THE ART AND PREGNANCY OUTCOME IN PATIENTS WITH DIMINISHED OVARIAN RESERVE

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AGE DISTRIBUTION (YEARS) OF WOMEN TREATED WITH IVF AND ICSI

Data generated from European registers by ESHRE

2002 – 2003 - 2004

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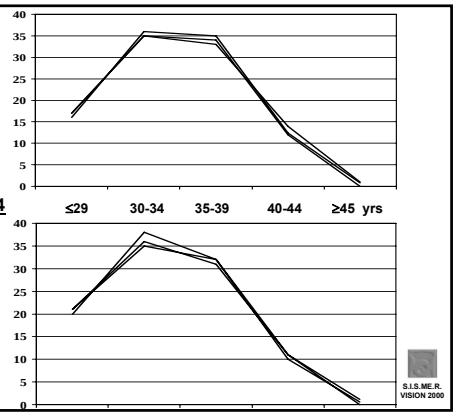
TOTAL



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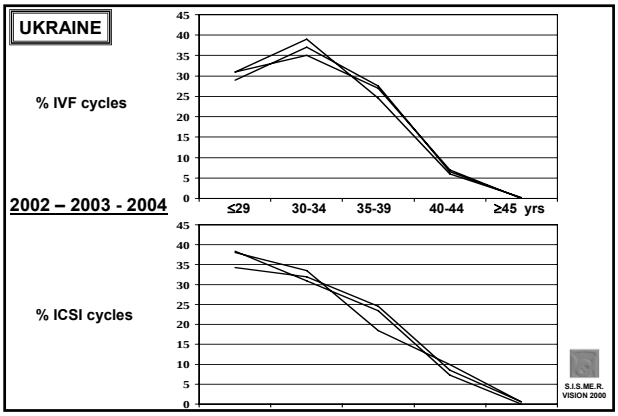
UKRAINE
% IVF cycles
2002 – 2003 - 2004
% ICSI cycles
≤29
30-34
35-39
40-44
≥45 yrs
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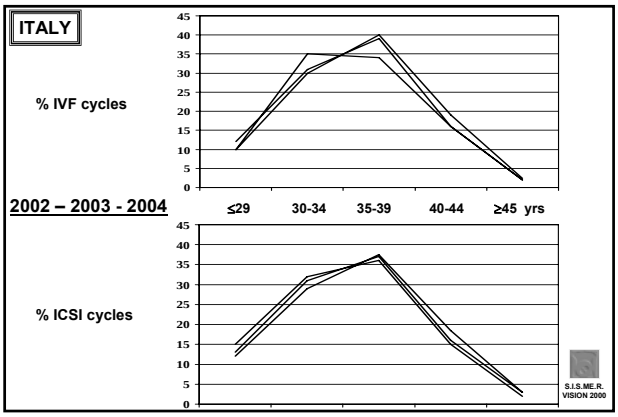
ITALY
% IVF cycles
2002 – 2003 - 2004
% ICSI cycles
≤29
30-34
35-39
40-44
≥45 yrs
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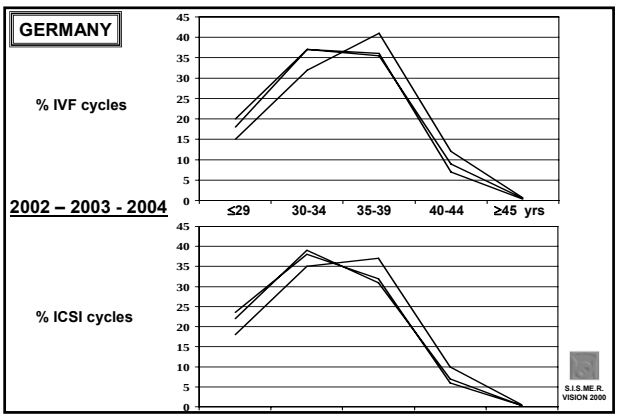
GERMANY
% IVF cycles
2002 – 2003 - 2004
% ICSI cycles
≤29
30-34
35-39
40-44
≥45 yrs
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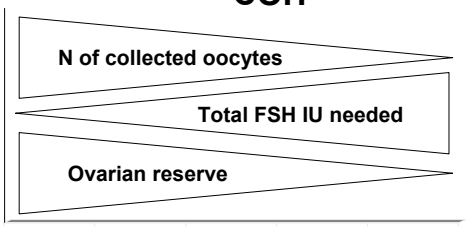
COH



In young women, the dosage of exogenous FSH can influence the amount of ovarian response. In older women the ovarian response is more related to the ovarian reserve

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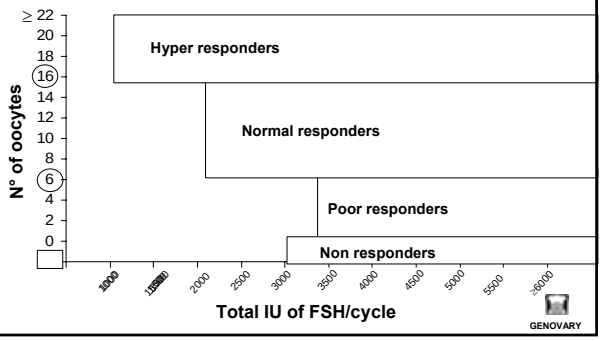
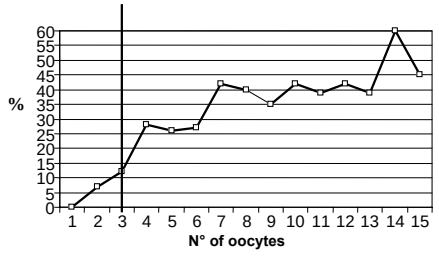
Ovarian response to COH



GENOVARY

PREGNANCY RATE IN RELATION TO THE NUMBER OF COLLECTED OOCYTES (2000 CYCLES)



Cut-off point of statistically significant difference

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09-2002

INTRODUCTION

Even if most patients show optimal response to controlled ovaran hyperstimulation despite LH suppression by GnRH therapy,in some women the initial recruitment by the conventional starting dose of FSH is followed by a plateau in the follicular growth.

HYPORESPONDERS WOMEN

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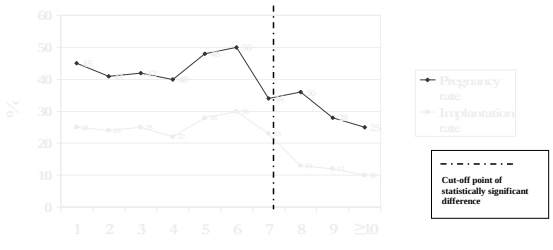
Patient's age (yrs)	Treatment days 1	2	3	4	5	6	7		Need to increase	Need to decrease the dosage (max 6 a/d)
	FIXED DOSAGE									
< 30	2	2	2	2	2	2		Monitoring	21%	5%
30-34	3	3	3	2	2	2			40%	5%
35-37	4	4	4	3	3	3			40%	15%
≥ 38	4	4	4	4	4	4			49%	12%

Normal and Hypo-responders (≥6 oocytes)



n. of FSH ampoules (75 I.U.) for each collected oocytes

GENOVARY

PGD FOR ANEUPLOIDY

508 patients → 714 cycles → 13 16 18 21 22 X Y 15
Normal karyotype

Indication to PGD	No. cycles	Mean age	Previous cycles
Maternal age (≥ 36 years)	567	39.9±2.6	2.5±2.5
Repeated cycles (≥ 3)	128	32.7±2.1	4.1±1.6
Recurrent abortions (≥ 3)	19	31.9±1.9	1.9±1.9

Updated from: Gianaroli et al. (2000) Gonadal activity and chromosomal constitution of in vitro generated embryos. Molec Cell Endocrinol 161, 111-116

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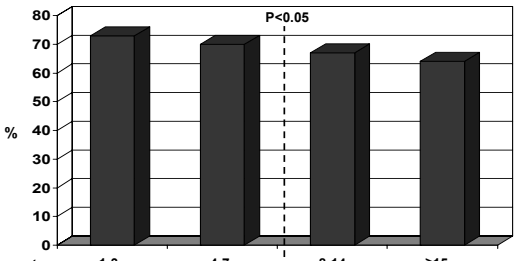
PGD FOR ANEUPLOIDY

CHROMOSOMALLY ABNORMAL EMBRYOS ACCORDING TO THE NUMBER OF COLLECTED OOCYTES



No. oocytes	1-3	4-7	8-14	≥15
Maternal age	41.4±3.7^{abc}	38.4±3.7^{a}	38.1±3.7^{b}	37.8±4.1^{c}

^{abc}P<0.001

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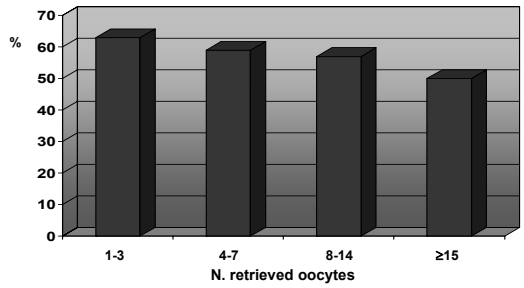
CHROMOSOMAL ANALYSIS ON OOCYTES

INCIDENCE OF ANEUPLOIDY IN RELATION TO THE NUMBER OF RETRIEVED OOCYTES

n=1130



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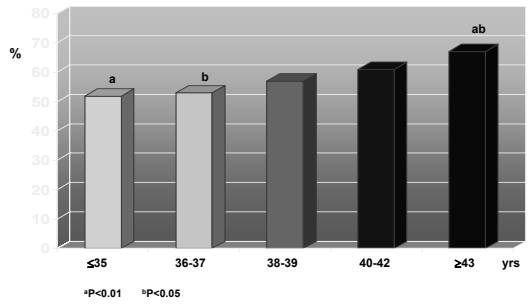
CHROMOSOMAL ANALYSIS ON OOCYTES

INCIDENCE OF ANEUPLOIDY IN RELATION TO MATERNAL AGE

n=1130



[a]P<0.01 [b]P<0.05

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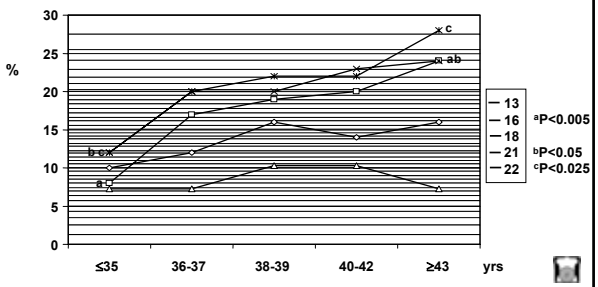
CHROMOSOMAL ANALYSIS ON OOCYTES

FREQUENCY OF ANEUPLOIDY IN OOCYTES ACCORDING TO AGE

No. observations= 5.650



[a]P<0.005
[b]P<0.05
[c]P<0.025

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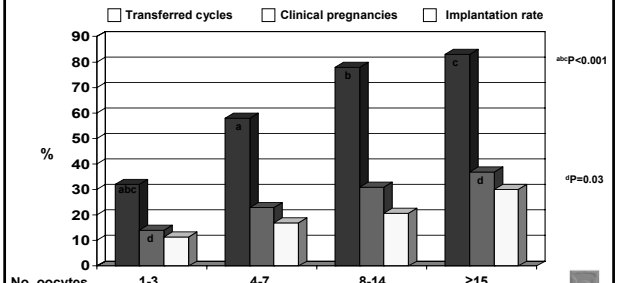
PGD FOR ANEUPLOIDY

CLINICAL OUTCOME ACCORDING TO THE NUMBER OF COLLECTED OOCYTES



[abc]P<0.001

[d]P=0.03

[abc]P<0.001

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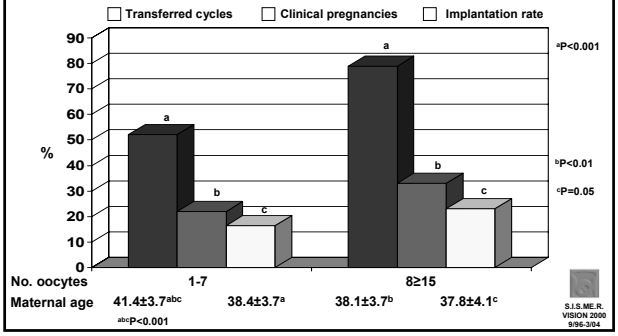
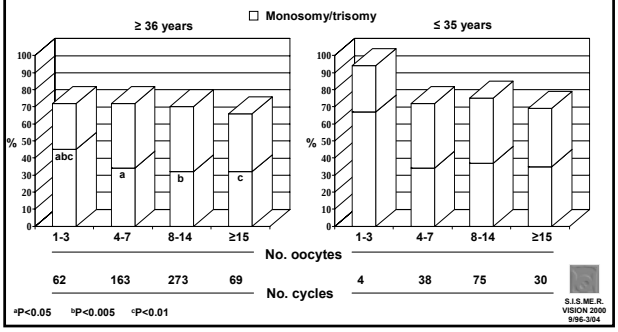
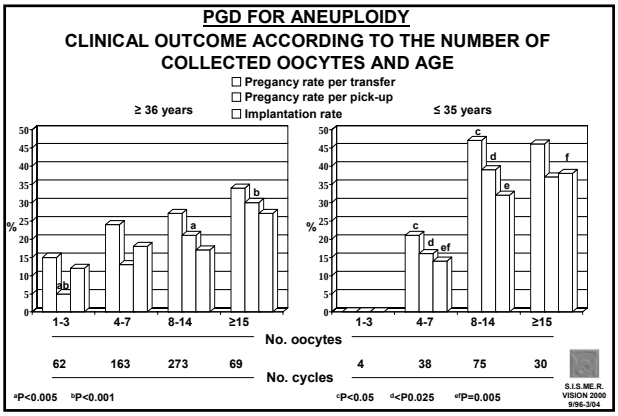
PGD FOR ANEUPLOIDY
CLINICAL OUTCOME ACCORDING TO THE NUMBER OF COLLECTED OOCYTES

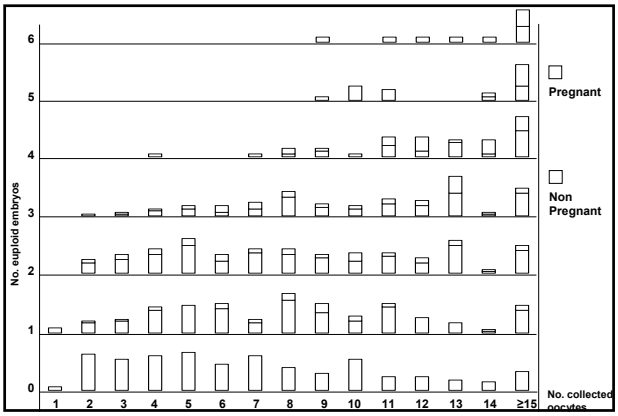


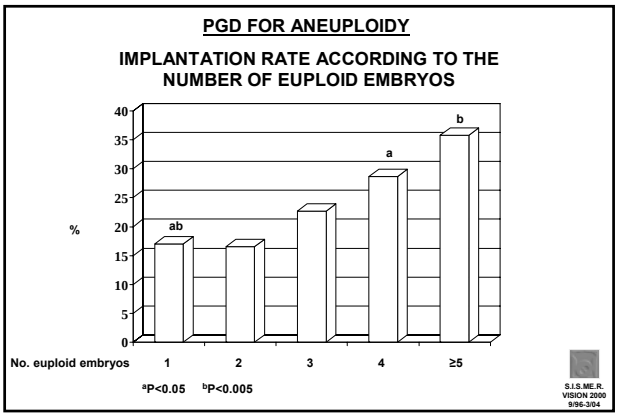
PGD FOR ANEUPLOIDY
CHROMOSOMALLY ABNORMAL EMBRYOS ACCORDING TO THE NUMBER OF COLLECTED OOCYTES AND AGE



PGD FOR ANEUPLOIDY
CLINICAL OUTCOME ACCORDING TO THE NUMBER OF COLLECTED OOCYTES AND AGE




No. euploid embryos
0
1
2
3
4
5
6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 ≥15
No. collected oocytes
Pregnant
Non Pregnant


PGD FOR ANEUPLOIDY
IMPLANTATION RATE ACCORDING TO THE NUMBER OF EUPLOID EMBRYOS
%
0
5
10
15
20
25
30
35
40
ab
a
b
No. euploid embryos
1
2
3
4
≥5
aP<0.05 bP<0.005
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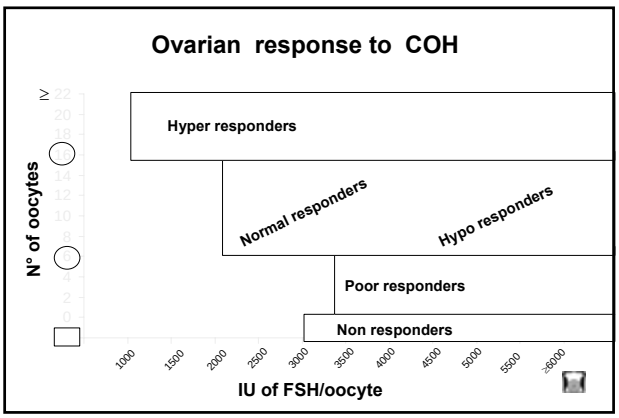
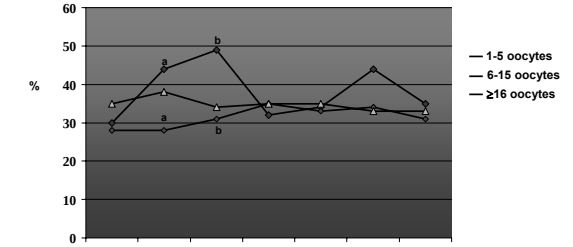

Ovarian response to COH
N° of oocytes
Hyper responders
Normal responders
Hypo responders
Poor responders
Non responders
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
≥6000
IU of FSH/oocyte

PGD - AS

DISTRIBUTION OF ABNORMALITIES PER ANALYZED CHROMOSOME ACCORDING TO THE NUMBER OF OOCYTES



Chromosomes	XY	13	15	16	18	21	22
No. observations	531	529	372	473	528	515	393

$^{ab}P<0.05$

Repeated IVF

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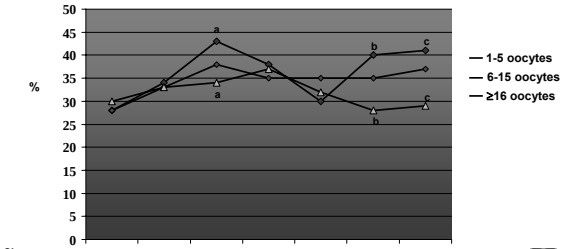
PGD - AS

DISTRIBUTION OF ABNORMALITIES PER ANALYZED CHROMOSOME ACCORDING TO THE NUMBER OF OOCYTES



Chromosomes	XY	13	15	16	18	21	22
No. observations	2219	2191	1899	2155	2192	2159	1988

$^{a}P<0.05$; $^{b}P<0.005$; $^{c}P<0.01$

Maternal age

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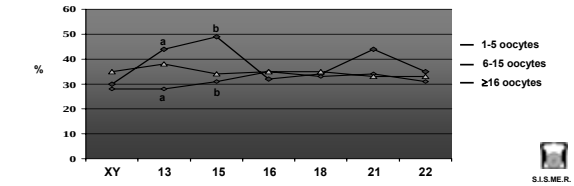
PGD aneuploidy

Predictive of pregnancy

Predictive of reproductive life-span

Repeated IVF



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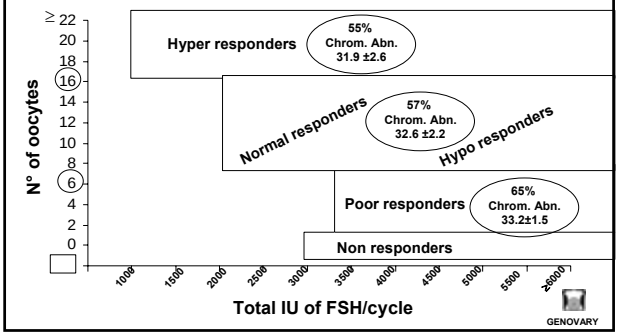
Ovarian response to COH



ROLE OF EXOGENOUS LH SUPPLEMENTATION DURING OVARIAN STIMULATION

⇩

hyporesponders

⇩

Hypothesis:

Mean number of MII similar to normoresponders
Lower live-birth rate

The need of higher doses of FSH ← **LH deficiency**

⇩

Oocyte competence

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PATIENTS

- Group A	50 patients 31.7±2.8	Increased dosage of FSH
- Group B	54 patients 31.5±3.2	Increased dosage of FSH + rLH
- Group C	22 patients 32.0±4.1	HMG
- Group D	54 patients 31.8±3.0	Normal reponders

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SERUM LH (mIU/ml) ON CYCLE DAY 7 AND PROGESTERONE (ng/ml) LEVELS ON THE DAY OF HCG

	Group A (n=50)	Group B (n=54)	Group C (n=22)	Group D (n=54)
LH level (M±SD)	0.99± 0.7	1.02± 0.9	1.3±1	0.93±0.6
Range	0.22-2.43	0.2-2.71	0.5-3.6	0.26-2.19
Progesterone (M±SD)	0.55±0.2	0.51±0.1	0.5±0.2	0.52±0.2
Range	0.4-0.99	0.3-0.79	0.2-0.8	0.3-1.05

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OOCYTES, FERTILIZATION AND EMBRYO DEVELOPMENT

	Group A (n=50)	Group B (n=54)	Group C (n=22)	Group D (n=54)
N. collected oocytes (M±SD)	412 (8.2±3.8)	600 (11.1±5.5)	218 (9.9±4.9)	530 (9.8±5.6)
N. inseminated oocytes	346	505	192	417
N. 2pn (%)	245 (71)	326 (65)	141 (73)	288 (69)
N. cultured 2pn	228	225	87	233
N. day 2 embryos (%)	213 (93)	210 (93)	78 (90)	219 (94)

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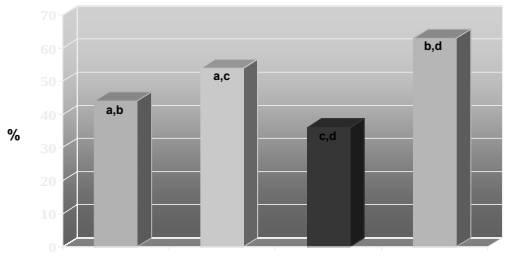
EMBRYO DEVELOPMENT
Day 3, grade 1, no fragments



$^{a}P<0.05$ $^{bd}P<0.001$ $^{c}P<0.01$

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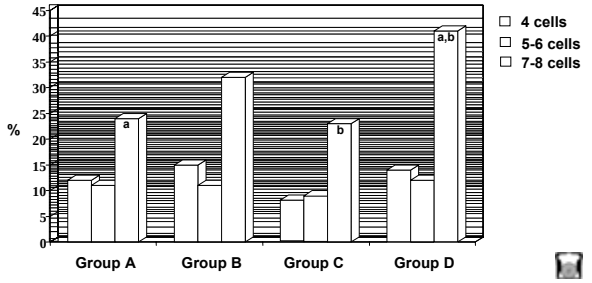
EMBRYO DEVELOPMENT
Day 3, grade 1, no fragments



$^{a}P<0.001$ $^{b}P<0.01$

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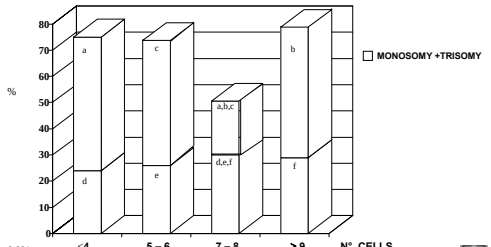
CHROMOSOMAL ABNORMALITIES AND CELLULAR STAGE
NORMAL KARYOTYPE n=4249



a, c, d, e $P < 0.001$
b $P < 0.005$
f $P < 0.01$

AT 62 HOURS POST – INSEMINATION

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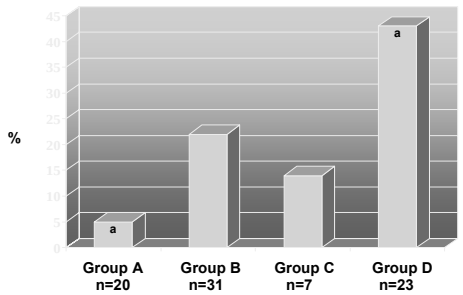
0.96-12.03

BLASTOCYST DEVELOPMENT



$^{a}P<0.05$

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CLINICAL OUTCOME

	Group A (n=50)	Group B (n=54)	Group C (n=22)	Group D (n=54)
N. fresh embryo transfers	45	41	18	41
N. embryos/ET (mean)	1.93	1.85	1.63	1.92
N. pregnancies/ET (%)	11(24)	22(54)*	2(11)	17(41)
Implantation rate %	14.1 (12/85)	36.8 (24/65)**	7.4 (2/27)	35.4 (29/79)
N. pregnancies post 2PN thawing	1	2	2	5
Total N. abortions	1	2	0	2
Live-birth rate/started cycle % (n)	22 (11)	40.7 (22)	18 (4)	37 (20)

*B vs A and C: P<0.05
** B vs A and C: P<0.05

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CONCLUSIONS

- Embryo development and implantation is

  → higher in Group B (Increased dosage of FSH + rLH)
  vs. Group A (Increased dosage of FSH)
  vs. Group C (HMG)

  → similar in Group B (Increased dosage of FSH + rLH)
  and Group D (Normal responders)

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CONCLUSIONS

- Hyporesponse to FSH could be

  → Related to iatrogenic LH deficiency

  → Negative effect on oocyte competence

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  Addition of small amount of rLH rescues oocyte competence to generate viable embryos

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CONCLUSIONS

Increasing FSH dosage can rescue follicular growth in cases of hyporesponse, but the addition of small amount of exogenous LH in these patients significantly increased the oocytes competence to produce viable embryos.

Hyporesponse to conventional FSH dosage in normovulatory young women could be related to iatrogenic LH deficiency that affects oocyte competence.

Hyporesponse was not predicted by the LH serum levels.

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Recombinant LH in Poor response

Two protocols under evaluation

- 450 IU/day of r-FSH from cycle day 2 plus r-LH (75 or 150IU) from cycle day 7 in antagonist regimen

Poor responders

(≤ 40 years)

	rFSH	rFSH+rLH
N° of cycles	49	24
Cancelled cycles	15 (31%)	11 (42%)
Oocytes/pu	3.8± 1.6	3.7 ± 2.5
N° of tranfers	21	10
N° of clinical preg	9	0

Rationale do not use LH in late follicular phase in poor responders

- **Poor responders generate an higher numbers of aneuploids embryos compared to similar age normal responders**
- **The most frequents aneuplidies are monosomy and trisomy, suggesting a premature ovarian aging**
- **Excessive LH can induce post-maturity in already aged oocytes,compromising meiosis and early mitosis process**

Recombinant LH in Poor response

Two protocols under evaluation

- 450IU/day of r-FSH from cycle day 2 plus r-LH (75 or 150IU) from cycle day 7 in antagonist regimen
- Pre-treatment with LH in low dose agonist regimen

Poor responders

- Down-regulation with dayly GnRH agonist half dose,pre-treatment with rLH before FSH stimulation……

- … to render the cohort of follicles more sensitive to FSH

Preliminary results in repeated poor responders

N° of patients	8
age	36.7±3
N° of previous cycles with poor response	5.4±2
N° of cancelled cycles	2
N° of oocytes/pu	2.2±0.5
N° of transfers	6
N° of pregnancies	2
IR	27%