Recurrent Implantation Failure

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Implantation Failure

≥ 10 good quality embryos

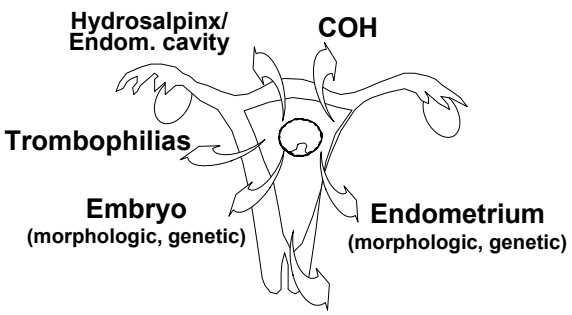
Tan et al. 2005
ESHRE PGD Consortium 2002

≥3 ET w/o pregnancy in women < 37 years

or

≥2 ET w/o pregnancy in women ≥ 37 years

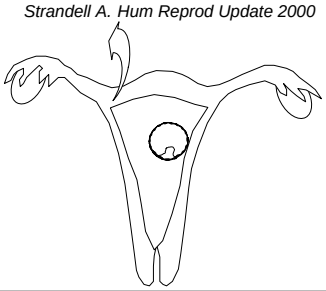
Implantation Failure



Factors involved in IF

Hydrosalpinx: Laparoscopic salpinguectomy previous to IVF is benefitial in patients with ultrasonographic visible hydrosalpinges

Strandell A. Hum Reprod Update 2000



Factors involved in IF

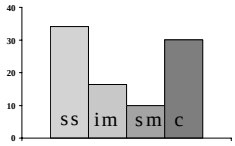
Polyps/submucous myomas / uterine septum

Raga et al. Hum Reprod 1997

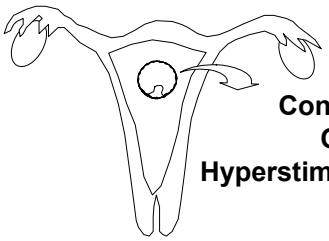
Hysteroscopic resection

Intramural myomas >4 cm

Oliveira et al. Fertil Steril 2004

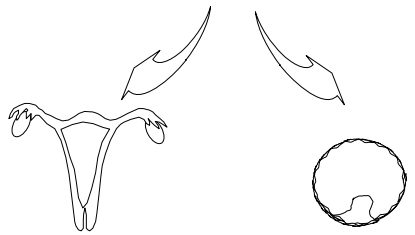


Factors involved in IF



Controlled Ovarian Hyperstimulation

High levels of estradiol

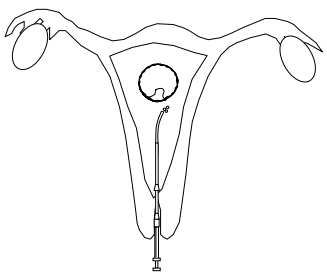


ENDOMETRIUM ? **EMBRYO ?**

Low implantation in high responders

- **Clinical studies showing low IR in high responder patients**
  (Pellicer et al. Hum Reprod 1989; Simón C et al. Hum Reprod 1995; Pellicer at al. Fertil Steril 1996; Valbuena et al, Hum Reprod 1999)
- **Endometrial receptivity but not embryo quality is affected**
  (Simón C et al. Hum Reprod 1995; Valbuena et al, Hum Reprod 1999)
- **Evidence of altered endocrine milieu in the periimplantation period**
  (Pellicer A et al. Fertil Steril 1996)
- **Increased IR when E2 levels were lower in subsequent cycles**
  (Simón C et al. Fertil Steril 1998; 70:234-9)
- **Extremely high E2 levels are embryotoxic for the embryo**
  (Valbuena et al. Fertil Steril 2001)

Factors involved in IF



Embryo transfer technique

Factors involved in IF

EMBRYO TRANSFER "ART"

- **Aspirate cervical mucus**
- **Atraumatic negotiation of cx canal**
- **Mock transfer**
- **Atraumatic ET**
- **US guided**
- **Physician experience**

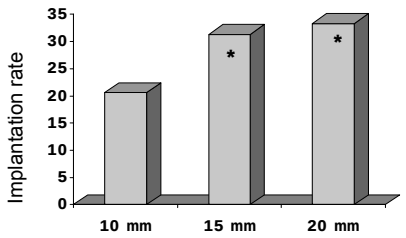
Schoolcraft W et al. Fertil Steril 2001

US guided embryo transfer

Reference	US vs "clinical feel"	p
Coroleu et al, 2000	50 % vs 33.7%	0.002
Prapas et al, 2001	47 % vs 36%	<0.001
Tang et al, 2001	26% vs 23.5%	N.S.
Matorras et al, 2002	26.3% vs 18.1%	< 0.05
Sallam et al, 2002	OR: 1.57 (1.08-2.2)	E.S.
Gª Velasco et al, 2002	59.9% vs 55.1 % (*)	N.S.
Coroleu et al, 2002	34.4 vs 19.7 (**)	< 0.05

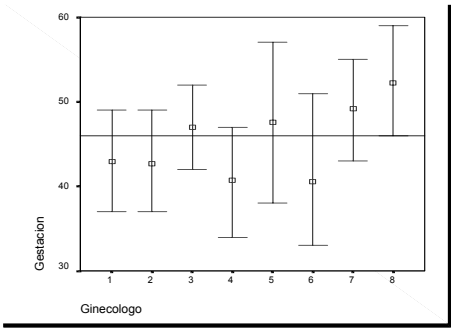
*** egg donation**
**** frozen ET**

Distance to the fundus (n=180 IVF cycles)



Coroleu et al. Hum Reprod 2002

The human factor: the physician (n=1875 tranfers 2005)



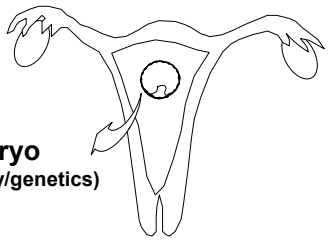
Difficult vs easy ET

- **Meta-analysis of controlled studies**
- **PR 22.3 vs 31.6%**
- **OR 0.74 (0.64 – 0.87)**

Subjective evaluation
Cervical dilation previously
TET in selected cases?

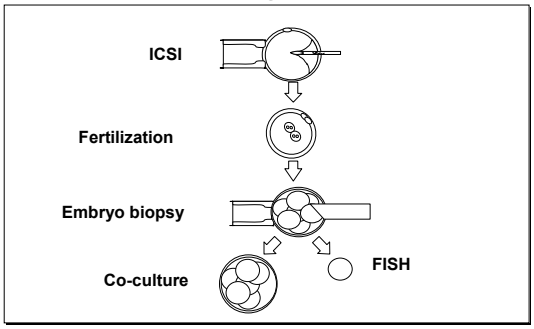
Sadek et al. 2004

Factors involved in IF



Embryo
(morphology/genetics)

Preimplantation Genetic Diagnosis



PGD – AS pitfalls

- Incomplete information
- 4% loss rate
- Embryo quality after biopsy?
- Mosaicism on day 3?
- Poor thawing after biopsy
- Lack of RCT

Platteau et al 2006

PGD – AS in implantation failure

- **n= 22, ≥ 2 failed cycles, 34.8±5.6 years**
- **(chromosomes analyzed X,Y,13,18,21)**
  - **≥ 3 failed cycles: 55% abnormal**
  - **≥ 5 failed cycles: 67% abnormal**
  - **# cells on day 3:**
    - **3-4 cells: 74% abnormal**
    - **5-6 cells: 61% abnormal**
    - **7-8 cells: 41% abnormal**

Gianaroli L et al. Hum Reprod 1997

PGD – AS in implantation failure

- **n= 27 cycles, ≥ 3 failed cycles**
- **138 embryos (X,Y,13,14,15,16,18,21,22)**
  - **Chromosomally abnormal embryos 54%.**
  - **25% PR; 17.3% IR**
  - **monosomy/trisomy ratio:**
    - **3.5:1 in IF**
    - **1:1 in ≥ 36 y.o.**

Gianaroli L et al. Fertil Steril 1999

IF vs. control

	IF	Control
Nº cycles	194	35
Nº analyzed embryos	1158	215
Nº abnormal embryos (%)	**745 (64,3)***	**97 (45,1)**
Mean # ET	1.9 ±0.8	1.8 ±1.3
Reached ET (%)	154 (79,4)	31 (88,6)
PR/ embryo transfer (%)	**40 (32,5)**	**9 (29,0)**
IR	21,4	20,6
Miscarriage (%)	9 (22,5)	0

** p<0.0001 (IF vs. controls)*

High incidence of aneuploidy and mosaicism in embryos of young women

- 60 patients <38 y.o.
- Panel of 10 chromosomes
- 196 embryos analyzed
- ONLY 36% were normal on day 3
- 50% showed mosaicism
- Confirmation rate of 54%

Baart et al. Hum Reprod 2006

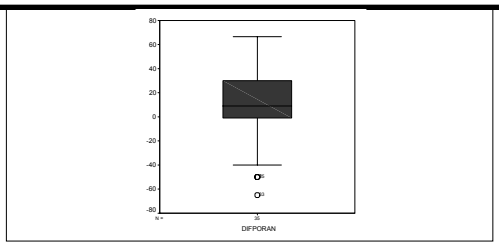
IF <37 years

	IF	Control
Nº cycles	129	15
Nº analyzed embryos	810	111
Nº abnormal embryos (%)	496 (61,2)*	37 (33,3)
Mean # ET	1,9 ±0,7	2,1 ±1,4
Reached ET (%)	107 (83,6)	15 (100)
PR/ embryo transfer (%)	37 (34,6)	7 (46,7)
IR	24,04	32,4
Miscarriage (%)	5 (13,5)	0

** p<0.0001 (IF vs. controls)*

Differences in % abnormal embryos between 1st and 2nd PGD cycle

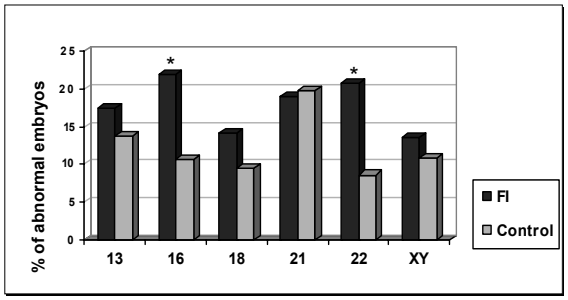
(Boxplot graffic)



IF<37 years: # failed cycles

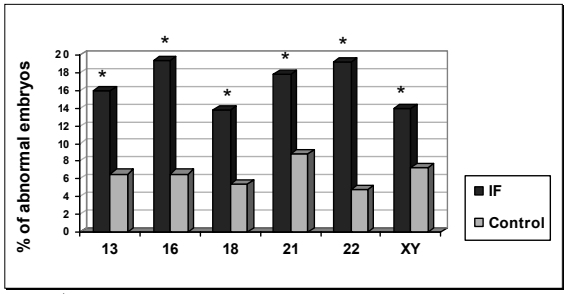
	2-3 cycles	4-6 cycles	≥ 7 cycles
Nº cycles	59	58	10
Nº analyzed embryos	367	368	69
Nº abnormal embryos (%)	220 (59,9)	232 (63,1)	39 (56,5)
Mean # ET	1,9 ±0,7	2,0 ±0,7	2,1 ±0,9
Reached ET (%)	49 (83,0)	50 (86,2)	7 (70,0)
PR/ embryo transfer (%)	18 (36,7)	16 (32,0)	2 (28,6)
IR	26,0	24,2	13,3
Miscarriage (%)	4 (22,2)	1 (6,2)	0

IF vs. controls



*p<0.05 (IF vs. Control)

IF <37 years



*p<0,05 (IF vs. Control)

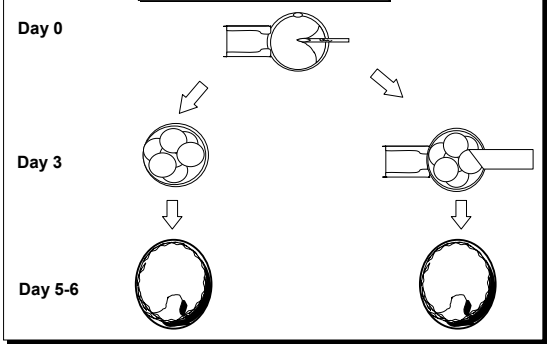
IF: hysteroembryoscopy

9 miscarriages after PGD

<37
- 3 w/o diagnosis
- 1 case 46,XX
- 1 case 46,XY

≥37
- 3 w/o diagnosis
- 1 case 46,XX

Estrategies



Problems:

1) <u>Higher cancellation rate</u>

Evaluate embryo quality on D3
*** ≥ two 8-cell embryos**
Levitas E et al. Fertil Steril 2004
*** ≥ three 7-cell embryos**
de los Santos MJ et al. Placenta 2003

2) <u>Morphology vs chromosomes (discordant)</u>

Add PGD to extended embryo culture

Chromosome abnormalities are reduced during the preimplantation period

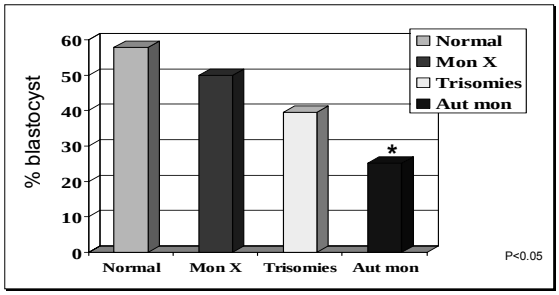
n=216 D5 embryos

- 66% normal embyros reach blastocyst stage
- 37% trisomy
- 9% monosomy
- 21% polyploid
- 0% haploid

reach Blastocyst Stage

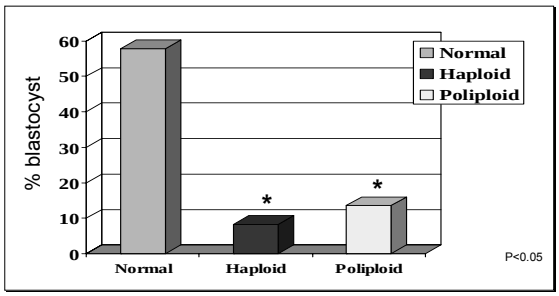
Sandalinas et al. Hum Reprod 2001

Embryo development and chromosomal abnormalities



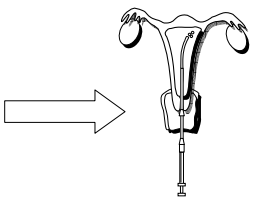
Rubio et al. Hum Reprod 2003

Embryo development and chromosomal abnormalities



Rubio et al. Hum Reprod 2003

Embryo selection



Blastocyst stage ET only partially prevents chromosomally abnormal embryo development

Future

gene arrays focussed on implantation

⇓

Genetic PGD

CGH

CGH vs FISH:

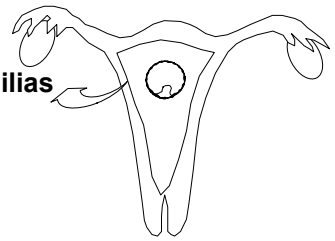
60% incorrect (5)

40% incorrect (9)

Wilton 2005

Factors involved in IF

Trombophilias



Antiphospholipid syndrome

lupus anticoagulant

anticardiolipin

Factor V Leiden

Protein C and S deficiency

Antithrombin III deficiency

MTHFR

Prothrombin G2021OA gene

Hereditary trombophilic gene mutations may have a role in IF, especially in unexplained infertility

Unexplained infertility subgroup (n =21):
61.9 % trombophilias
42.8% w/o C677T MTHFR

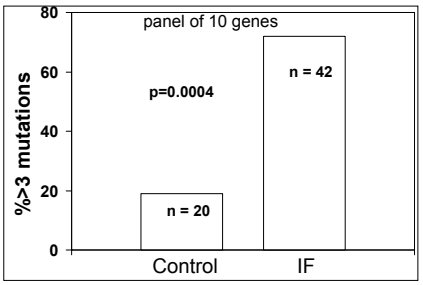
≥ 4 IF (n = 45): 44.4 % trombophilias
(≥ 3 GQE) 26.7 % w/o C677T MTHFR

Healthy (n = 44): 18.2 % thrombophilias
9.1 % w/o C677T MTHFR

DS

Azem et al. Hum Reprod 2004

Multiple trombophilic gene mutations are risk factors for implantation failure



Coulam et al. 2006

Acquired and inherited thrombophilia: implication in recurrent IVF and embryo transfer failure

Hussein S.Qublan[1,7], Suhair S.Eid[2], Hani A.Ababneh[3], Zouhair O.Amarin[4], Aiman Z.Smadi[1], Farakaid F.Al-Khafaji[5] and Yousef S.Khader[6]

Table II. Frequency of thrombophilic factors in the study groups

Thrombophilic factors	Study group	Control group	
	Group A (n = 90)	Group B (n = 90)	Group C (n = 100)
Factor V Leiden			
Heterozygous	9 (10)	1 (1.1)	2 (2)
Homozygous	4 (4.4)	0	0
Methylenetetrahydrofolate reductase (C677T) mutation			
Heterozygous	7 (7.8)	8 (8.9)	9 (9)
Homozygous	13 (14.4)	3 (3.3)	2 (2)
Prothrombin G20210A gene			
Heterozygous	5 (5.6)	3 (3.3)	3 (3)
Homozygous	1 (1.1)	1 (1.1)	0
Protein C deficiency	2 (2.2)	1 (1.1)	0
Protein S deficiency	3 (3.3)	2 (2.2)	3 (3)
Antithrombin III deficiency	1 (1.1)	0	1 (1)
Lupus anticoagulant	8 (8.9)	2 (2.2)	2 (2)
Anticardiolipin	9 (10)	2 (2.2)	3 (3)
Combined thrombophilia	32 (35.6)	4 (4.4)	3 (3)

No evidence for treatment benefit

Assisted Hatching in IF

Poor embryo quality → Blocked → No implantation

AHA+ FA: Effective? IF and AMA

Edi-Osagie E et al. Hum Reprod 2003; 18:1828:35

Magli M et al. Hum Reprod 1998; 13:1331-5

INDICATION:

Chromosomally normal embryos with poor morphologic quality with a high % of arrested embryos

Factors involved in IF

- **23 RCT (2668 women)**
- **Pregnancy rate: OR 1.33 (1.12 . 1.57)**
- **Miscarriage rate: OR 1.23 (0.73 – 2.05)**
- **MPR : OR 1.83 (1.19 – 2.83)**

Not enough evidence to recommend its use (live birth rate)

Seif et al. Cochrane Database Syst Rev 2006

IF: research treatments

- hrLIF
- NK cell tests
- IVIG's infussion
- Allogenic lymphocyte therapy (Th1/Th2)
- ……

Human Reproduction Vol.21, No.12 pp. 3290–3294, 2006 doi:10.1093/humrep/del312
Advance Access publication October 4, 2006

Intrauterine administration of autologous peripheral blood mononuclear cells promotes implantation rates in patients with repeated failure of IVF–embryo transfer

S.Yoshioka[1], H.Fujiwara[1,3], T.Nakayama[1], K.Kosaka[1], T.Mori[2] and S.Fujii[1]

	PBMC treated	Non-treated
Characteristics of the patients		
N	17	18
Age	37.5 ± 4.4	36.6 ± 4.4, n.s.
Number of IVF–embryo transfer previous attempts	5.76 ± 2.5	5.2 ± 1.4, n.s.
Endometrial thickness (mm) on day of oocyte retrieval	9.59 ± 1.47	10.7 ± 1.97, n.s.
Number of embryos transferred	2.76 ± 0.56	2.72 ± 0.58, n.s.
Number of good quality embryos	1.65 ± 0.70	1.50 ± 0.71, n.s.
Clinical outcome		
Clinical pregnancy rate	41.2% (7/17)	11.1% (2/18) ($P = 0.042$)
Implantation rate	23.4% (11/47)	4.1% (2/49) ($P = 0.011$)
Live birth rate	35.3% (6/17)	5.5% (1/18) ($P = 0.028$)

Clinical Management of Implantation Failure

at IVI

Transvaginal US → ↓ Hysteroscopy →	Hydrosalpinx Submucous myo. or >3 cm Endometrial polyp Uterine septum Sinechiae	Salpinguectomy Myomectomy Polypectomy Resection Adhesiolysis
Maternal chromosome	High order IF	PGD/ Egg donation
Trombophilias	APCR, FVL, AT, prot. C &S, MTHFR & f II, APS	Anticoagulation Folic ac.+B12+B6
COH (GnRH antag, step-down)	Hyperresponder → Low or no responder →	Cryopreservation HRT frozen cycle Egg donation
Gamete quality	Poor	Gamete donation
Embryo quality	Poor → Good →	Fragment asp + AHA Gamete/embryo donation Blastocyst after PGD
Delicate ET	Difficult	Cx hysteroscopy
Failed gamete/embryo donation: Surrogacy / alternative therapies		

IVI MADRID

Thank you!