

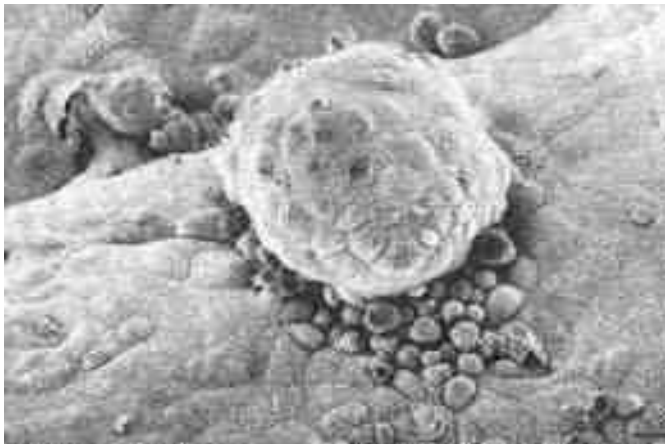
**Systematic and standardized hysteroscopic endometrial injury for
treatment of recurrent implantation failure (RIF):
Preliminary results of a prospective and randomized trial**

Müberra Namlı Kalem ,MD



Successful implantation requires:

- a receptive endometrium
- a normal and functional embryo at the blastocyst developmental stage
- a synchronized dialogue between maternal and embryonic tissues



Etiology of Implantation Failure

■ Embryo

Chromosomal abnormality

Low quality



■ Endometrial receptivity

Immune Factors

Endometriosis

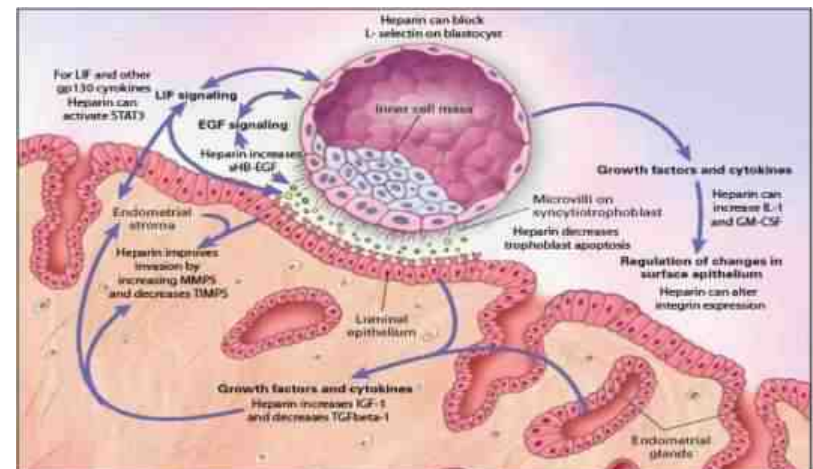
Hydrosalpinx

Leiomyomas,

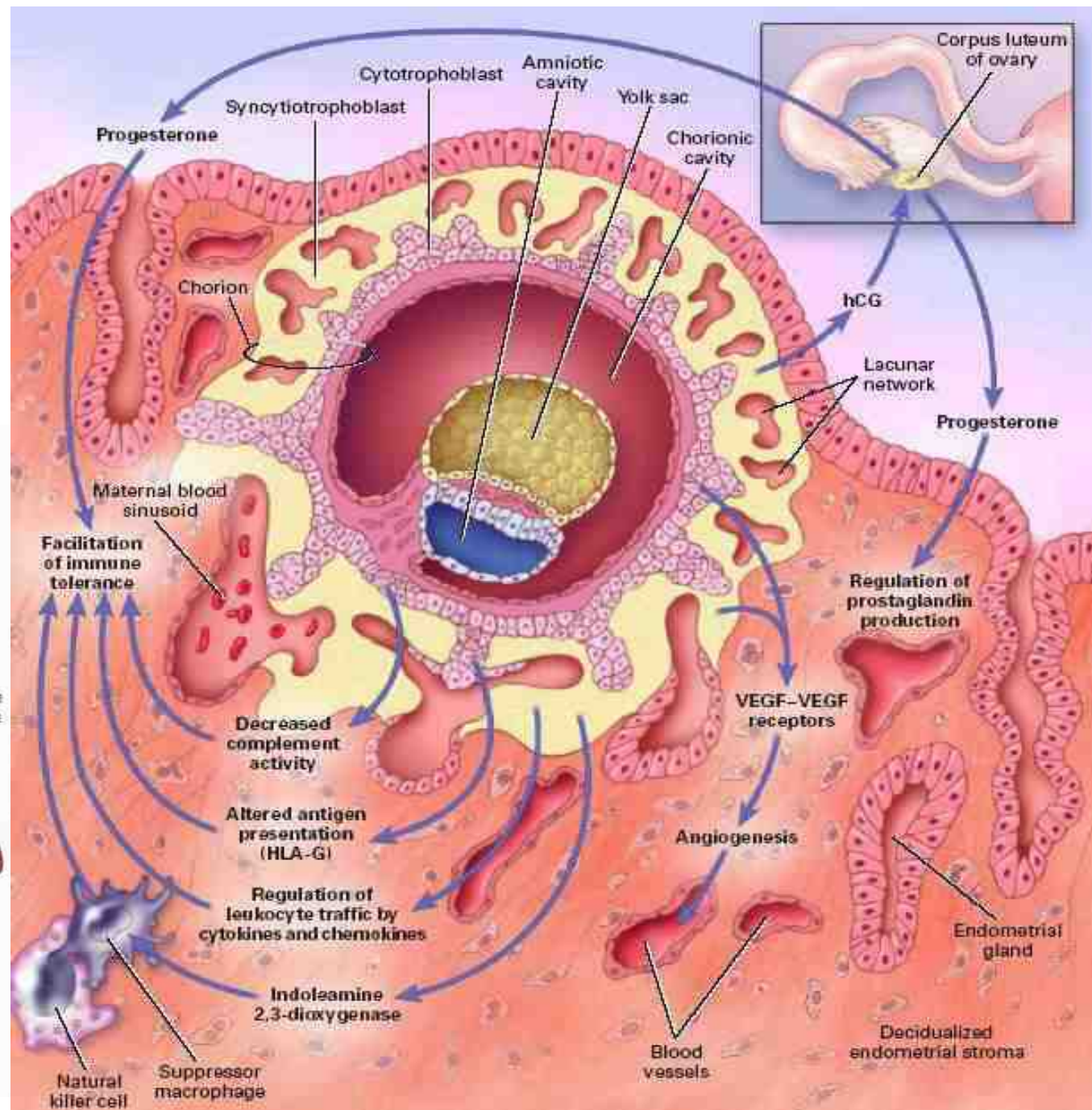
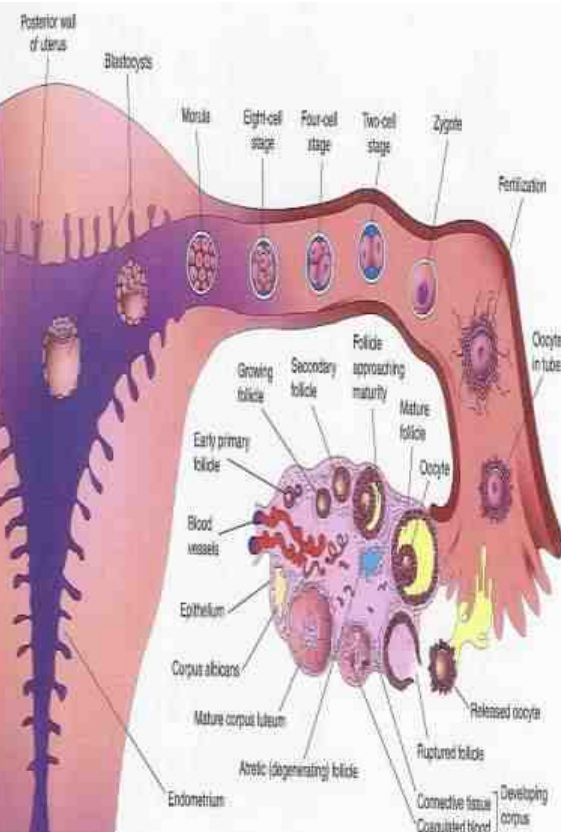
Adenomyosis,

PCOS,

Polyps, endometritis ..



Immune system & Implantation

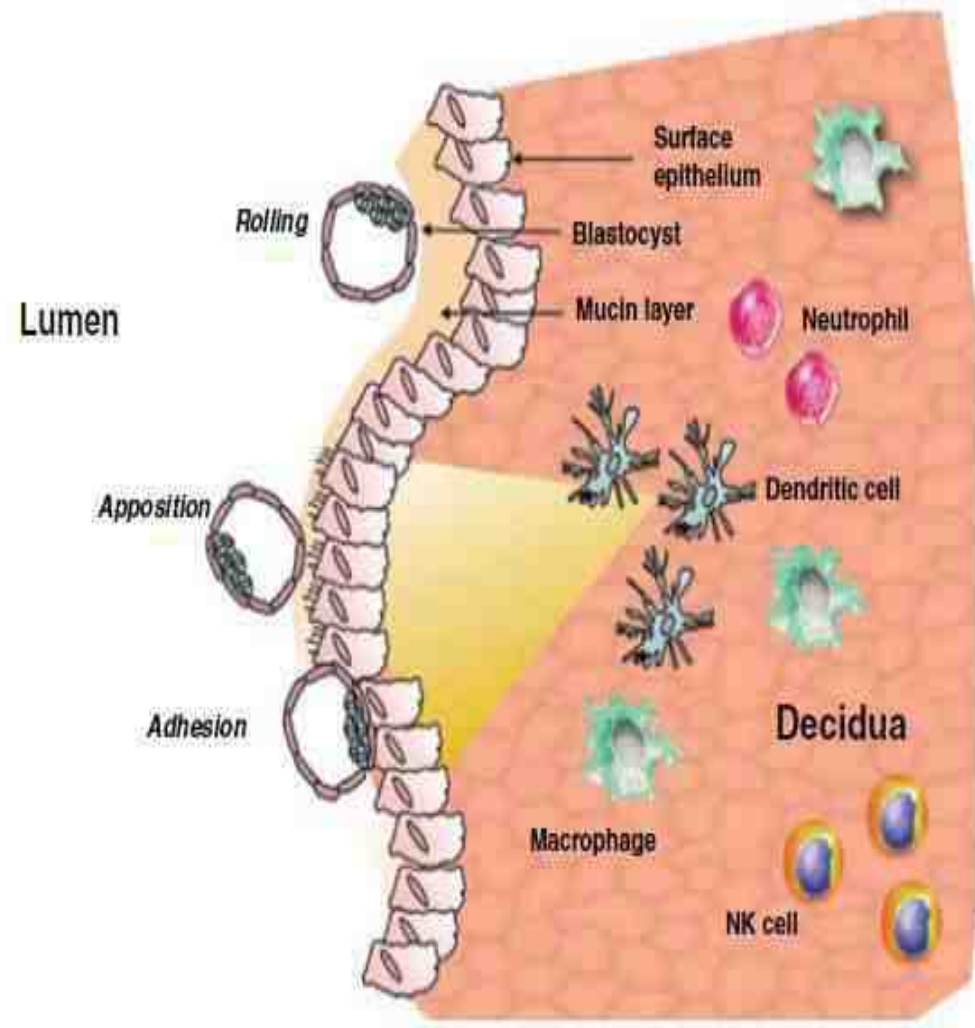
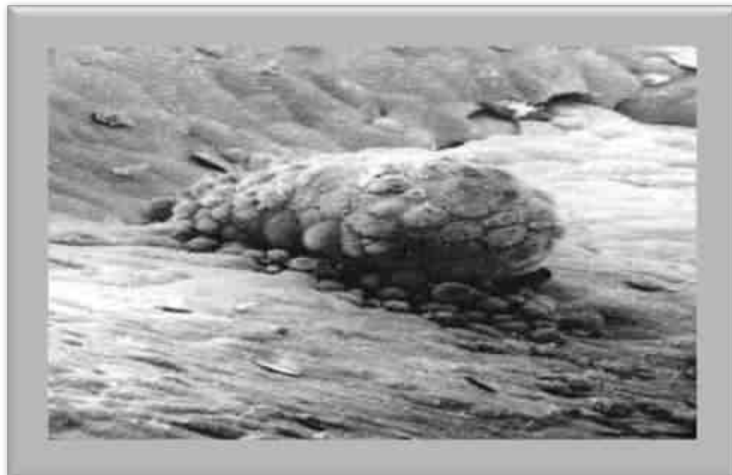


The role of immune system at the implantation site

- High level of the proinflammatory T helper cells (Th-1) and cytokines (IL-6, IL-8, TNF alpha characterize) early implantation
- Cytokines: Secreted by the endometrial cells and by the cells of immune system that are recruited to the site of implantation
- NK cells : regulates trophoblast invasion, secretes angiogenic factors to induce vascular growth and decidualisation,
- Macrophages:
 - Pivotal role on cytokine balancing at the maternal-fetal interface
 - Essential for successful decidualisation
 - Plays central role in the process of tissue renewal and differentiation
- Dendritic cells : Initiate and coordinate the innate immune adaptive immune response and also support the effect of macrophages

Three stages of implantation

- Apposition :Trophoblast cells adhere to the receptive endometrium
- Adhesion: Blastocyst anchor to the endometrial basal lamina and stromal extracellular matrix and embryo-endometrial linkage achieve
- Invasion: Blastocyst penetration through the luminal epithelium



**Inflammation is essential
for implantation !!!**

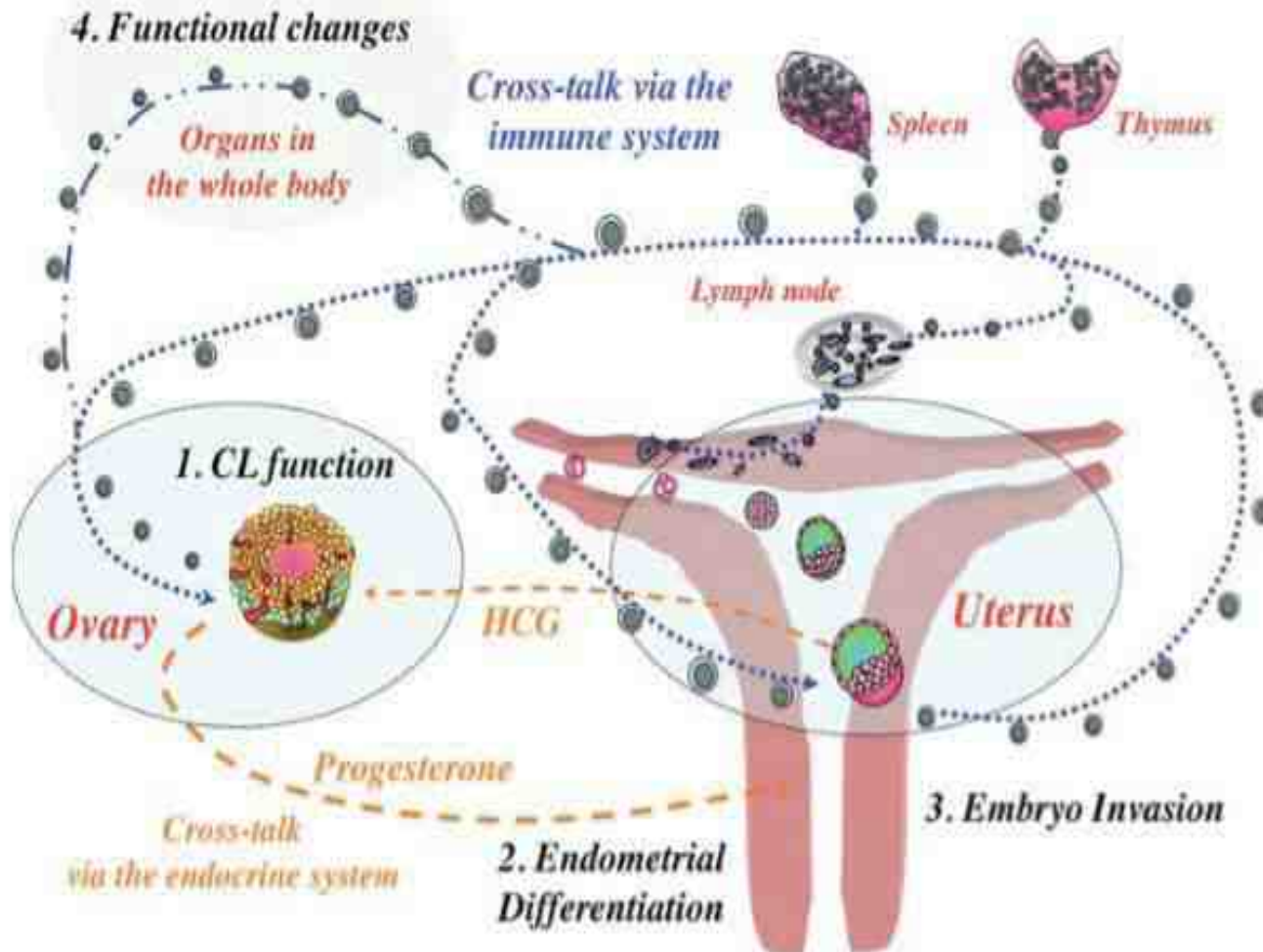
Immune and endocrine system & Implantation

Do circulating blood cells contribute to maternal tissue remodeling and embryo–maternal cross-talk around the implantation period?[†]

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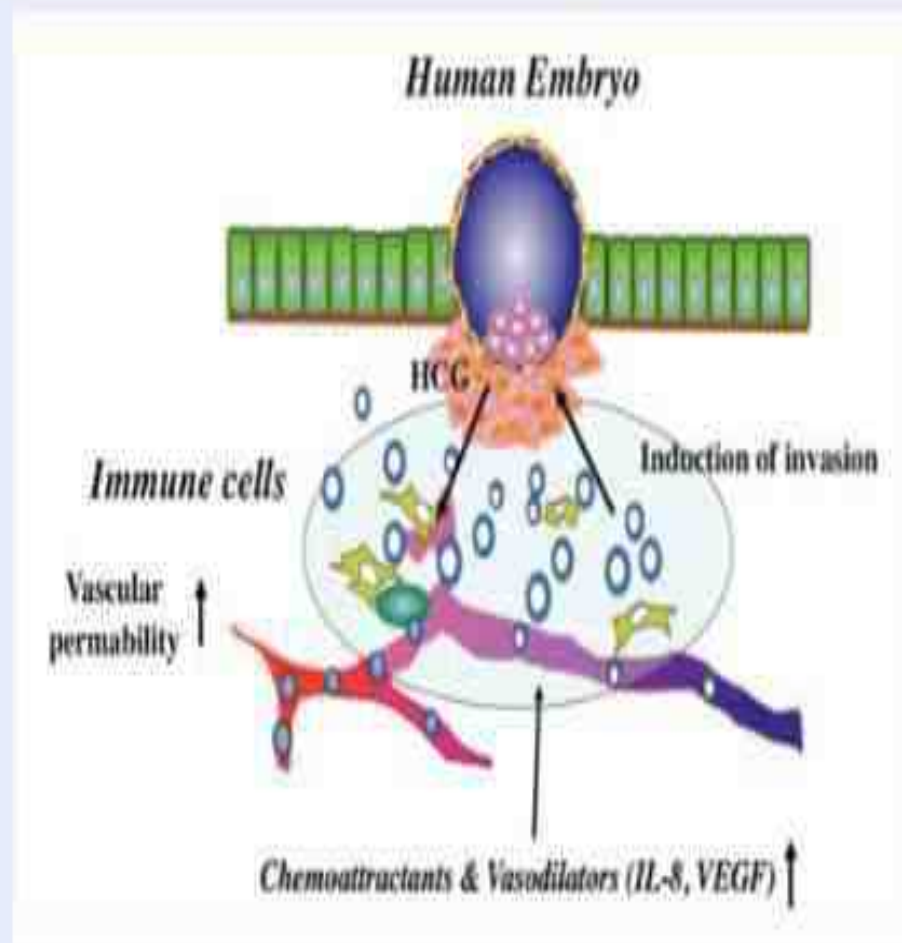


Figure 2 The possible roles of HCG in human embryo invasion. The invading human embryo locally secretes HCG at high concentration and stimulates recruited or resident immune cells to produce chemoattractants and then these factors in turn induce embryo invasion toward endometrial stromal tissue.

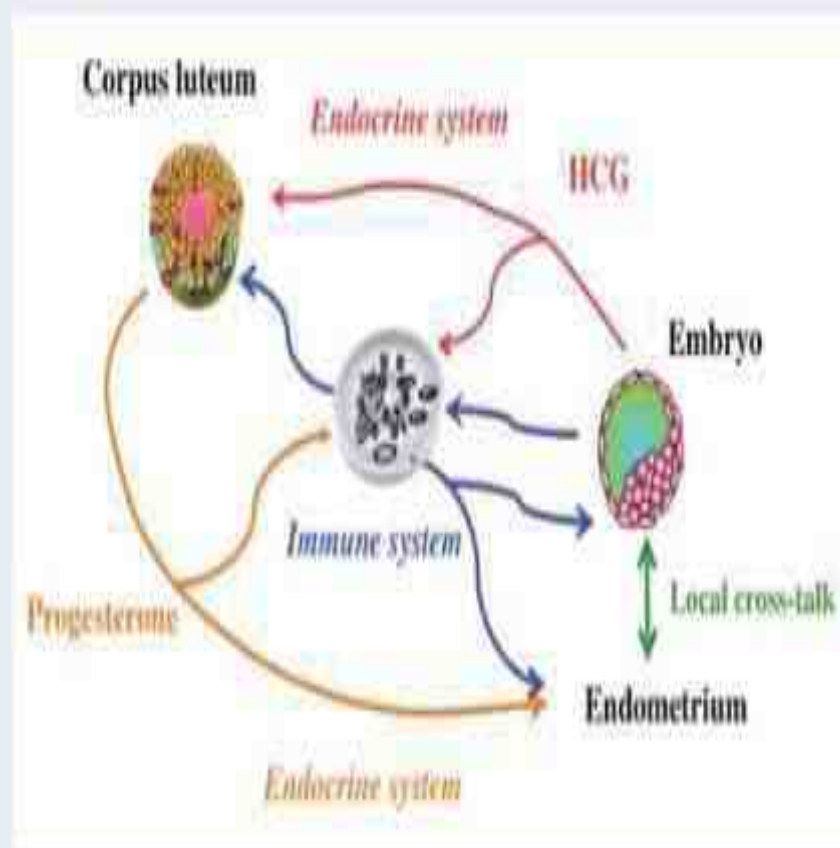
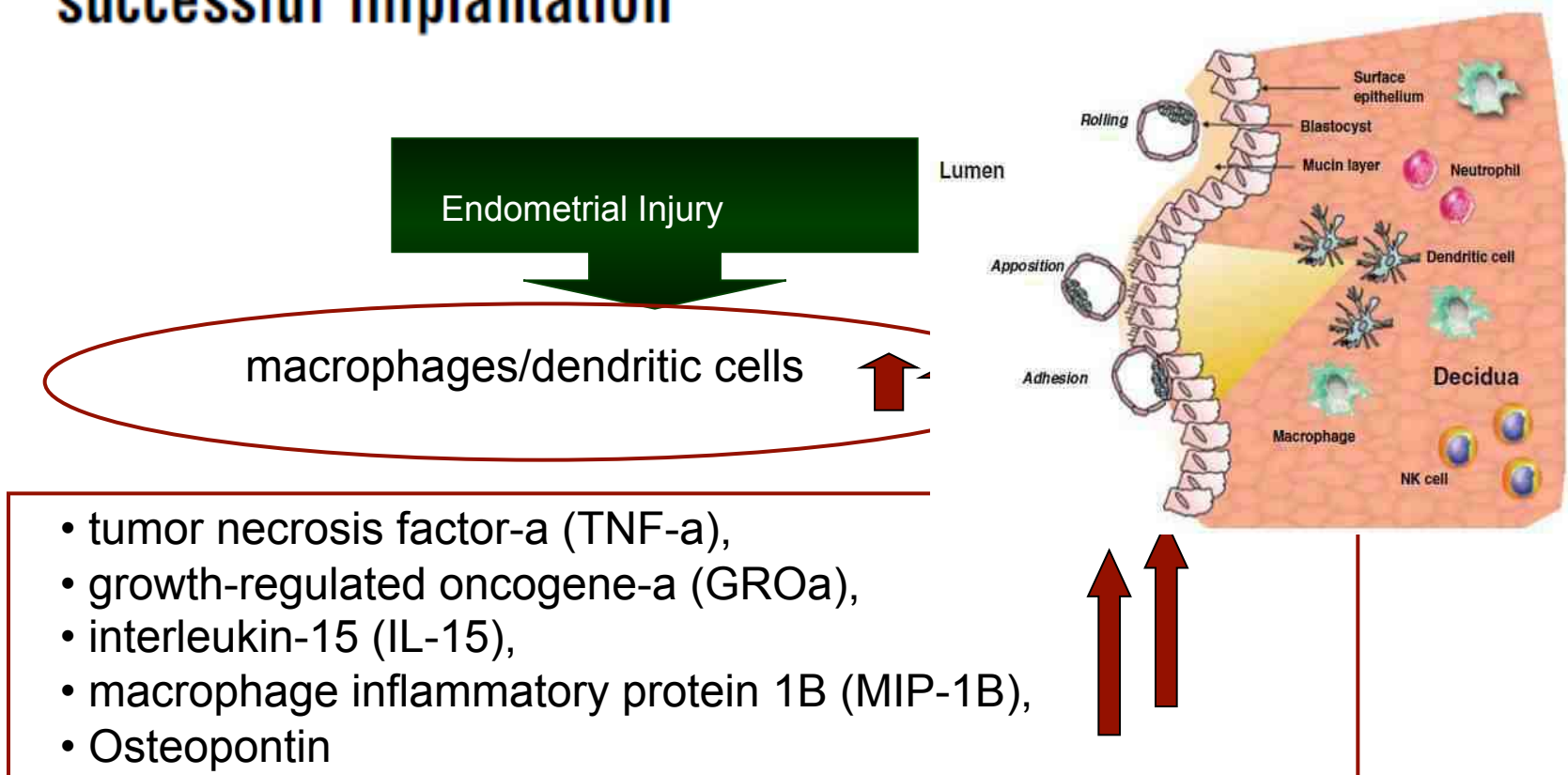


Figure 3 Cross-talk between the endocrine and immune systems. Cross-talk between the endocrine (HCG and progesterone) and immune systems may occur parallel to the direct local cross-talk between mother (endometrium) and embryo in the uterus during early pregnancy. Both systems cooperatively contribute to embryo implantation and maintenance.

Local injury of the endometrium induces an inflammatory response that promotes successful implantation



A positive correlation was found between the levels of macrophages/dendritic cells, MIP-1B expression, and TNF- α expression & the pregnancy outcome.

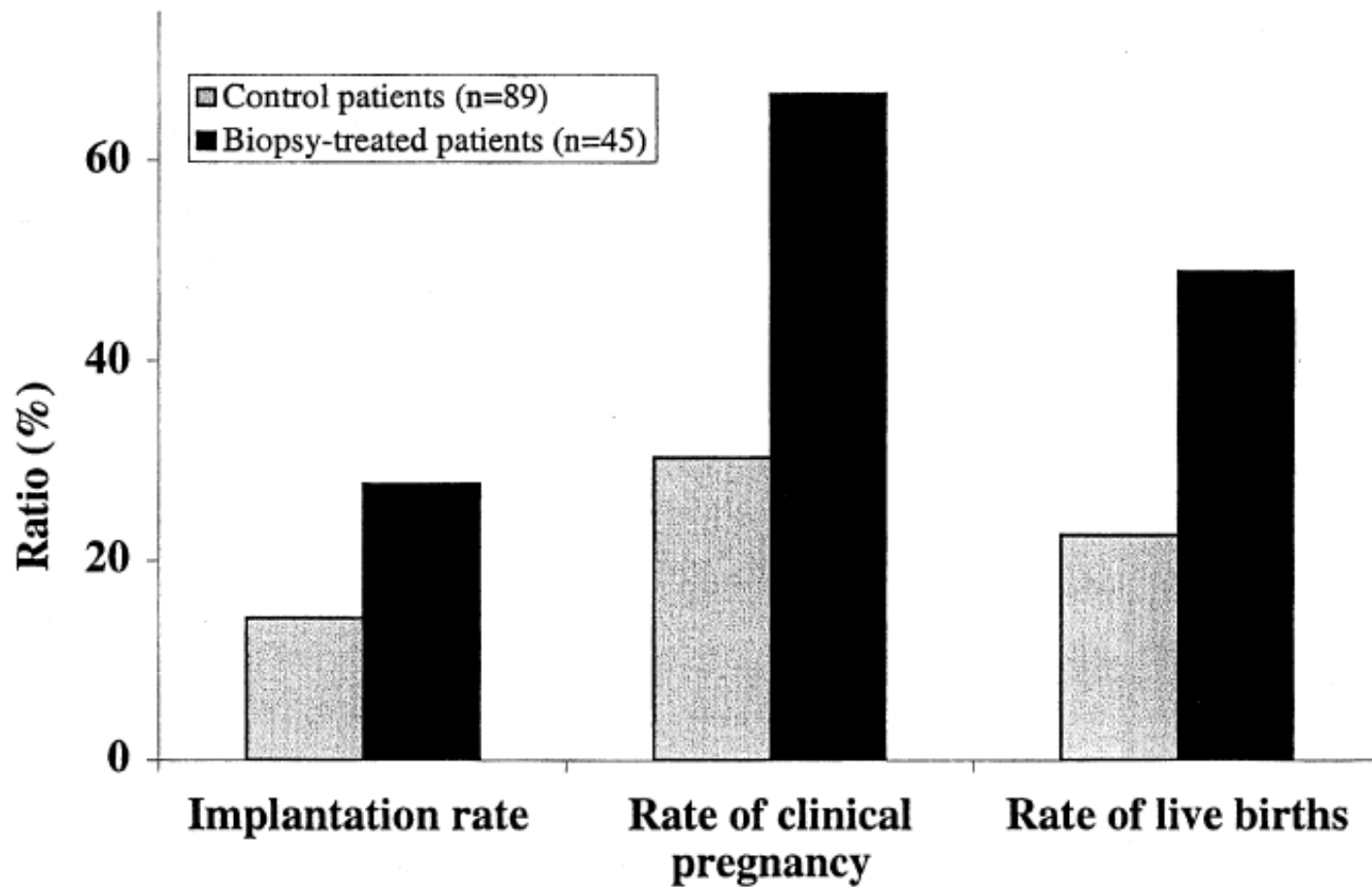
In vitro fertilization

Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization

Amihai Barash, M.D.^a, Nava Dekel, Ph.D.^b, Sheila Fieldust, Bs.C.^a, Ilana Segal, Bs.C.^a, Edna Schechtman, Ph.D.^c, Irit Granot, Ph.D.^a  

Results: Endometrial sampling of IVF patients using a biopsy catheter substantially increases their chances to conceive at the following IVF-embryo transfer cycle. By transferring a similar number of embryos in the study and control groups, the authors achieved an implantation rate of 28 versus 14%, a clinical pregnancy rate of 67 versus 30% and a live birth rate per embryo transfer of 49 versus 23%.

Conclusion: These results suggest that IVF treatment that is preceded by endometrial biopsy **doubles the chance** for a take-home baby.



Significant increase in clinical pregnancy and live birth rate

Site-specific endometrial injury improves implantation and pregnancy in patients with repeated implantation failures

Shang Yu Huang[†], Chin-Jung Wang[†], Yung-Kuei Soong, Hsin-Shih Wang, Mei Li Wang, Chieh Yu Lin and Chia Lin Chang

Abstract

Background: To test whether a site-specific hysteroscopic biopsy-induced injury in the endometrium during the controlled ovarian hyperstimulation cycle improves subsequent embryo implantation in patients with repeated implantation failure, a total of 30 patients who have had good responses to controlled ovulation stimulation but have failed to achieve pregnancy after two or more transfers of good-quality embryos were recruited in this prospective study.

Methods: A single, site-specific hysteroscopic biopsy-induced injury was generated on the posterior endometrium at midline 10-15 mm from the fundus during the D4-D7 period of the ongoing controlled ovarian hyperstimulation cycle in six patients.

Results: Patients received endometrial biopsy protocol achieved a pregnancy rate of 100%. By contrast, only 46% of patients with similar clinical characteristics ($N = 24$) achieved pregnancy without the hysteroscopic biopsy-induced endometrium injury ($p < 0.05$).

Conclusions: Our proof-of-concept study demonstrates that a site-specific hysteroscopic endometrium injury performed during the ongoing in vitro fertilization (IVF) cycle, instead of injuries received during prior cycles, significantly improves clinical outcomes in patients with repeated implantation failure.

Keywords: hysteroscopy, endometrium biopsy, IVF, repeated implantation failure, pregnancy

Endometrial scratching to improve pregnancy rate in couples with unexplained subfertility: A randomized controlled trial

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¹Department of Obstetrics and Gynecology, and ²Department of Public Health, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Abstract

Aim: The aim of this study was to examine the effect of endometrial scratching in women with unexplained infertility.

Material and Methods: A randomized controlled trial was conducted in Mansoura University Teaching Hospital and a private practice setting. A total of 105 couples with unexplained infertility were randomly allocated into two groups: group A comprised 54 women who underwent endometrial scratching in the luteal phase of a spontaneous menstrual cycle; and group B included 51 women who underwent a placebo procedure. The main outcome measured was cumulative clinical pregnancy rate after 6 months and miscarriage rate.

Results: Clinical pregnancy rate was significantly higher in the women experiencing endometrial biopsy than in the control group (25.9% and 9.8%, respectively, $P = 0.04$). There was no significant difference in miscarriage rate between pregnant women in the endometrial injury group and pregnant women in the control group (12.5% and 16.5%, respectively, $P = 0.79$).

Conclusions: Endometrial scratching may improve clinical pregnancy rates in couples with unexplained infertility. Adequately powered studies are mandated to confirm or refute the findings.

Key words: biopsy, endometrium, infertility, scratching, unexplained.

Reprod Sci. 2015 Sep 3. pii: 1933719115602776. [Epub ahead of print]

Endometrial Scratch Injury Induces Higher Pregnancy Rate for Women With Unexplained Infertility Undergoing IUI With Ovarian Stimulation: A Randomized Controlled Trial.

Maged AM¹, Al-Inany H², Salama KM³, Souidan II³, Ragab HM³, Elmassary N².

Author information

Abstract

OBJECTIVE: To explore the impact of endometrial scratch injury (ESI) on intrauterine insemination (IUI) success.

METHODS: One hundred and fifty four infertile women received 100 mg of oral clomiphene citrate for 5 days starting on day 3 of the menstrual cycle. Patients were randomized to 2 equal groups: Group C received IUI without ESI and group S had ESI. Successful pregnancy was confirmed by ultrasound.

RESULTS: 13, 21, and 10 women got pregnant after the first, second, and third IUI trials, respectively, with 28.6% cumulative pregnancy rate (PR). The cumulative PR was significantly higher in group S (39%) compared to group C (18.2%). The PR in group S was significantly higher compared to that in group C at the second and third trials. The PR was significantly higher in group S at the second trial compared to that reported in the same group at the first trial but nonsignificantly higher compared to that reported during the third trial, while in group C, the difference was nonsignificant. Eight pregnant women had first trimester abortion with 18.2% total abortion rate with nonsignificant difference between studied groups.

CONCLUSION: The ESI significantly improves the outcome of IUI in women with unexplained infertility especially when conducted 1 month prior to IUI.



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ARTICLE

Local endometrial injury and IVF outcome: a systematic review and meta-analysis

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Tarek El-Toukhy is a consultant in reproductive medicine and surgery and preimplantation genetic diagnosis (PGD) at the Assisted Conception Unit and PGD Centre at Guy's and St Thomas' Hospital in London. His clinical and research interests are in the fields of recurrent IVF implantation failure; prevention of ovarian hyperstimulation syndrome; embryo freezing; PGD and minimal access surgery. He has published over 80 original articles, reviews and opinion papers.



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REVIEW

Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis

Neelam Potdar^{a,*}, Tarek Gelbaya^b, Luciano G Nardo^c

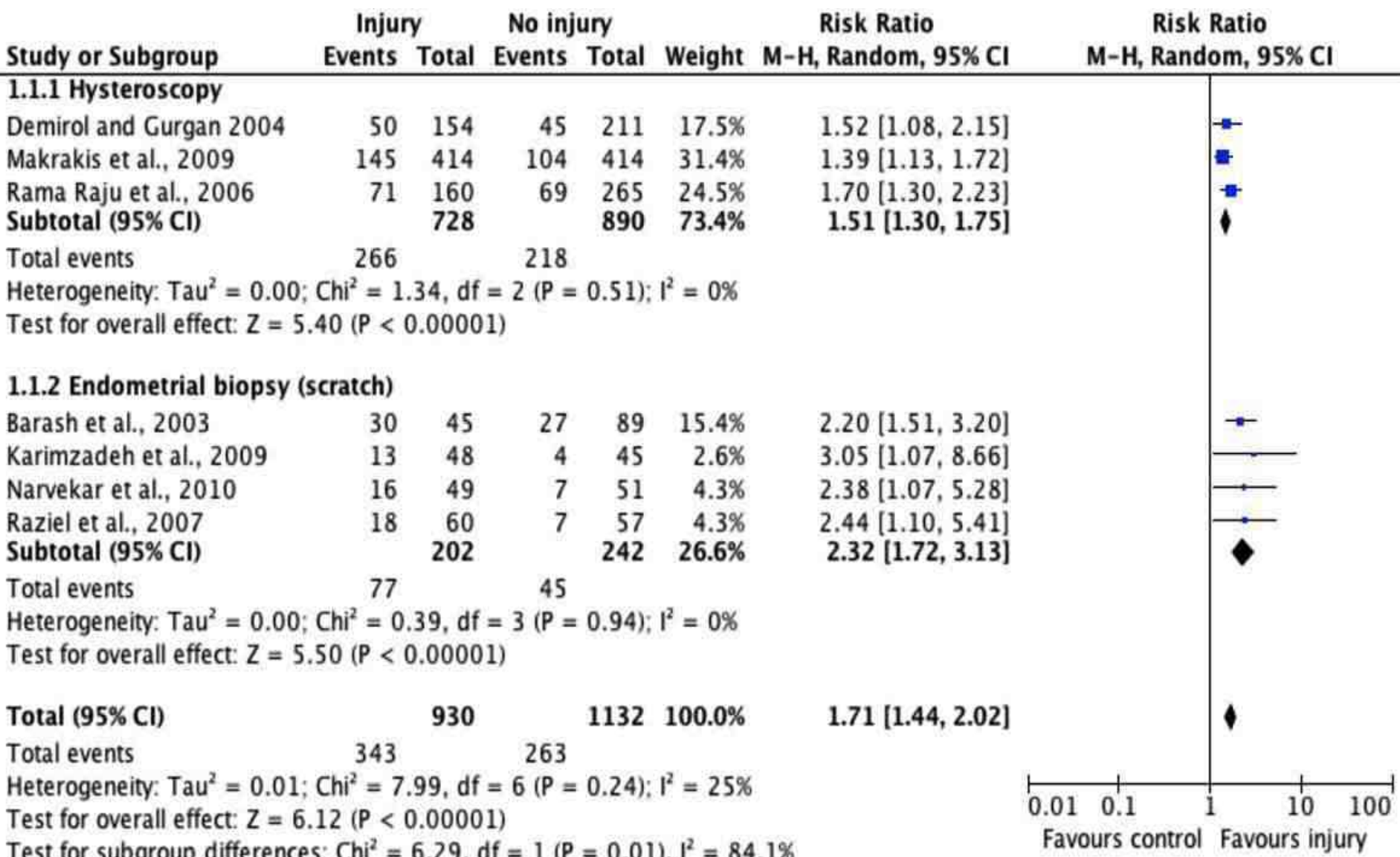
^a Leicester Fertility Centre, University of Leicester and University Hospitals of Leicester, Leicester, UK; ^b Leicester Fertility Centre, University Hospitals of Leicester, Leicester, UK; ^c Reproductive Medicine and Surgery Unit, Gynhealth, Manchester, UK

^{*} Corresponding author. E-mail address: neelam.potdar@yahoo.co.uk (N Potdar).



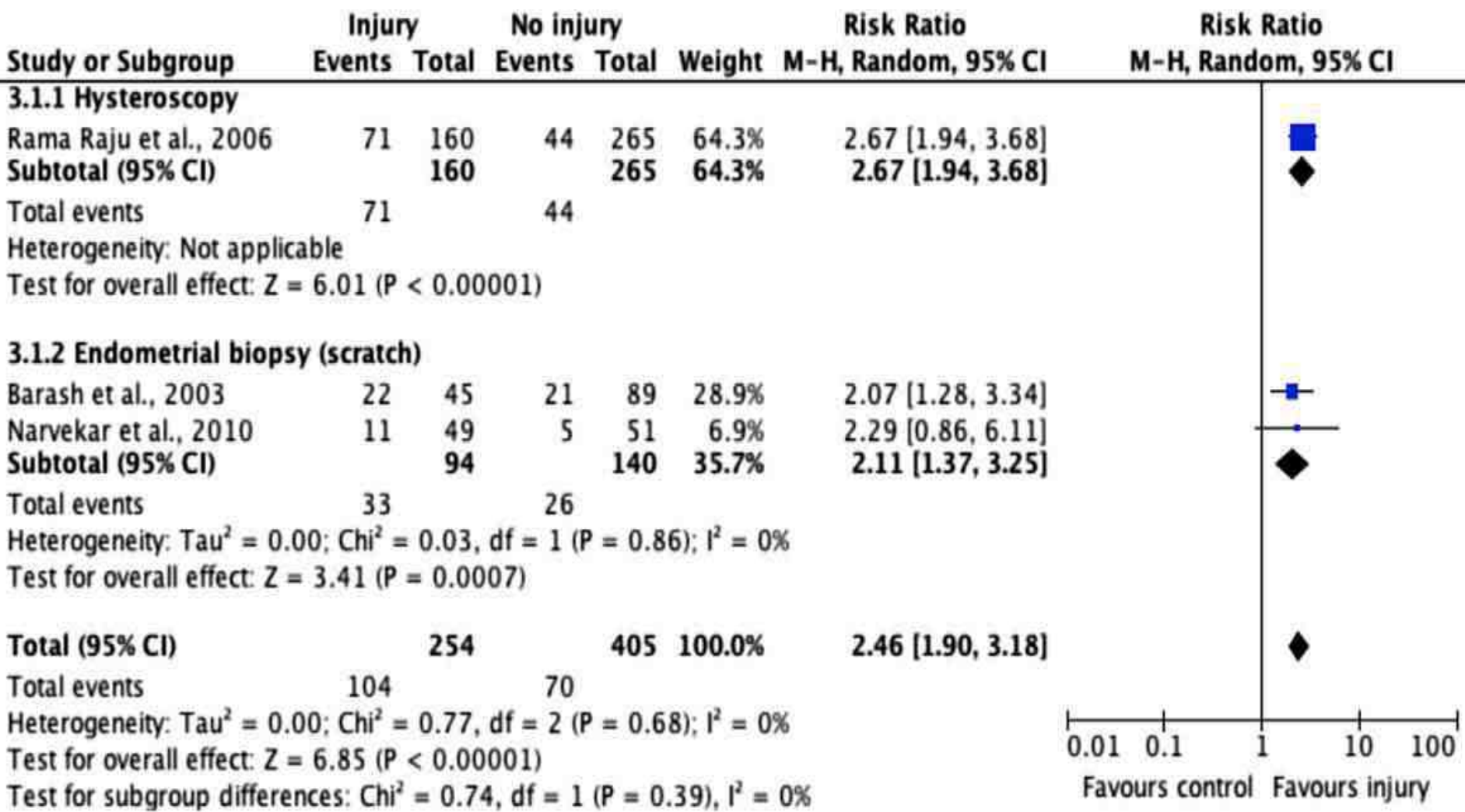
Neelam Potdar, MS, MD, MRCOG commenced her specialty training in the UK in 2001, thereafter joined research programme and obtained her MD degree from the University of Leicester in 2009. Since then she has been working as a subspecialist trainee in reproductive medicine and surgery and a clinical lecturer at the University of Leicester. Her research interests are implantation failure, lifestyle factors associated with subfertility and early pregnancy loss, and fertility preservation.

Clinical pregnancy rate in the endometrial injury (hysteroscopy and endometrial biopsy) and control groups.



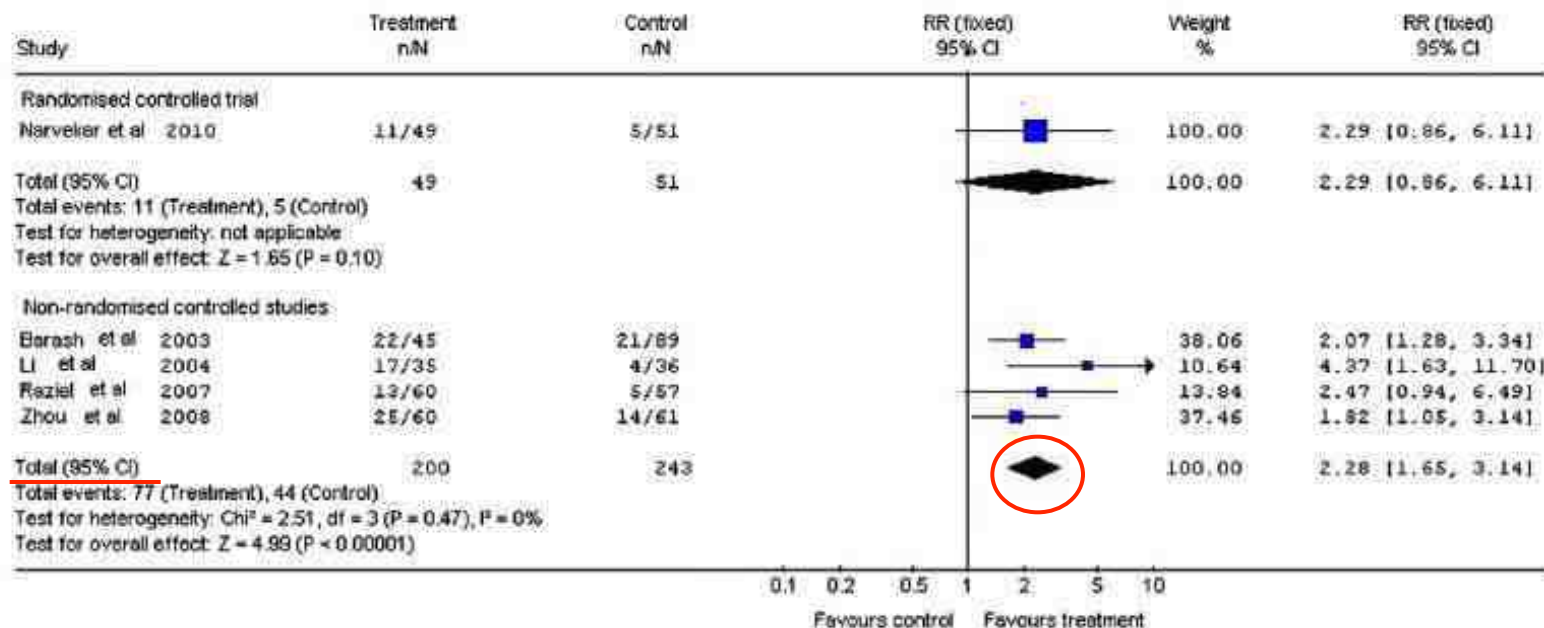
Endometrial injury favors implantation

Live birth rate in the endometrial injury (hysteroscopy and endometrial biopsy) and control groups



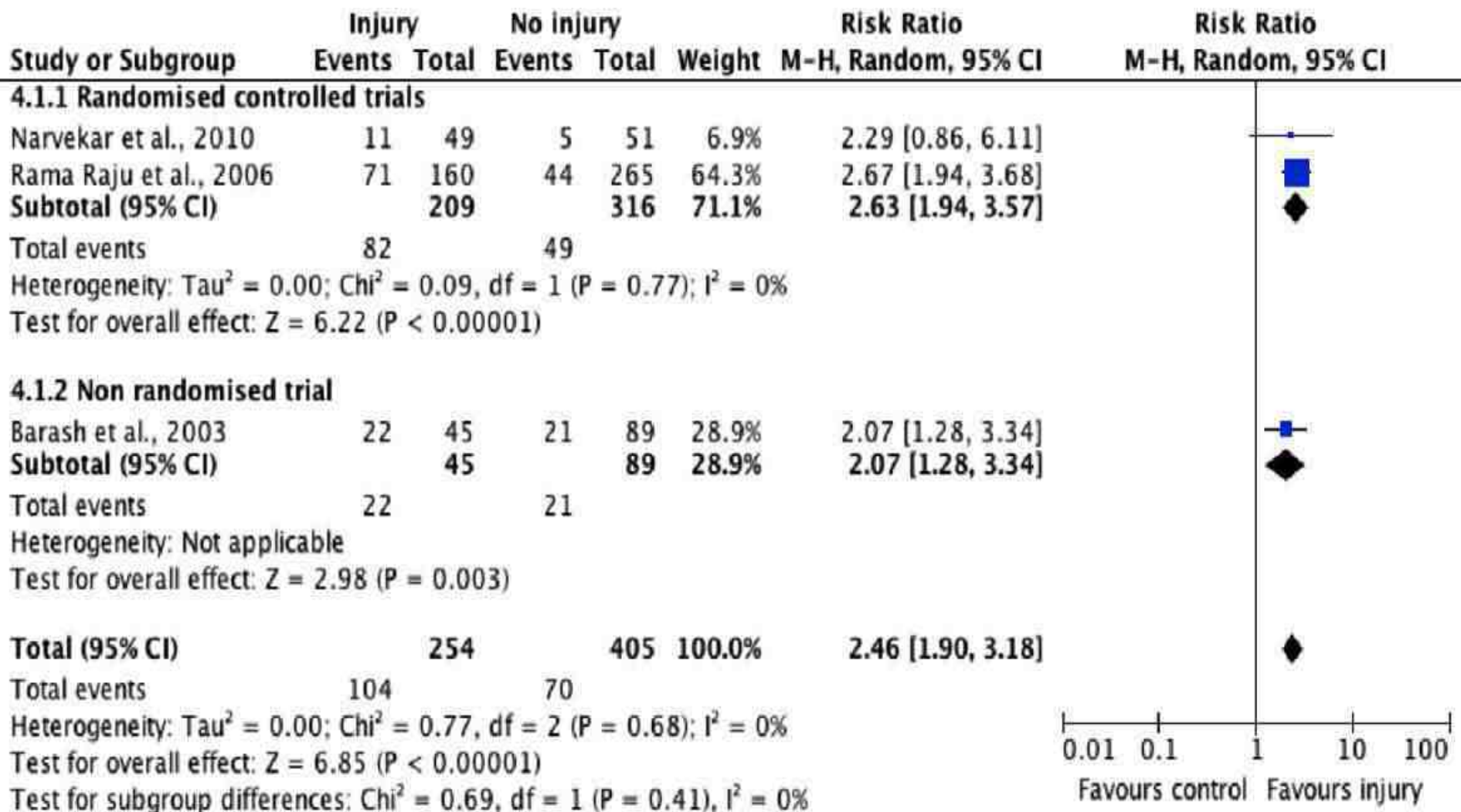
Endometrial injury improves live birth rate

Summary of the live birth/ ongoing pregnancy rate for the 5 studies included in the systematic review



Improvement of live birth/ongoing pregnancy rate

Live birth rate in the randomized and non-randomized studies for endometrial injury and control groups.



Endometrial injury improves live birth rate

Endometrial injury in women undergoing assisted reproductive techniques (Review)

Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, Martins WP



This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 3

<http://www.thecochranelibrary.com>

Figure 5. Forest plot of comparison: I Effectiveness, outcome: I.I Live birth per randomly assigned woman.

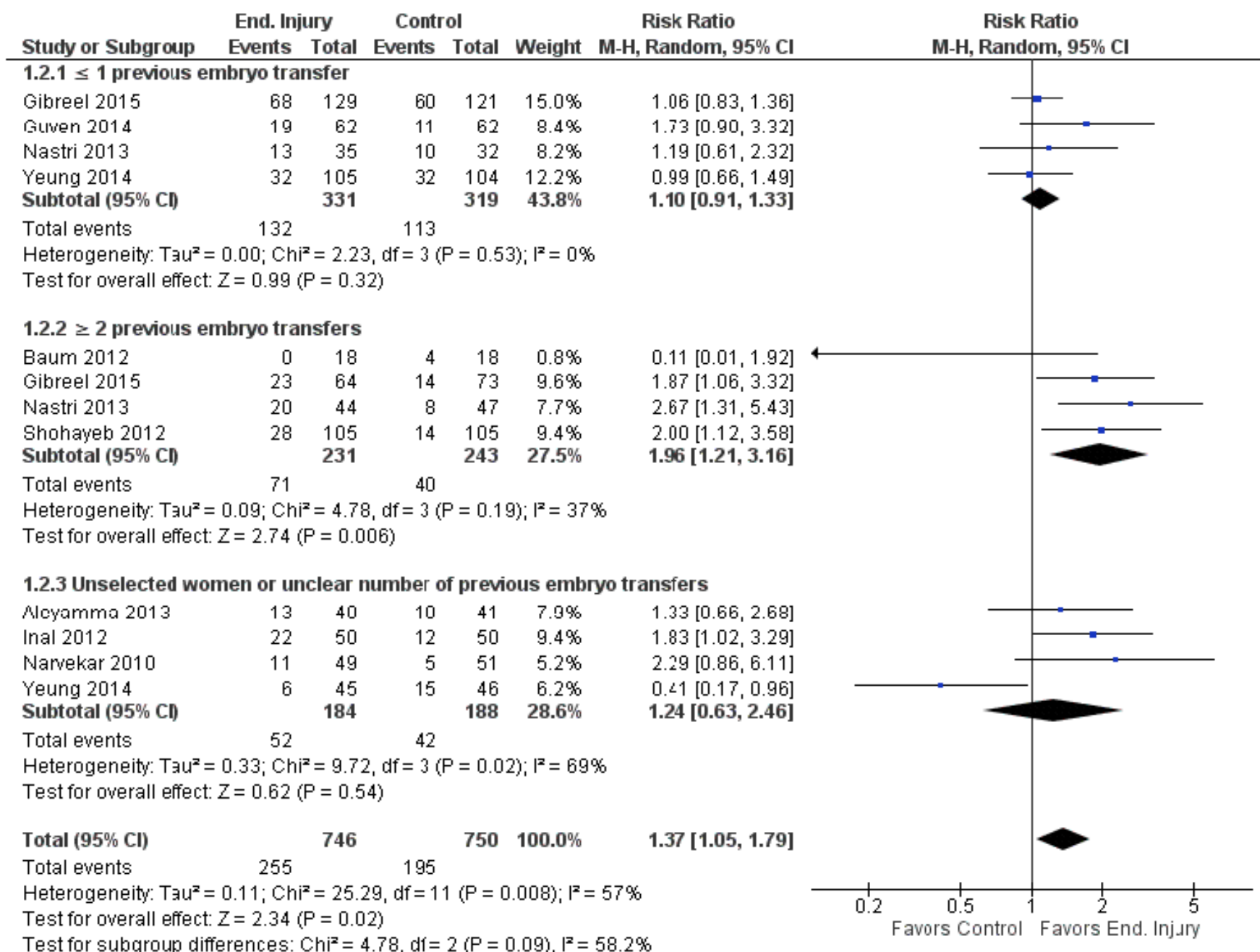
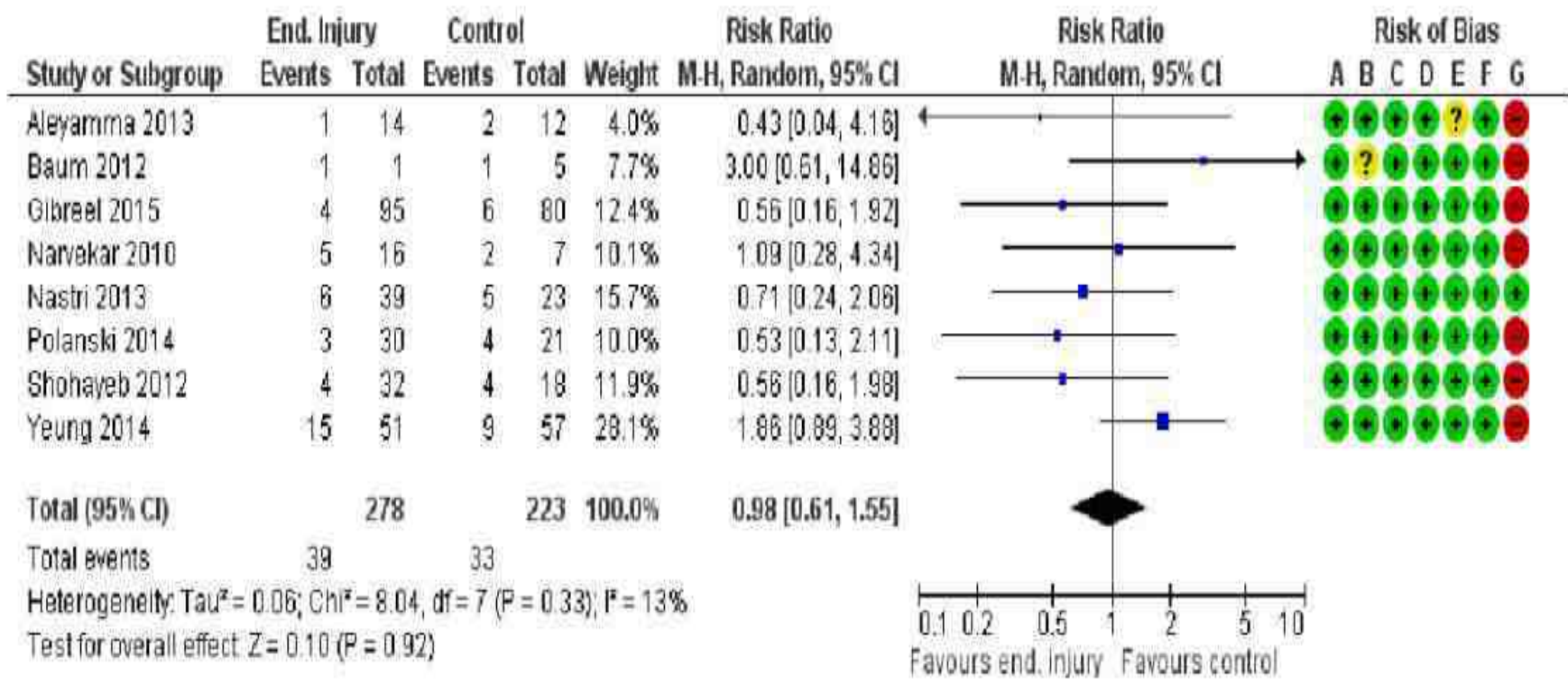


Figure 6. Forest plot of comparison: I Endometrial injury vs no injury, outcome: I.3 Miscarriage per clinical pregnancy.



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Scratching beneath ‘The Scratching Case’: systematic reviews and meta-analyses, the back door for evidence-based medicine

Carlos Simón^{1,2,*} and José Bellver¹

ABSTRACT: Endometrial scratching or injury was first suggested a decade ago as a simple intervention to improve endometrial receptivity in patients undergoing ART. More than a decade later, based on weak evidence some doctors have adopted this strategy, although there is not yet agreement about its real benefit. In this opinion paper, we analyze the methodological and plausibility problem beneath ‘the Scratching Case’. This is also applicable to several other examples of spurious associations reported in the literature. In particular, we emphasize what should be done so as not to dilute evidence-based medicine by a vicious circle created by the over-exploitation of inadequate or insufficient data to compute incorrect or incomplete conclusions.

Peer review is the basis for the creation of solid and trustable knowledge that we can implement in the treatment of our patients. Now, this concept is being tainted and diluted by a vicious circle created by the use of **inadequate or insufficient data** to compute incorrect or incomplete conclusions that are touted as evidence-based medicine, creating confusion instead of clarification.

Endometrial stratching has not proven benefit yet.

This intervention must not be advertised as an established practice to improve implantation until real good data demonstrate that it does and biological plausibility is demonstrated.

Simon C and Bellver J, HR,2014

Early proliferative phase

Demirel and Gurgan 2004

Magrakis et al 2009

Rama Raju et al 2006

Early proliferative and luteal phases

Barash et al 2003

Narvekar et al 2010

Luteal phase

Karimzadeh et al 2009

Raziel et al 2007

Once

Zhou et al, 2008

Shohayep & El-Khayat 2012

Coughlan et al, 2013

Twice

Raziel et.al, 2007(days 21,26)

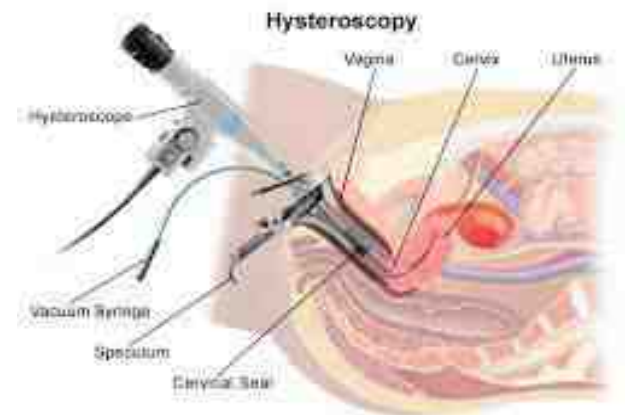
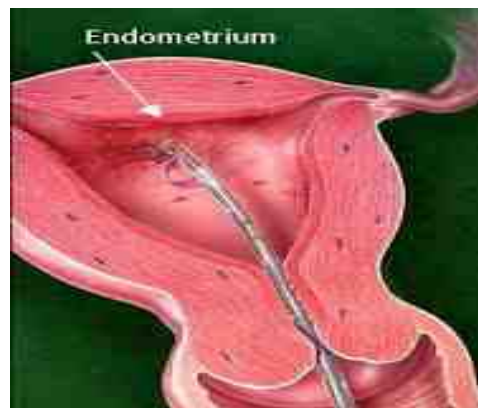
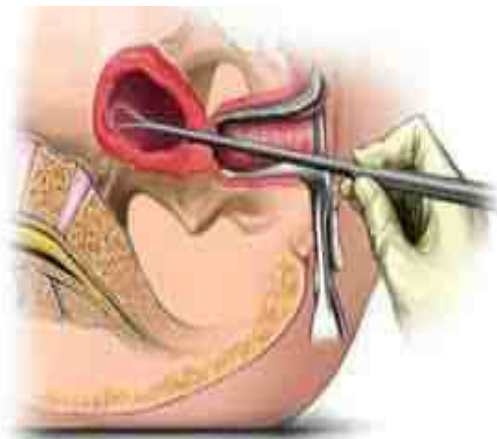
Four times

Barash et al,2003

(days 8,12,21,26)

CONFUSIONS

- Type of injury (biopsi/injury)
- Instrumentation(curette/ pipelle/hysteroscopy)
- Degree of injury (endometrium/myometrium)
- Number of injury
- Localization of injury
- Day /phase of menstruel cycle
- Time between endometrial injury and embryo transfer cycle
- Unselected population or previous failures



Our Technique :

- Symmetric, systematic Injury on the fundus
 - a. One transverse incision
 - b. Symmetric vertical incisions (6-8) around line
- Hysteroscopy
- Follicular phase
- Previous cycle before ET
- RIF



Our RIF criteria:



Recurrent implantation failure: definition and management

C Coughlan ^a, W Ledger ^b, Q Wang ^c, Fenghua Liu ^d, Aygul Demiroglu ^e, Timur Gurgan ^e, R Cutting ^a, K Ong ^f, H Sallam ^g, TC Li ^{a,*}

RIF(Recurrent Implantation Failure):

Failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years.

Systematic and standardized hysteroscopic endometrial injury for treatment of recurrent implantation failure (RIF): Preliminary results of prospective and randomized trial.

Timur Gürkan¹, Ziya Kalem¹, Işın Kocabaş¹, Müberra Namlı Kalem², Halil Ruso¹, Antonis Makrigiannakis³

1: Gürkan Clinic Women's Health and IVF Centre, Ankara, Turkey.

2:Turgut Özal University Hospital, Department Obstetrics and Gynecology, Ankara, Turkey.

3: University of Crete, Department of Obstetrics and Gynecology, Crete, Greece

Purpose: To investigate the effect of hysteroscopic symmetrical endometrial injury for RIF patients.

Method: This is a prospective and randomized controlled trial for RIF patients investigating the effect of systemic and symmetric endometrial injury using office hysteroscopy. Endometrial injury was performed on the follicular phase of the menstrual cycle under general anesthesia. The main variant analyzed was the clinical pregnancy rates. Statistical calculations were performed on GraphPad Prism version 6.0 and $p < 0.05$ were considered statistically significant.

Findings: Following randomized controlled trial we propose that the systemic endometrial injury model can be standardized to increase the odds of implantation in RIF patients to achieve clinical pregnancy.



Systematic and standardized hysteroscopic endometrial injury for treatment of recurrent implantation failure (RIF): Preliminary results of prospective and randomized trial.

Gurgan et al.

	Control (n=40)	Injury (n=44)
Average female age	30.76	33.48
Av. BMI	23.28	24.35
Av. No of previous cycles	3.57	3.57
Av. No of cumulative ET	6.29	6.26
Av. No of COCs	6.17	6.51
Av. No of MII eggs (%)	73.81	77.12
Av. Fertilisation rate (%)	96.53	89.24
Average ET day	3.14	3.09
Av. no of embryos transferred	1.9	2.02
Av. Endometrial thickness on hCG day	10.33	9.46
Injury Performed	NO	YES
Av. cycle day of Injury	-	10.86
Av. time from Injury to ET (days)	-	56.02
Clinical Pregnancy	17.50%	40.91% (p=0.02)

