Università degli Studi di Padova - Dipartimento di salute della Donna e del Bambino
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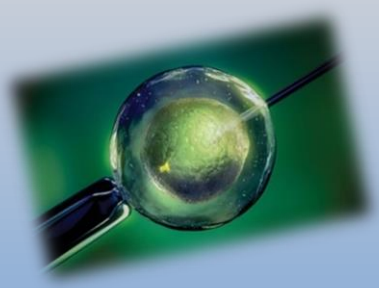


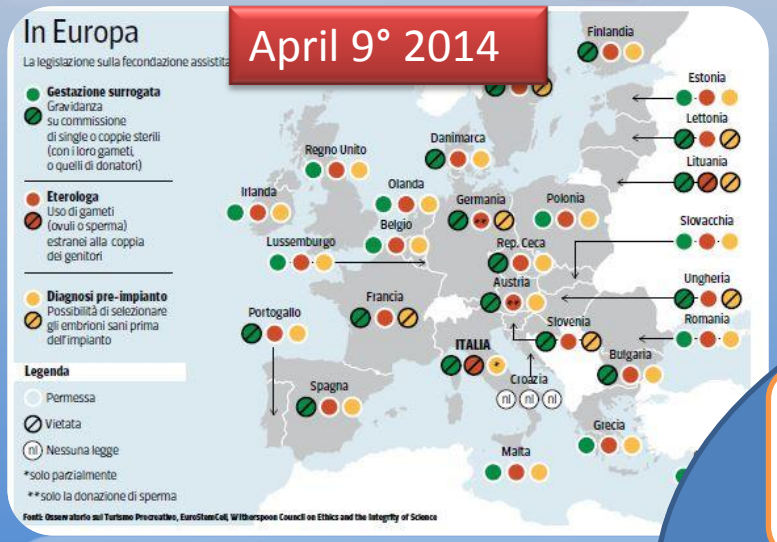

# CHRONIC ENDOMETRITIS:

# A NEW POSSIBLE EXPLANATION FOR UNEXPLAINED INFERTILITY AND REPEATED IMPLANTATION FAILURES?

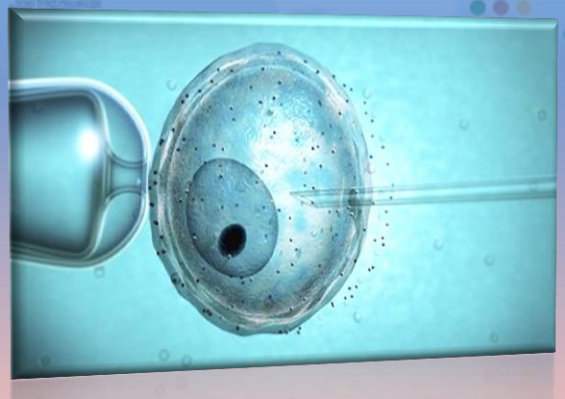
Dott. A. Vitagliano








April 9° 2014



PRE IMPLANTATION GENETICS

FREEZE ALL

SINGLE EMBRYO TRANSFER

UTERINE TRANSPLANTATION

EEVA

DOUBLE STIMULATION

ERA

ENDOMETRIAL REGENERATION

OVARIAN PRESERVATION

Journal of Reproduction & Infertility
Avicenna Research Institute

# Unexplained Infertility, the Controversial Matter in Management of Infertile Couples

Mohammad Reza Sadeghi, Editor-in-chief

Additional article information

30% of infertile couples worldwide are diagnosed with unexplained or idiopathic infertility and the problem is defined as the lack of an obvious cause for a couple's infertility and the females' inability to get pregnant after at least 12 cycles of unprotected intercourse or after six cycles in women above 35 years of age for whom all the standard evaluations are normal. The veracity of 'unexplained infertility' term has been challenged by many clinicians and researchers; they emphasize that the assignment of this title to an infertile couple is much dependent on the quantity, quality and nature of the applied diagnostic tests (1, 2).

According to the ESHRE guidelines, necessary tests for unexplained infertility are semen analysis, assessment of ovulation and the luteal phase, and assessment of tubal patency by hysterosalpingogram or laparoscopy.

However, there are controversial opinions about the value of endometrial biopsy, ovarian reserve (AMH, AFC), post-coital test and serum prolactin levels.

there is no cause for the disorder. Extensive research should be conducted

Management of infertile couples with idiopathic cause needs individualized treatment. Several key variables including age, infertility history, treatment history, costs, and risks should be considered in selection of the suitable treatment plan.

selection of the suitable treatment plan.

The rate of spontaneous conception in these couples is more than the couples with defined causes of infertility and several studies have reported that the rate of spontaneous pregnancy was 13-15% during the first year of attempt which increased to 35% during the next two years of attempt. Moreover, the rate could reach 80% in younger couples during the

rs of unprotected intercourse without any adjuvant

spontaneous pregnancy drastically declines with

of more than 3 years and in women over 30 years of

ral mathematical models such as Hunault's prog


# Diagnosis and Management of Female Infertility

2003

Samuel Smith, MD
Samantha M. Pfeifer, MD
John A. Collins, MD

**Table.** Distribution of Primary Diagnoses in 2198 Infertile Couples and Live Birth Rate by Diagnoses*

| | No. (%) | Live Birth Rate of Patients in Group, %† |
|---|---|---|
| Female factors | | |
| Ovulation disorders | 386 (17.6) | 41.5 |
| Oligomenorrhea | 294 (13.4) | 42.5 |
| Amenorrhea | 40 (1.8) | 47.5 |
| Hyperprolactinemia | 52 (2.4) | 30.8 |
| Tubal disease | 509 (23.1) | 21.8 |
| Complete obstruction | 212 (9.6) | 14.2 |
| Other | 297 (13.5) | 27.3 |
| Endometriosis | 146 (6.6) | 29.5 |
| Stage I and II | 93 (4.2) | 36.6 |
| Stage III and IV | 53 (2.4) | 17.0 |
| Male factors | | |
| Oligospermia | 369 (16.8) | 29.8 |
| Azoospermia | 156 (7.1) | 34.6 |
| Unexplained | 562 (25.6) | 32.2 |
| Other‡ | 70 (3.2) | 41.4 |

*Data based on Collins et al.[3]
†Live birth rate includes treatment-related and treatment-independent conceptions.
‡Luteal phase defect (n = 38), cervical defect (n = 17), and uterine defect (n = 15).

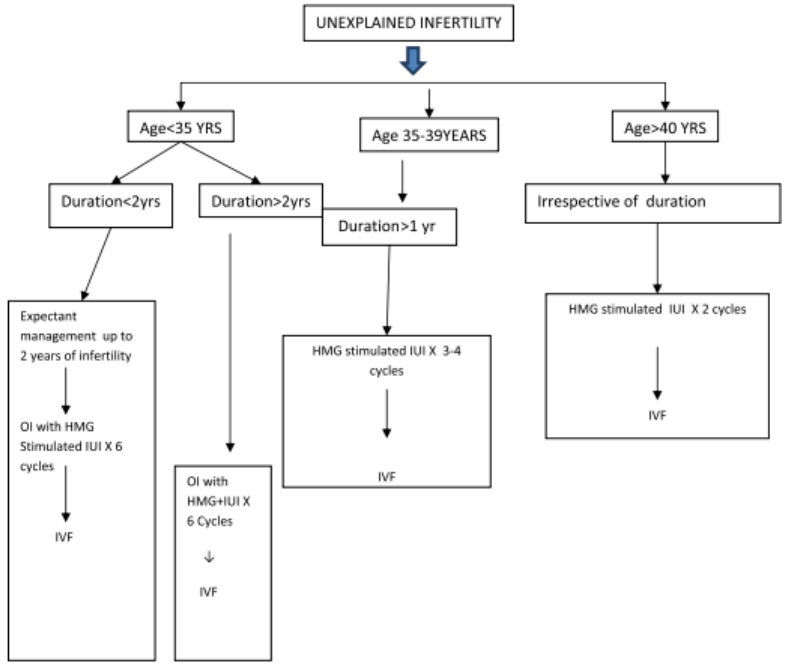
In summary, a uniform definition for unexplained infertility is needed. There is need for research to identify more subtle causes of infertility. The best approach to the management of the couple should be based upon the availability of resources, the age of the patient and the duration of infertility.

There is need for multicentre randomized controlled trials for different modalities of treatment in unexplained infertility.

## Unexplained infertility: an update and review of practice

2012

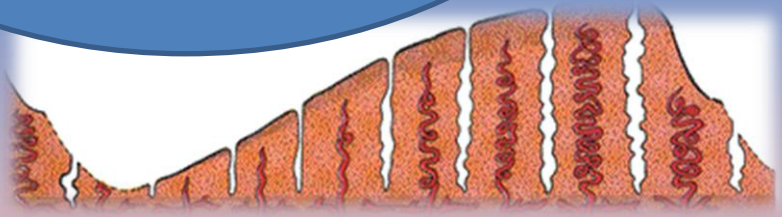
Arpita Ray *, Amit Shah, Anil Gudi, Roy Homburg




***«Need for individualization of treatments, and for clarification…»***

# Understanding causes…



ENDOCRINE SYSTEM

DIET

IMMUNE SYSTEM

GENETIC

?

REPRODUCTIVE PHYSIOLOGY

ENDOMETRIUM

# Assessment and treatment of repeated implantation failure (RIF)

**Alex Simon · Neri Laufer**

Received: 30 June 2012 / Accepted: 5 September 2012 / Published online: 14 September 2012


**Abstract** Repeated implantation failure (RIF) is determined when embryos of good quality fail to implant following several in vitro fertilization (IVF) treatment cycles. Implantation failure is related to either maternal factors or embryonic causes. Maternal factors include uterine anatomic abnormalities, thrombophilia, non-receptive endometrium and immunological factors. Failure of implantation due to embryonic causes is associated with either genetic abnormalities or other factors intrinsic to the embryo that impair its ability to develop in utero, to hatch and to implant. New methods of time-lapse imaging of embryos and assessment of their metabolic functions may improve selection of embryos for transfer, and subsequent outcomes for IVF patients, as well as for those diagnosed with RIF. This review discusses the various causes associated with RIF and addresses appropriate treatments.

**Keywords** Implantation · Recurrent implantation failure · Repeated implantation failure · RIF · In vitro fertilization · IVF failure

## Introduction

Repeated implantation failure (RIF) is determined when transferred embryos fail to implant following several in vitro fertilization (IVF) treatment cycles. However, there are no formal criteria defining the number of failed cycles or the total number of embryos transferred in these IVF attempts. Accordingly, different fertility centers practicing IVF may use different definitions for RIF [93]. Considering the current success rate of IVF treatments and the mean number of embryos transferred in each cycle, we recommend defining RIF as failure of implantation in at least three consecutive IVF attempts, in which 1–2 embryos of high grade quality are transferred in each cycle.

*Capsule* Successful implantation depends on well functioning endometrium and healthy embryo. An abnormality in one or both these variables can cause repeat implantation failure. The condition should be assessed for its different causes and be treated accordingly.

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The process of implantation involves two main components, a healthy embryo that should have the potential to implant and a receptive endometrium that should enable implantation. The "cross-talk" between the embryo and the endometrium that finally leads to apposition, attachment, invasion of embryos is mandatory for successful implantation and subsequent normal placentation. These processes are under thorough investigation and seem to involve mediators originating in the embryo, as well as in the endometrium, and to also involve the maternal immune system [1, 37, 42]. Any abnormality attributed to the embryo, the endometrium or the immune system will result in implantation failure. Therefore, in assessing RIF, the embryo should be evaluated, with reference to the uterus and functional endometrium. Accordingly, treatment should be targeted to the abnormality detected, and correction of any potential malfunction that might contribute to the failure of implantation [61, 93].

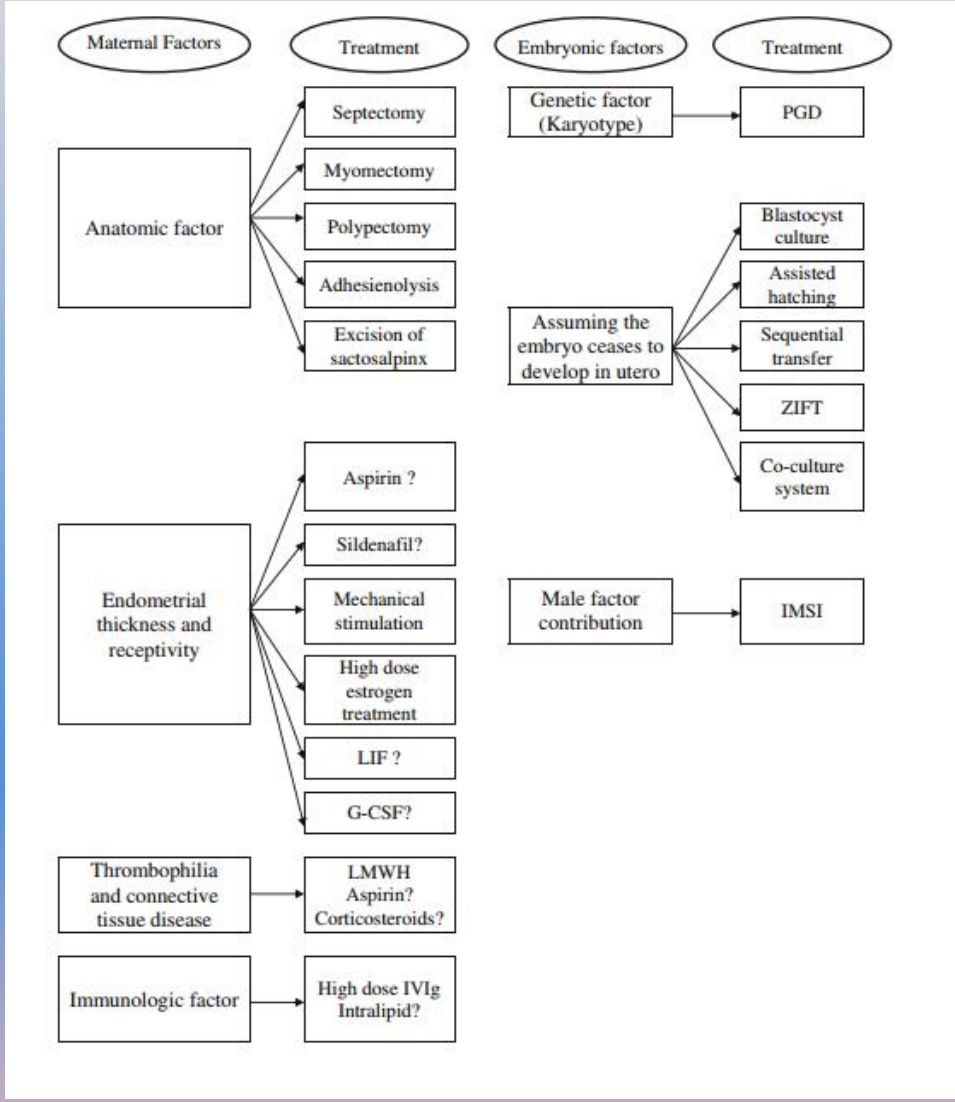
Figure 1 represents a clinical approach for assessing and treating RIF. We set out to investigate maternal factors (including, but not limited to, factors relating to the endometrium) and embryonic factors that contribute to RIF. Treatment should be targeted according to the maternal and embryonic factors that are present, or that are considered to be potentially associated with RIF.

fertilization (IVF) treatment cycles. However, there are no formal criteria defining the number of failed cycles or the total number of embryos transferred in these IVF attempts. Accordingly, different fertility centers practicing IVF may use different definitions for RIF [93]. Considering the current success rate of IVF treatments and the mean number of embryos transferred in each cycle, we recommend defining RIF as failure of implantation in at least three consecutive IVF attempts, in which 1–2 embryos of high grade quality are transferred in each cycle.

| Author | Number of ET * | Number of embryos ** |
|---|---|---|
| Coulam, 1995 | several | 12 |
| Tan et al., 2005 | 2-6 | ≥10 |
| PGD Consortium | ≥3 | ≥10 |
| Margalioth et al., 2006 | 3 | 3 |
| Rinehart, 2007 | several | ≥8<br>8-cell embryos<br>≥5 blastocysts |
| Coughlan et al., 2014<br>woman under the age of 40 years | ≥3 | 4 |

MATERNAL FACTORS

- ANATOMY
- ENDOMETRIUM
- THROMBOPHILIA
- IMMUNOLOGY




EMBRYONIC FACTORS

- GENETICS
- UNEVOLUTION
- MALE FACTOR

# CASE REPORT

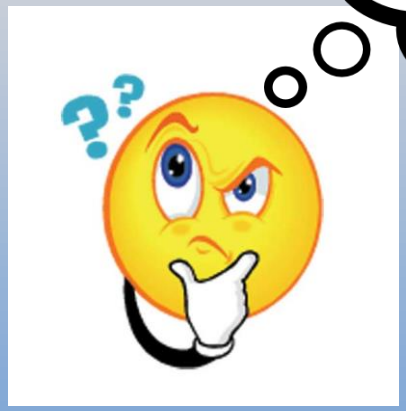
**3 years of infertility**

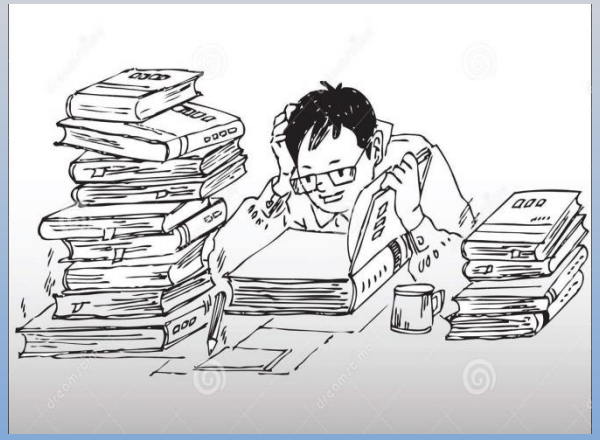
- 39 years, BMI 24
- Familiarity for endometriosis (I dg)
- No previous major surgery, no systemic disease and chronic drugs assumption
- Smoking 10 cig/day in last 20 yrs
- CUC after internal abortion in 2012
- Recurrent cystitis

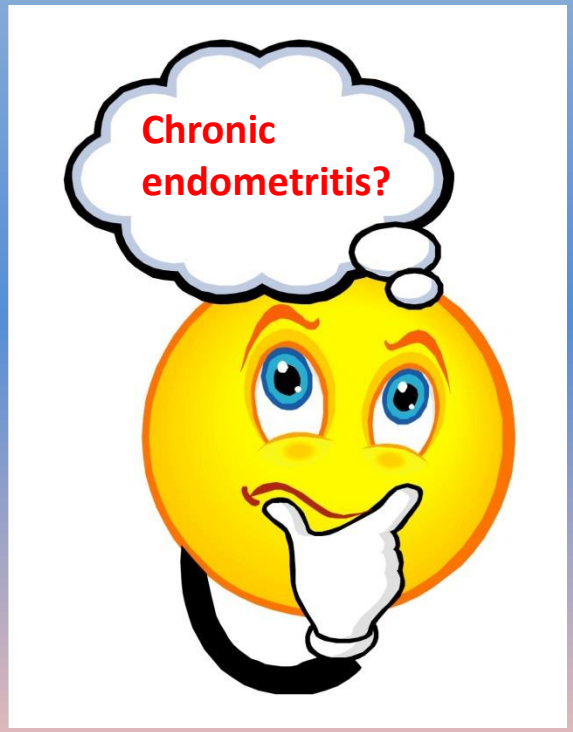
- 42 years, BMI 26
- Familiarity for Type II diabetes (I dg)
- No testicular trauma or surgery, no systemic disease and chronic drugs assumption
- Smoking 20 cig/day in last 25 yrs
- Inguinal ernia repair in 2005

- Day 3 FSH 5 IU/ml, E2 120 pg/ml, AMH 1.9 mg/ml
- AFC 15
- Tubal patency test regular (SHSG)
- Normal karyotype
- Coagulation screening regular
- CFTR regular
- Mycropolipoid endometrium at HSC
- 2 previous IVF failures (5 good quality embryos)
- Negative cervico-vaginal swab

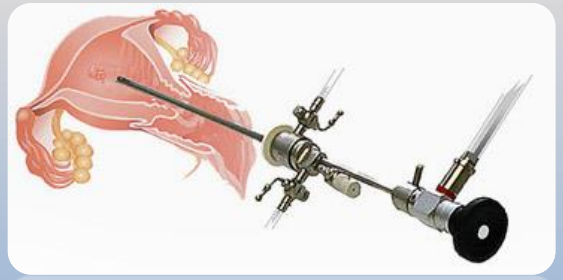
- Hormonal assessment regular
- Normal karyotype
- CFTR regular
- Seminogram within the normal range
- Scrotal ultrasound negative
- Negative Uretral swab and seminal culture

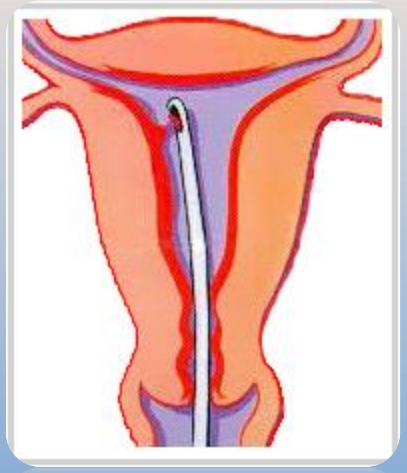

Micropolypoid endometrium…

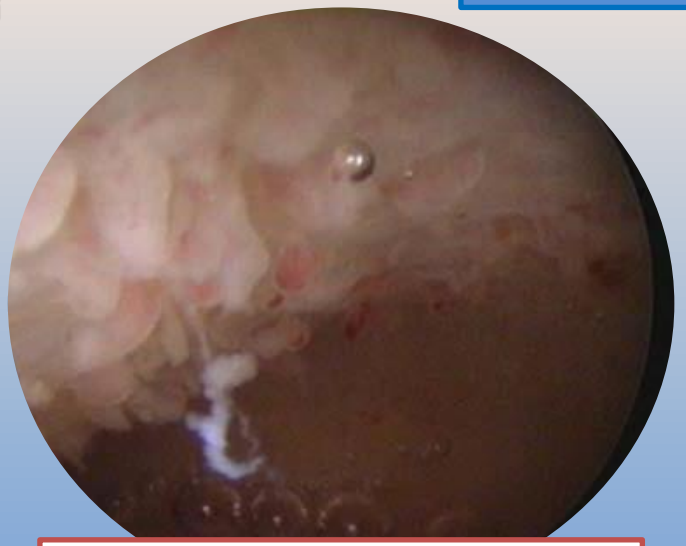



Chronic endometritis?









Mycropolipoid endometrium

Staphilococcus hominis

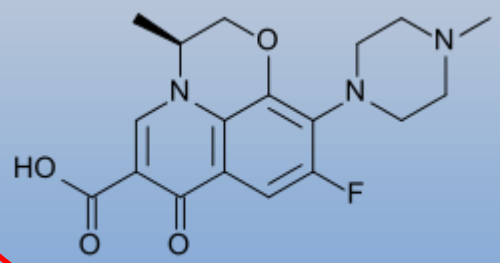
Organismo selezionato: Staphylococcus hominis ssp hominis

Informazioni sull'antibiogramma

| Antimicrobico | MIC | Interpretazione | Antimicrobico | MIC | Interpretazione |
|---|---|---|---|---|---|
| Cefoxitina screening | | | Teicoplanina | 2 | S |
| Benzilpenicillina | | | Vancomicina | 1 | S |
| Oxacillina | >= 4 | R | Tetraciclina | 4 | R |
| Gentamicina | 1 | *R | Tigeciclina | <= 0,12 | S |
| Levofloxacina | <= 0,12 | S | Fosfomicina | | |
| Resistenza inducibile alla Clindamicina | NEG | - | Acido fusidico | 1 | S |
| Eritromicina | >= 8 | R | Mupirocina | | |
| Clindamicina | <= 0,12 | S | Rifampicina | <= 0,03 | S |
| Linezolid | 1 | S | Trimetoprim/Sulfametossazolo | <= 10 | S |
| Daptomicina | 0,25 | S | | | |

+= Antibiotici dedotti *= Modificato AES **= Modificato utente

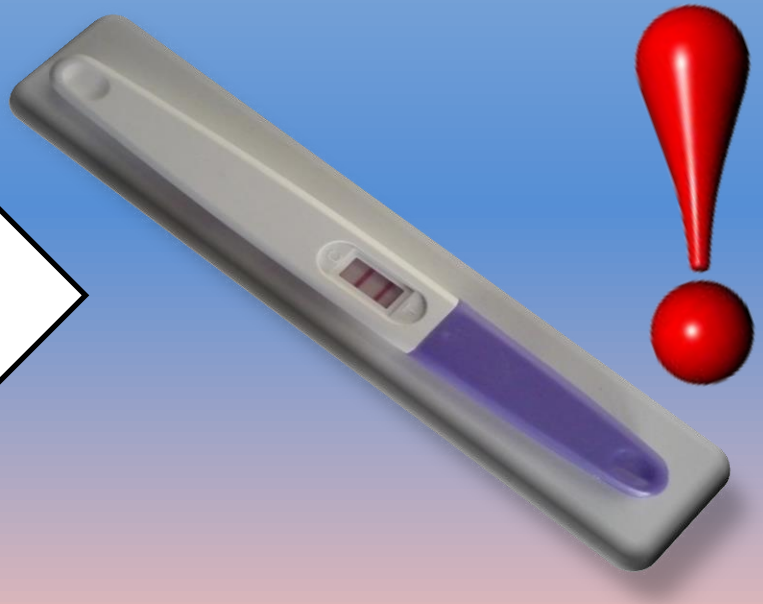
Levoxacin for 10 days…



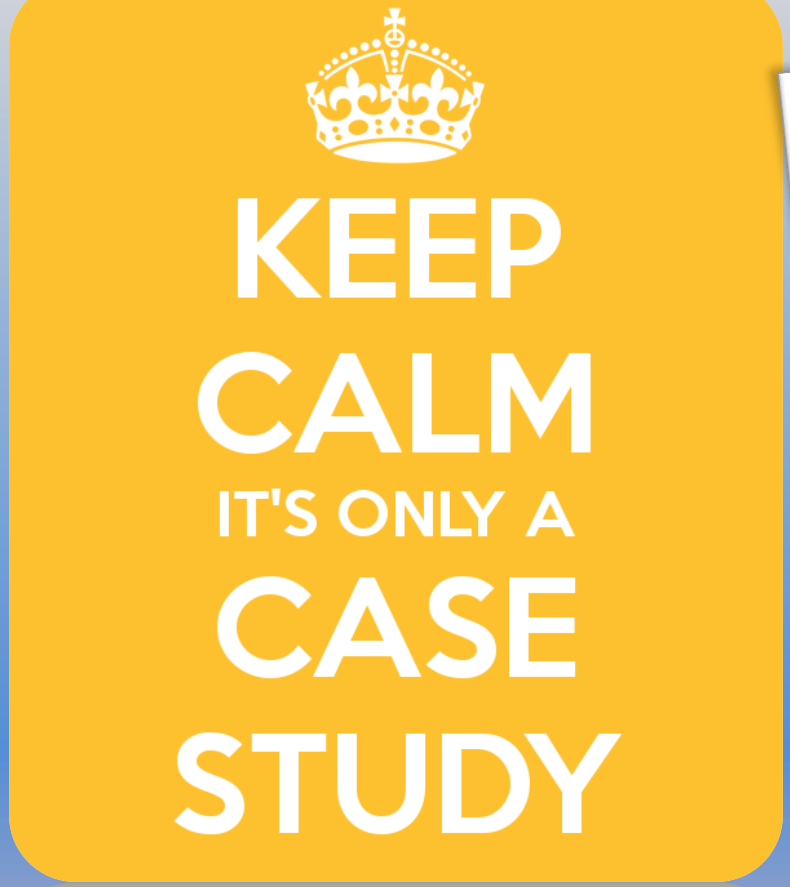

Regular endometrium

- Next moth patient underwent her 3° IVF cycle
- A short Gn-RH antagonist flexible protocol was chosen
- R-FSH was administered for COH
- R-HCG was chosen for ovulation induction

15 days later






KEEP
CALM
IT'S ONLY A
CASE
STUDY


But...


THAT'S
NOT WHAT
RANDOM
MEANS

REVIEW

# Bridging endometrial receptivity and implantation: network of hormones, cytokines, and growth factors

**Mohan Singh, Parvesh Chaudhry** and **Eric Asselin**

Research Group in Molecular Oncology and Endocrinology, Department of Chemistry-Biology, University of Quebec, Trois-Rivieres, 3351, Boulevard Des Forges, CP 500, Trois-Rivieres, Quebec G8Y 5H7, Canada

(Correspondence should be addressed to E Asselin; Email: eric.asselin@uqtr.ca)

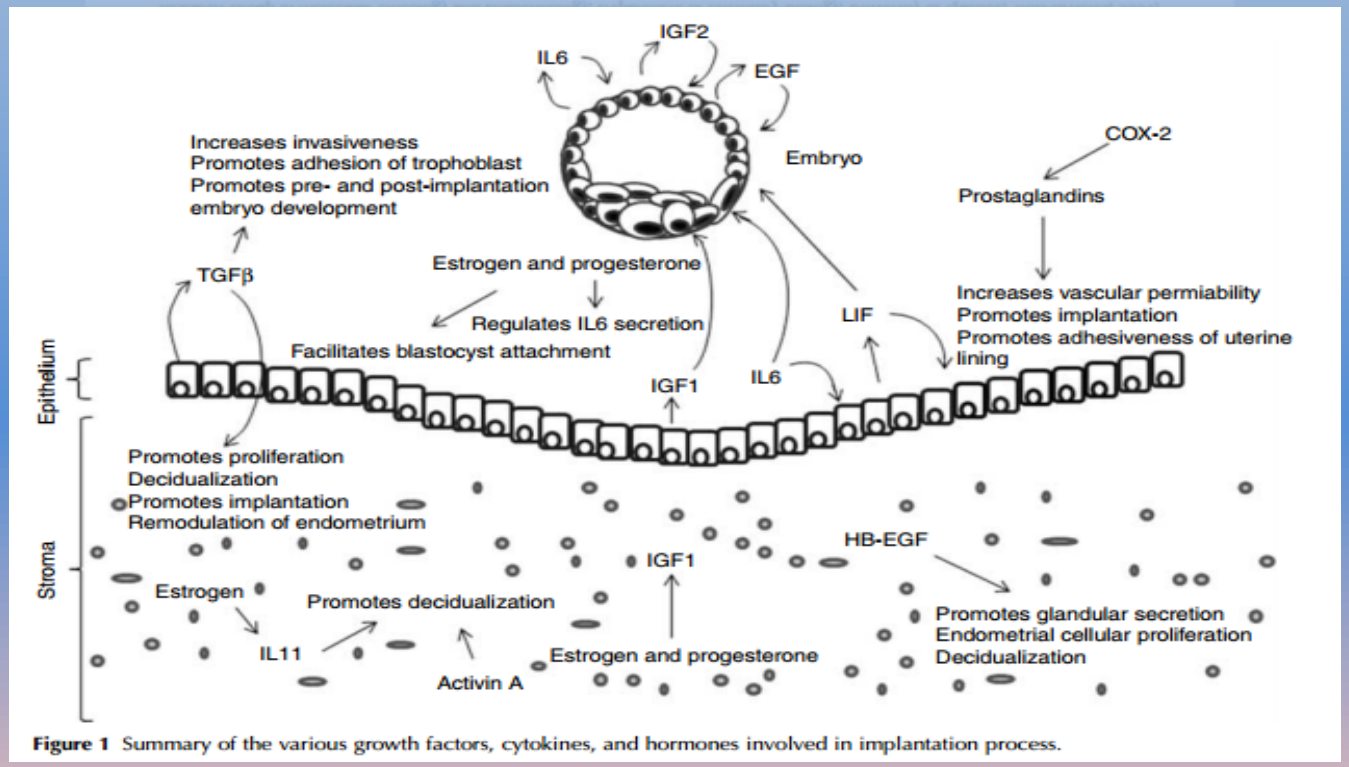



**Figure 1** Summary of the various growth factors, cytokines, and hormones involved in implantation process.

DIALOGUE

APPOSITION

ATTACHMENT

INVASION



# Sistematic Review

**Poor Reliability of Vaginal and Endocervical Cultures for Evaluating Microbiology of Endometrial Cavity in Women with Chronic Endometritis**

Ettore Cicinelli[a] Dominique De Ziegler[d] Roberto Nicoletti[a] Raffaele Tinelli[a] Nicola Saliani[a] Leonardo Resta[b] Marina Bellavia[a] Danila De Vito[c]

Departments of [a]Obstetrics and Gynaecology, [b]Pathology and [c]Odontostomatology and Surgery, Faculty of Medicine, University of Bari, Bari, Italy; [d]Department of Reproductive Medicine, University of Geneva, Geneva, Switzerland

**Detection of chronic endometritis at fluid hysteroscopy**

Ettore Cicinelli, MD, Leonardo Resta, MD, Roberto Nicoletti, MD, Massimo Tartagni, MD, Marco Marinaccio, MD, Carlo Bulletti, MD, and Giuseppe Colafiglio, MD

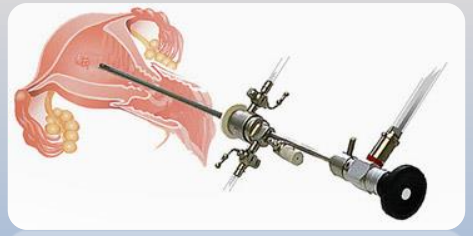
## Introduction

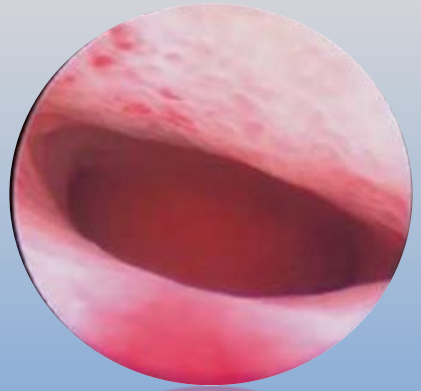
Chronic endometritis (CE) is a persistent inflammation of the endometrial lining, which may be asymptomatic or accompanied by mild symptoms including pelvic pain, abnormal uterine bleeding (AUB), dyspareunia and vaginal discharge [1–3]. Although symptoms of CE may remain moderate, it can have serious consequences for reproductive potential, with endometrial infection altering the chances of conceiving either spontaneously or after IVF treatment [4, 5]. Moreover, CE is a well-recognized cause of spontaneous preterm labor and delivery [6–11].

Diagnosis of CE is a challenging issue however, as there are no typical findings at clinical examination or during ultrasound investigation. Diagnosis of CE relies on histol-

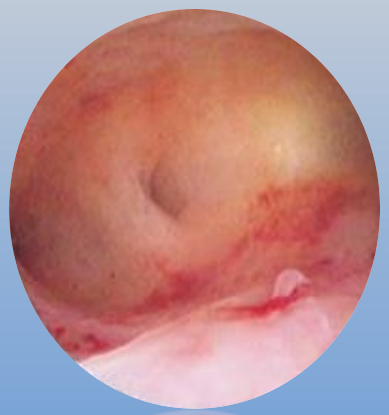
Chronic endometritis is a subtle condition that may cause abnormal uterine bleeding (AUB) and infertility.[1,2]

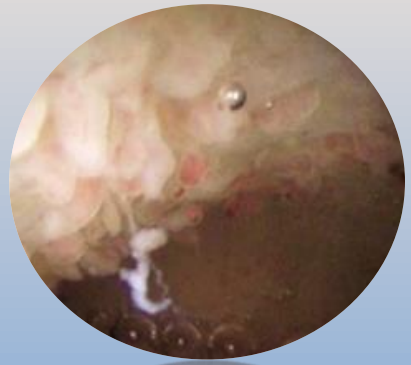
Clinically, chronic endometritis in most cases is asymptomatic or accompanied by mild disturbances like spotting, mild and undefined pelvic pain, and leukorrhea.[1,2] Vaginal bleeding is reported to be the major presenting symptom in up to 94% of patients with chronic endometritis.[2] Chronic endometritis may have severe reproductive consequences on fertility in spontaneous as well as in vitro fertilization (IVF) cycles.[1]

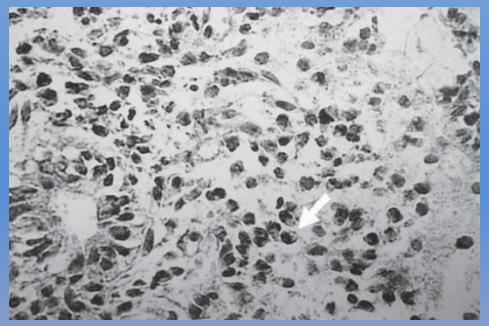


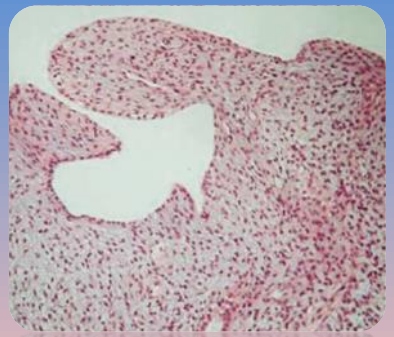


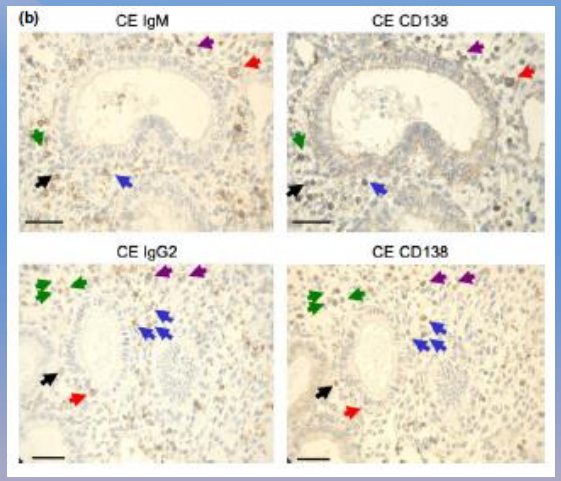
**Edema, hyperemia, mycropolyps, hyperemia**











Human Reproduction, Vol.30, No.2 pp. 323–330, 2015
Advanced Access publication on November 10, 2014 doi:10.1093/humrep/deu292

human reproduction ORIGINAL ARTICLE *Infertility*

# Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy

Ettore Cicinelli[1,*], Maria Matteo[2], Raffaele Tinelli[3], Achiropita Lepera[1], Raffaello Alfonso[1], Ugo Indraccolo[4], Sonia Marrocchella[2], Pantaleo Greco[2], and Leonardo Resta[5]

**Table I** Infectious agents found in endometrial cultures from 48 women with RIF.

| | No–(%) |
|---|---|
| *Enterococcus faecalis | 16–(33) |
| Mycoplasma/Ureaplasma | 14–(30) |
| *Escherichia coli | 11–(23) |
| *Streptococcus agalactiae | 5–(10) |
| Chlamydia | 4–(8) |
| Streptococcus bovis | 2–(4) |
| Candida | 1–(2) |
| Klebsiella pneumoniae | 1–(2) |
| Staphylococcus epidermidis | 1–(2) |
| Staphylococcus aureus | 1–(2) |
| Streptococcus milleri | 1-(2) |

Forty patients tested positive for a single agent and had multiple positivity. In three cases ureaplasma and common bacteria coexisted.
*Infectious agents with persistent positivity.

**Table II** Clinical characteristics of women, number of previous IVF attempts and results in terms of implantation rate, clinical pregnancy rate, live birth rate (LBR) and number of miscarriages at the first IVF attempt within 6 months after treatment.

| | Group 1 ($n$ = 46) | Group 2 ($n$ = 15) | $P$-value |
|---|---|---|---|
| Age (years) | 31.7 ± 4.2 | 32.0 ± 4.6 | NS |
| Partner age (years) | 33.9 ± 5.4 | 34.6 ± 4.7 | NS |
| BMI (Kg/m$^2$) | 23.0 ± 1.9 | 22.9 ± 2.1 | NS |
| Smokers (%) | 26 | 27 | NS |
| FSH day 3 mUI/ml | 7.1 ± 1.6 | 7.1 ± 1.7 | NS |
| No. of previous IVF attempts | 4.1 ± 1.0 | 4.1 ± 0.9 | NS |
| No. of embryos transferred | 1.95 ± 0.5 | 1.93 ± 0.4 | NS |
| No. of good quality embryos transferred | 1.3 ± 0.4 | 1.4 ± 0.5 | NS |
| Implantation rate (%) | 37 | 17 | NS |
| Clinical pregnancy rate at first IVF after treatment (%) | 65 | 33 | 0.039* |
| LBR at first IVF after treatment (%) | 61 | 13 | 0.02* |
| First trimester miscarriage (%) | 4 | 20 | NS |

Data are expressed as means ± SD unless stated otherwise. The limit of significance is a $P$ value ≤ 0.05.

## Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization

*Erika B. Johnston-MacAnanny, M.D.,[a] Janice Hartnett, M.D.,[b] Lawrence L. Engmann, M.D.,[a] John C. Nulsen, M.D.,[a] M. Melinda Sanders, M.D.,[c] and Claudio A. Benadiva, M.D.[a]*

**Conclusion(s):** Recurrent implantation failure warrants investigation of CE as a contributing factor. Women demonstrating CE on endometrial sampling have lower implantation rates in a subsequent IVF-ET cycle; however, there were no differences in subsequent clinical pregnancy or ongoing pregnancy rates after successful antibiotic treatment. (Fertil Steril® 2010;93:437–41. ©2010 by American Society for Reproductive Medicine.)

## The impact of chronic endometritis on reproductive outcome

*Jenneke C. Kasius, M.D.,[a] Human M. Fatemi, M.D., Ph.D.,[d] Claire Bourgain, M.D., Ph.D.,[e] Daisy M. D. S. Sie-Go, M.D., Ph.D.,[b] René J. C. Eijkemans, Ph.D.,[c] Bart C. Fauser, M.D., Ph.D.,[a] Paul Devroey, M.D., Ph.D.,[d] and Frank J. M. Broekmans, M.D., Ph.D.[a]*

**Conclusion(s):** Chronic endometritis can be rarely diagnosed in a population of asymptomatic infertile patients with a normal TVS before a first IVF/ICSI treatment. Moreover, the reproductive outcome after initiation of IVF/ICSI was not found to be negatively affected by chronic endometritis. In conclusion, the clinical implication of chronic endometritis seems minimal. (Fertil Steril® 2011;96:1451–6. ©2011 by American Society for Reproductive Medicine.)

Debate is open….



ORIGINAL ARTICLE: EARLY PREGNANCY

# Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise

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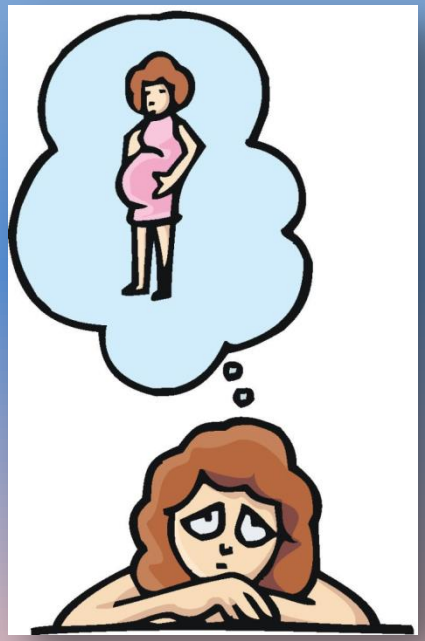



# *Grazie per l' attenzione*