 (Assisted hatching), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.31 (P = 0.19)					
2 Repeat attempt at IVF or ICSI					
Petersen 2005a	8/35	10/35		10.5 %	0.74 [0.25, 2.18]
Petersen 2005b	9/40	3/40		3.2 %	3.58 [0.89, 14.39]
Subtotal (95% CI)	**75**	**75**		**13.7 %**	**1.40 [0.62, 3.14]**
Total events: 17 (Assisted hatching), 13 (Control)					
Heterogeneity: Chi² = 3.09, df = 1 (P = 0.08); I² =68%					
Test for overall effect: Z = 0.81 (P = 0.42)					

22,7% vs 17,3%

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Is Assisted Hatching effective?

Both meta-analyses made recommendations for future research:

- multi-centre trials with appropriate design, adequate power and appropriate duration of follow up
- live birth, miscarriage and multiple pregnancy data
- women in older age groups
- following repeated implantation failure
- those with high early proliferative phase serum FSH levels
- monozygotic twinning
- congenital malformations

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The AHA-trial

A multicentre randomized controlled trial on the efficacy of laser assisted hatching in poor prognosis patients undergoing IVF or ICSI

Poor prognosis patients:

- **Female age over 35**
- **Repeated implantation failure**
- **Diminished ovarian reserve**

Prospectively randomized

Blinded to physician, patient couple, staff performing the embryo transfer, data analyst

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The AHA-trial

Primary endpoint: live birth rate per couple per started treatment cycle

Secondary endpoints:

- the pregnancy rate and ongoing pregnancy rate per
  - treatment cycle started
  - oocyte retrieval
  - embryo transfer
- the implantation rate per embryo transferred
- the multiple pregnancy rate
- the monozygotic twinning rate
- the percentage of major and minor malformations in the children born as assessed at birth

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The AHA-trial

Power analysis:

Effect size 6% (two tailed)
Alpha error 5%
Beta error 20% (Power = 80%)
20% ongoing pregnancy rate per started cycle

772 patient couples assigned to control group
772 patient couples assigned to intervention (assisted hatching)

Intention to participate:
Catharina Hospital, Eindhoven
Erasmus Medical Centre, Rotterdam

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Pilot AHA

Same inclusion criteria as in RCT

50 couples are offered 1 treatment cycle including AHA

Goal: to proof that the technical skill is available

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Pilot AHA, preliminary results

20 ovum pick ups
1 thawing cycle

1 OHSS, poor embryo quality, no cryopreservation
1 TFF, 1 oocyte

19 embryo transfers

8 biochemical pregnancies (42,1% per ET)
2 spontaneously aborted
3 clinical pregnancies (of which 2 ongoing and 1 yet unknown)
3 not yet confirmed by ultrasound

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