

Diagnosis and management of poor responders

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Les Chevreuils, 18 juin 2009

Definition of a poor response ?

- Varies according to whether an OE or a COS is considered
- No universal definition

Loutradis et al, *Curr Opin Obstet Gynecol*. 2008 Aug;20(4):374-8.

Shanbhag S et al, *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD004379.

- OE: absence of follicular development
- COS: recovery of less than 5 metaphase II oocytes

Consequences

- Cancellation of the cycle

Frydman R, J Gynecol Obstet Biol Reprod 2005 Nov;34:5S10-5S13.

- Low outcome ?

- Low Efficiency and low Effectiveness ?

- Insufficient evidence not to adapt to each case

- Frustration...

Causes: Age of the patient

Evaluation of oocyte depletion

$$Dy/dx = -y[0.0595 + 3716(11780 + y)]$$

X=age

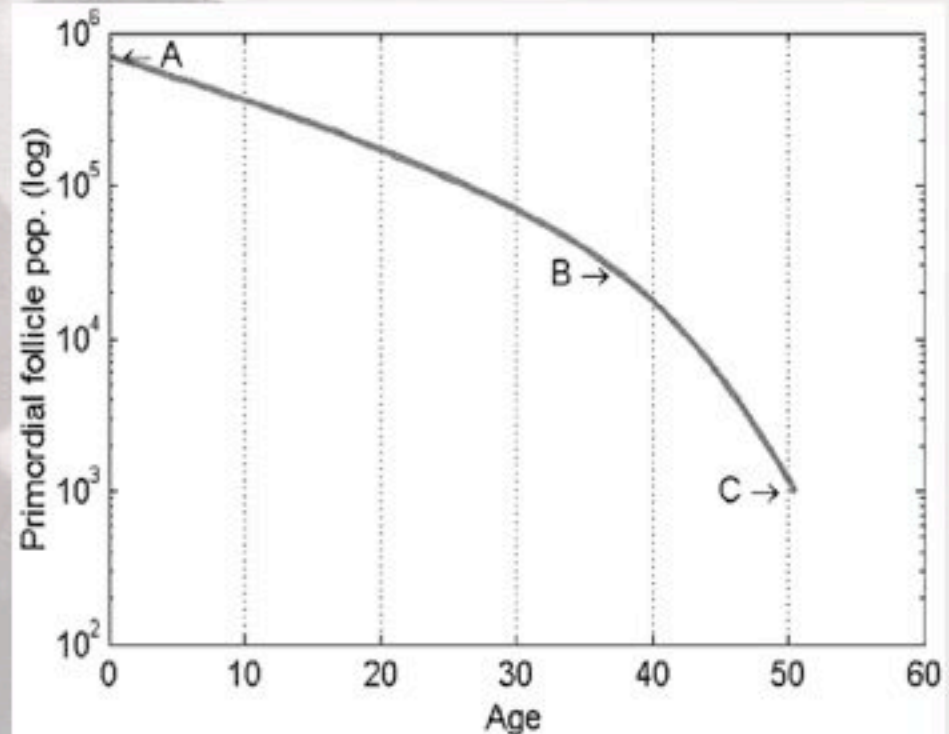
Y=number of primordial follicle

Equation of Fady-Gosden

A=701 000 follicles

B=25 000 follicles

C=1000 follicles



Causes

- Age of the patient
- Genetic origin : ie FSHR p.N680S polymorphism
Simoni M et al, Hum Reprod Update. 2008 Sep-Oct;14(5):459-84.
- Immunological origin
- Iatrogenic origin
- Biochemical (ie obesity) origin...
-would remain undiagnosed if no treatment were undertaken

Diagnostic Tools

- Ovarian volume
- Number of antral follicles
- AMH level of less than 3 ng/l
- FSH >12 IU/l
- Low E2
- BMI...
- No ideal combination
- A stimulation trial constitutes the ultimate step able to confirm the clinical prognosis

Predictive Tools

- **AFC and AMH** (but non conception depends on the age)

- **AFC:** the single best predictor

Jayaprakasan K et al, Fertil Steril. 2008 Nov 29

- **AMH superior to basal FSH and AFC**

Nardo LG et al, Fertil Steril. 2008 Nov 29

Kwee J et al, Fertil Steril. 2008 Sep;90(3):737-43. Epub 2007 Oct 17.

Nelson SM et al, Hum Reprod. 2007 Sep;22(9):2414-21

- **FSH >12 IU/l**

- **Careful review of past responses**

Loutradis D et al, Curr Opin Obstet Gynecol. 2008 Aug;20(4):374-8.

What is the best treatment ?

- Maximum dose: 450 IU
- Time at which treatment can be started (luteal or follicular phase) ?
- GnRH agonists ?
- GnRH antagonists ?

What is the best treatment ?

There is insufficient evidence to support the routine use of any particular intervention either for pituitary down-regulation, ovarian stimulation or adjuvant therapy in the management of poor responders to controlled ovarian stimulation in IVF

Shanbhag S et al , **Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF)**. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004379.

What is the best treatment ?

- Addition of growth hormone (GH): 5 studies.
- Addition of growth hormone-releasing factor (GHRF): 1 study.
- Addition of pyridostigmine: 1 study.
- Addition of oral L-arginine: 1 study.
- Addition of transdermal testosterone: 1 study.
- Addition of letrozole: 1 study.
- Short GnRH-agonist protocol (after oral contraceptive pretreatment) versus long GnRH-agonist protocol (after medroxyprogesterone acetate pretreatment) : 1 study.
- GnRH-antagonist versus long GnRH-agonist protocol: 1 study.
- Combination of clomiphene citrate with rFSH in a flexible GnRH-antagonist protocol versus long GnRH-agonist protocol: 1 study.
- GnRH-antagonist versus short GnRH-agonist protocol: 3 studies.
- Short GnRH-agonist protocol versus natural cycle IVF: 1 study.
- Stop versus nonstop long GnRH-agonist protocol: 2 studies.

What is the best treatment ?

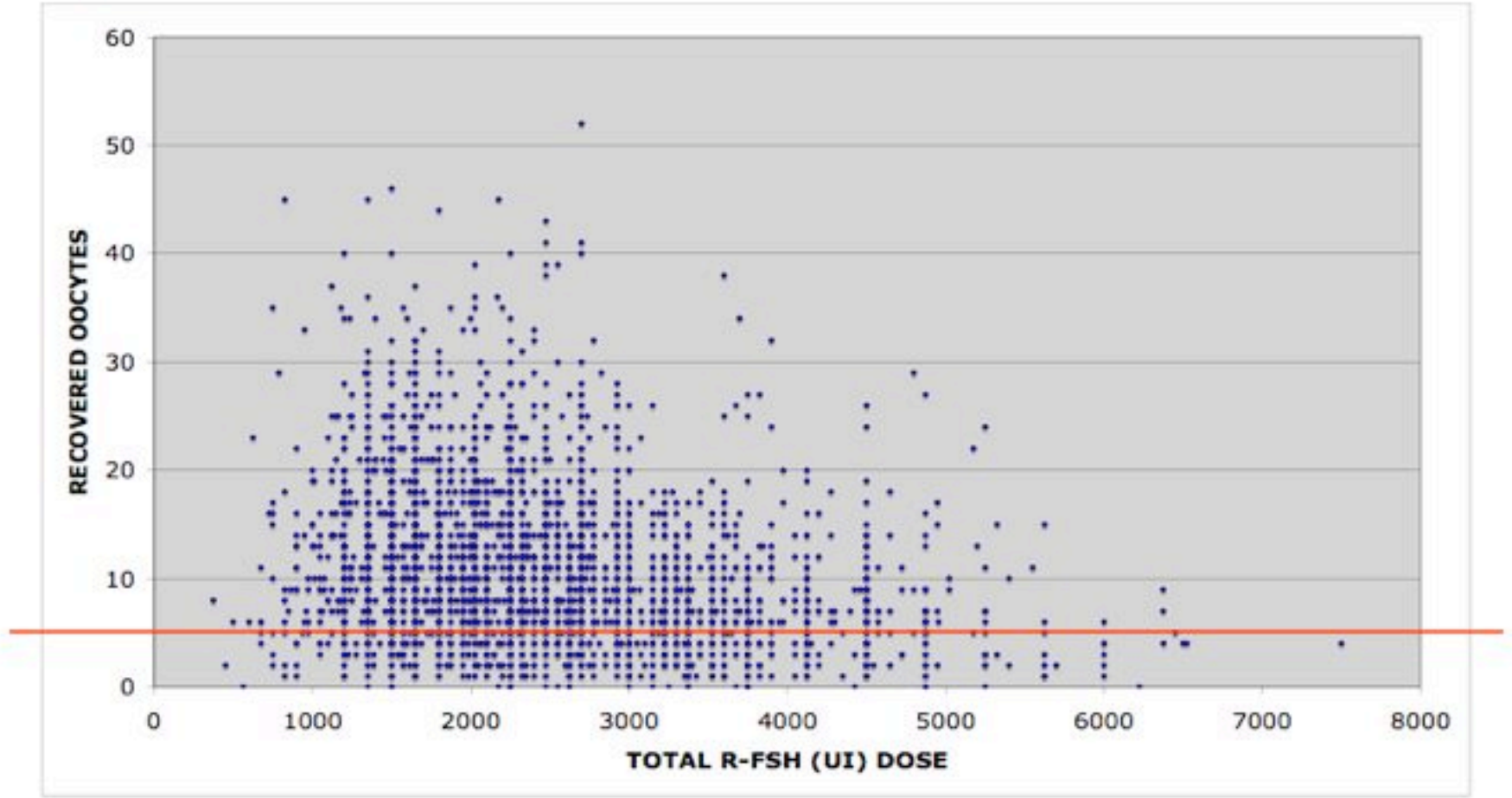
- Only two of the 15 interventions were associated with statistically significant improvements in the pregnancy rate.
- Adding **GH** to ovarian stimulation significantly increased the chance of pregnancy in poor responders, with an odds ratio for live birth of 5.22 (95 percent confidence interval 1.09-24.99). (Bergh et al, *Fertil Steril* **62** (1994), pp. 113-120)...
- Similarly, performing **embryo transfer on day 2** significantly improved the probability of pregnancy, producing an ongoing pregnancy rate of 27.7 percent compared with 16.3 percent for day 3 transfer (difference 11.4 percent; 95 percent confidence interval 1.6-21.0 percent). However, more embryos were transferred on day 2 (2.0 ± 0.8) than on day 3 (1.7 ± 0.8), and the effect of this difference on the result is unknown. (Bahceci et al, *Fertil Steril* **86** (2006), pp. 81-85)

Dimitra Kyrou et al, Fertility and Sterility

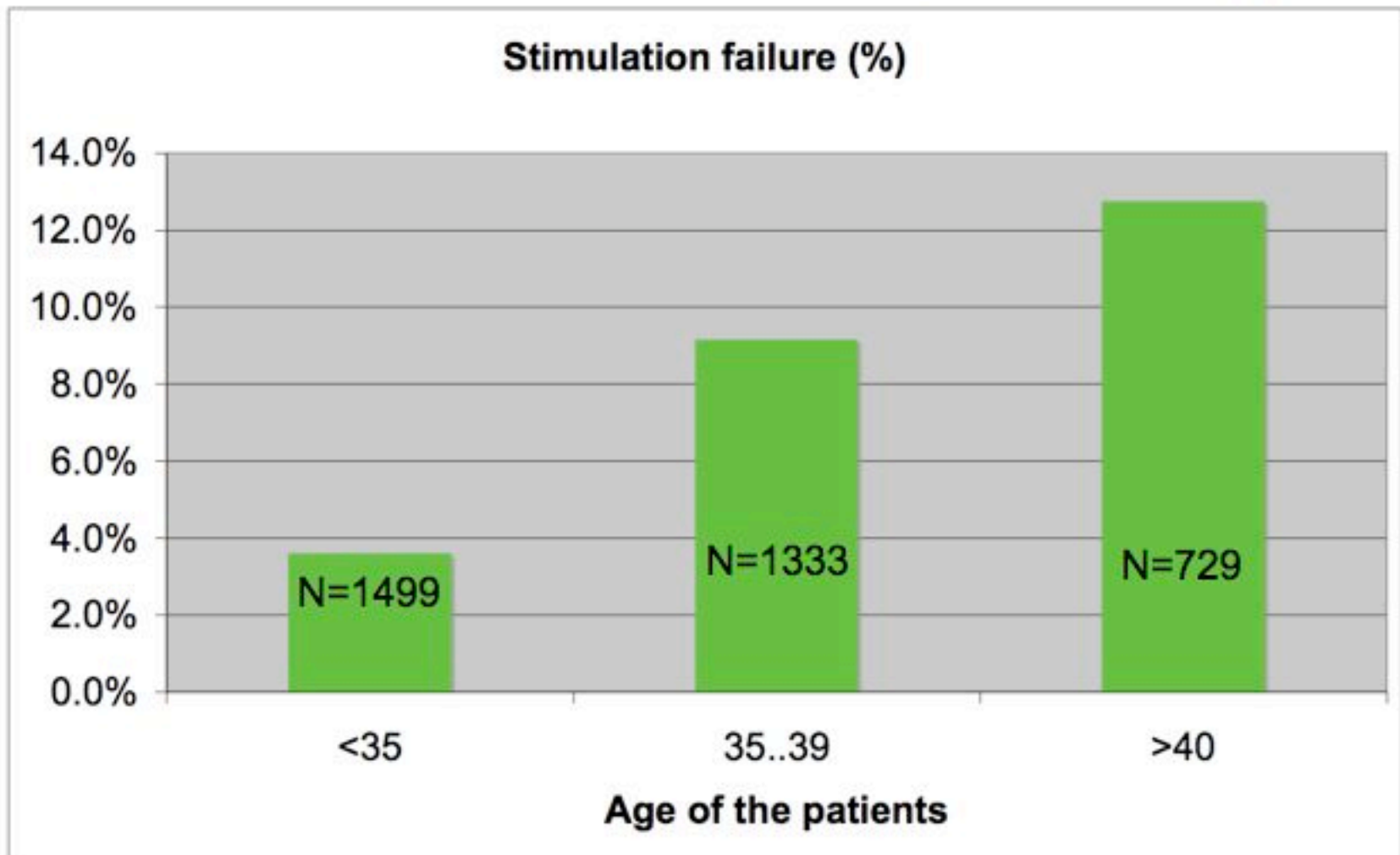
Our experience

- 3'561 OPU (r-hFSH)
- <35; 35-39; ≥ 40 years
- Results analysed retrospectively:
 - Oocyte and zygote numbers
 - Implantation rate
 - Delivery rate
- Data related to the number of FSH units
- Re-evaluated in the light of the patient's age.

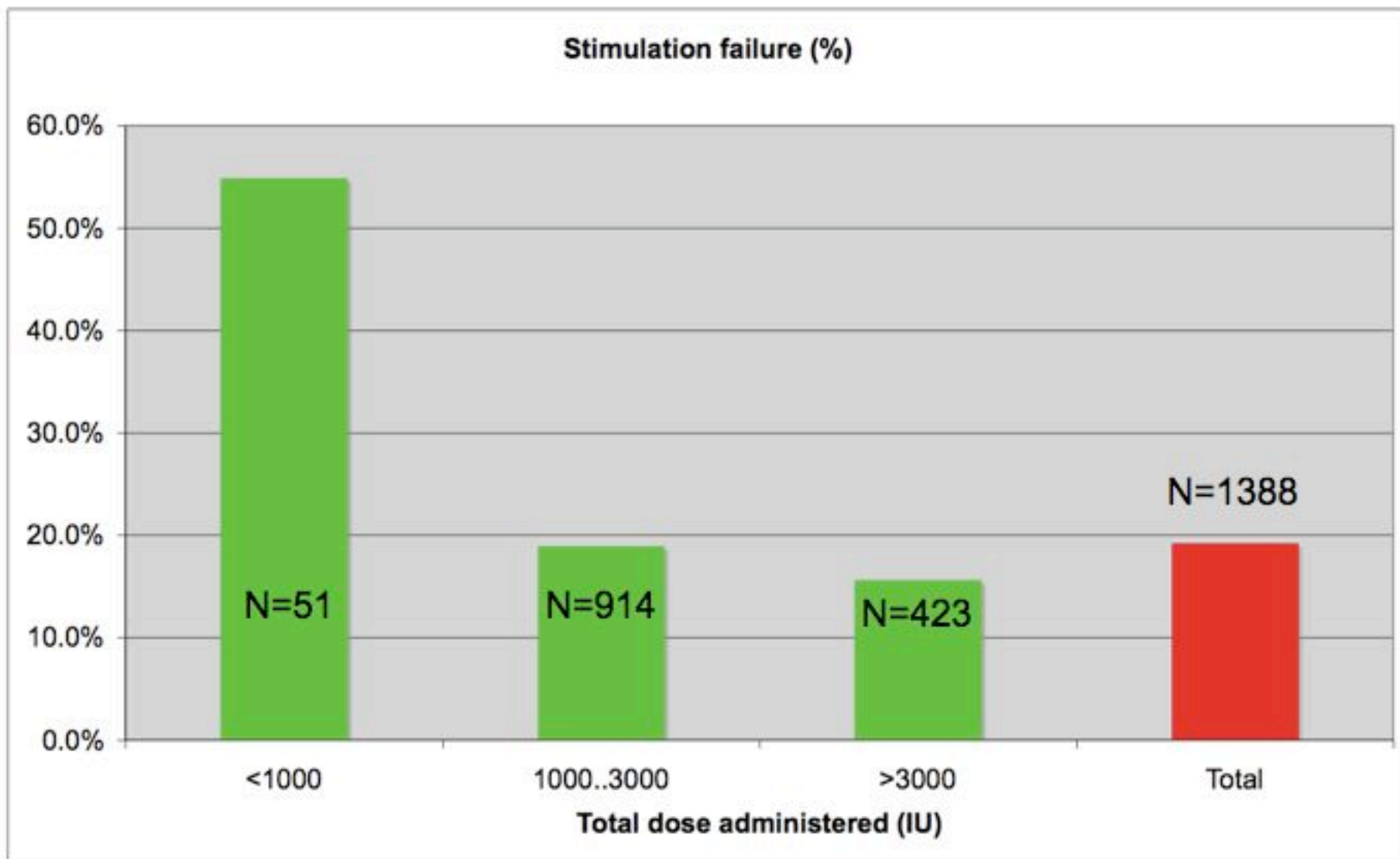
Collected oocytes related to the FSH IU administered (all ages included)



Cancellation rate related to patients' age



% Cancellation rate related with rFSH IU

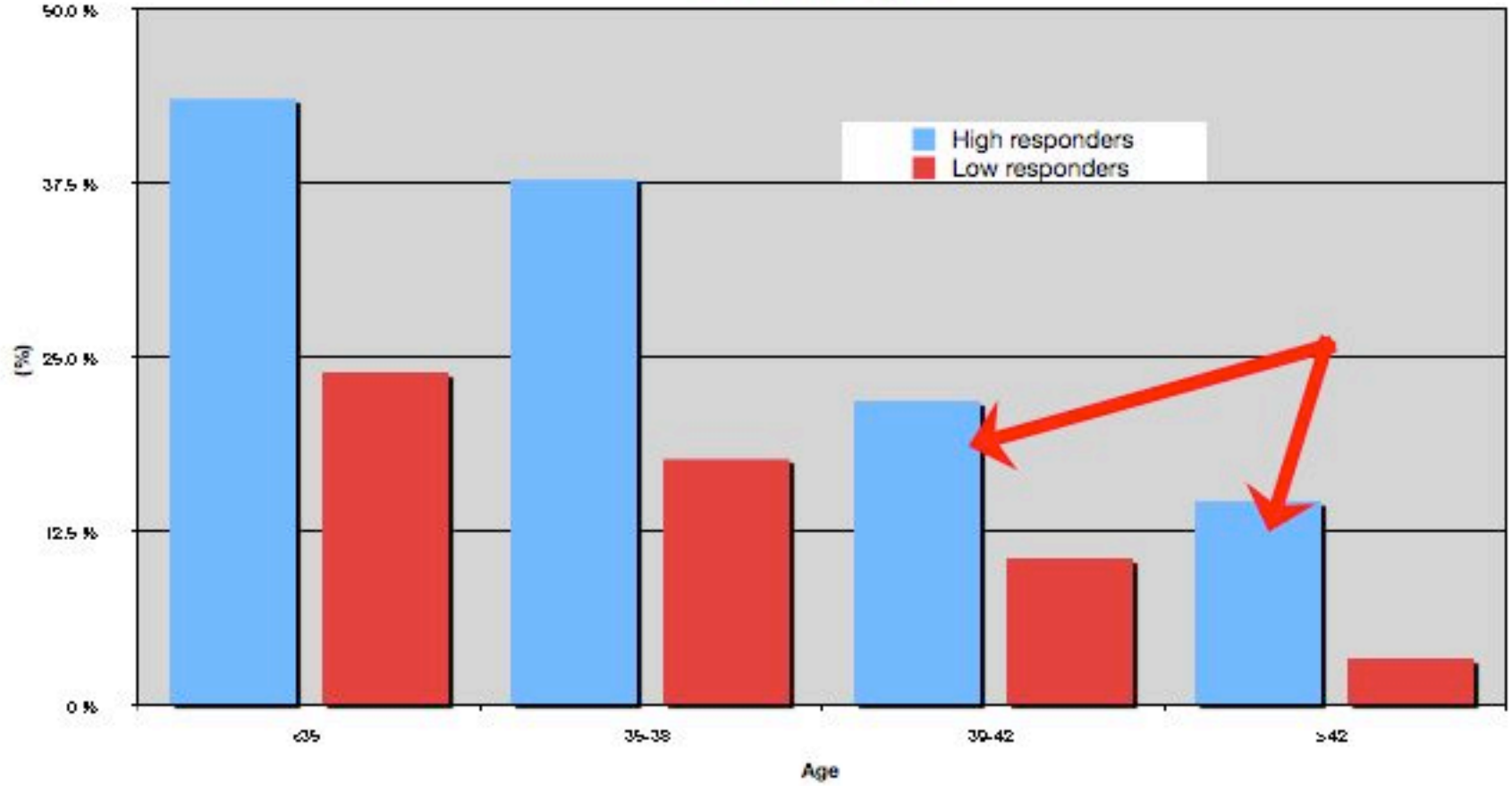


Can we improve this problem ?

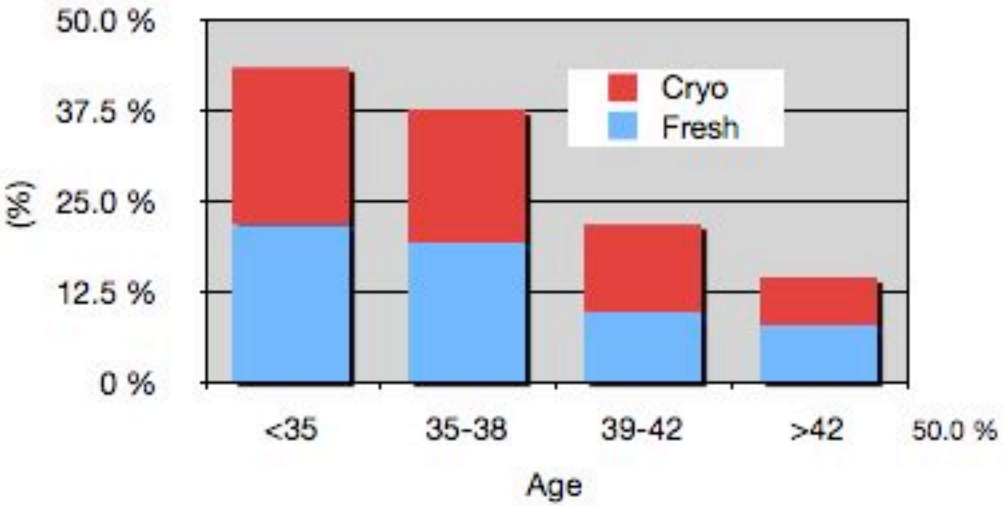
“ Gold Standard”



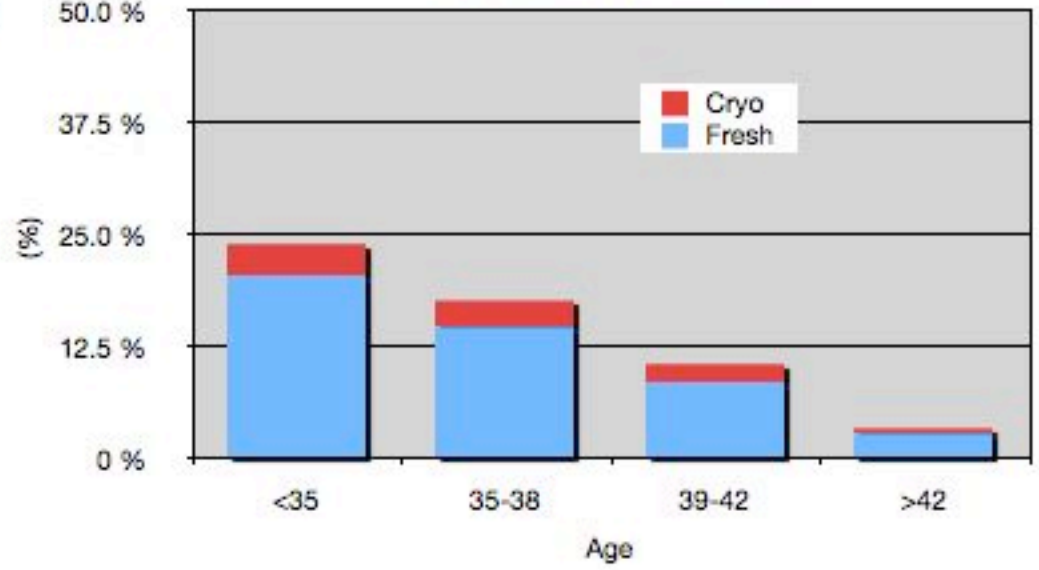
Cumulated delivery rates



High responders (≥ 8 oocytes)

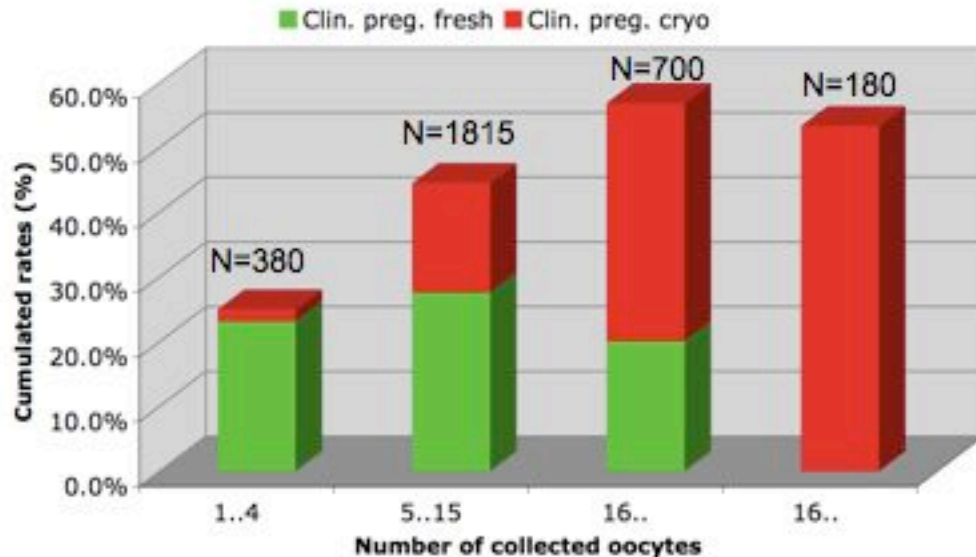


Low responders (<8 oocytes)



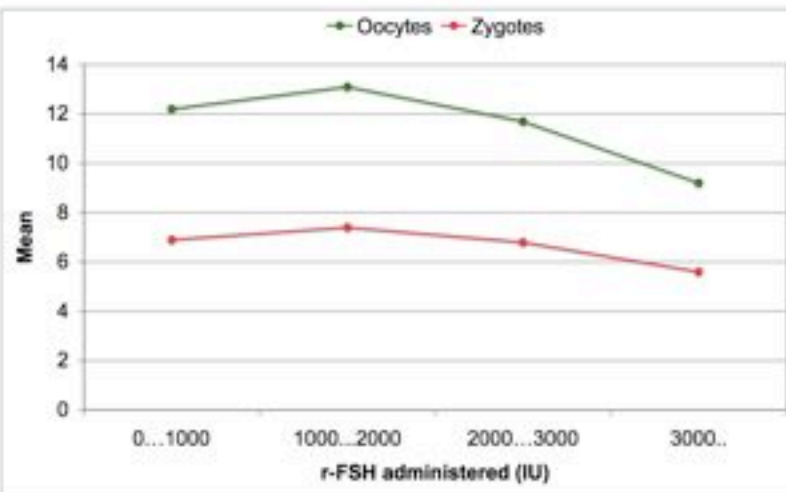
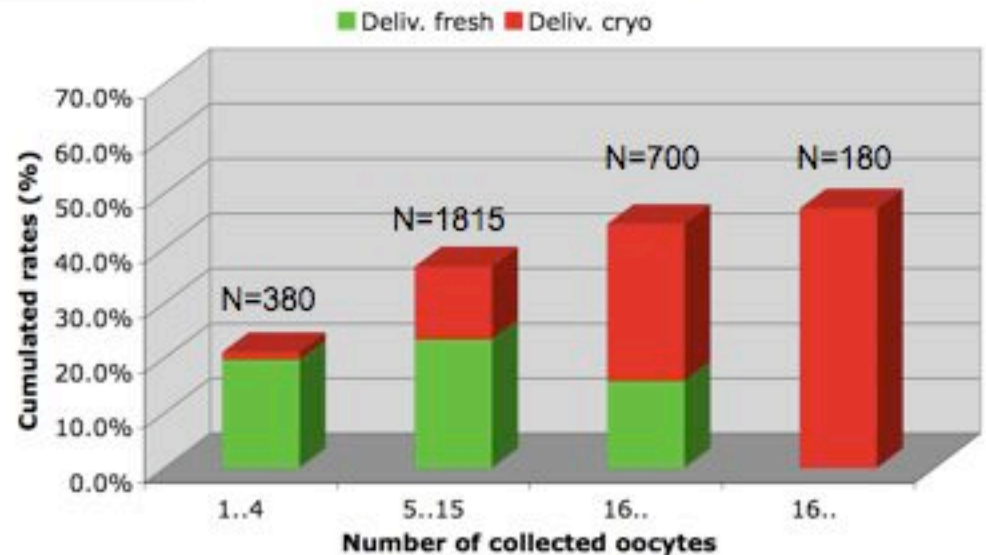
- CUDERA is related to:
- The ovarian response
 - The age of the patient

Cumulated pregnancy rates (<35 years)

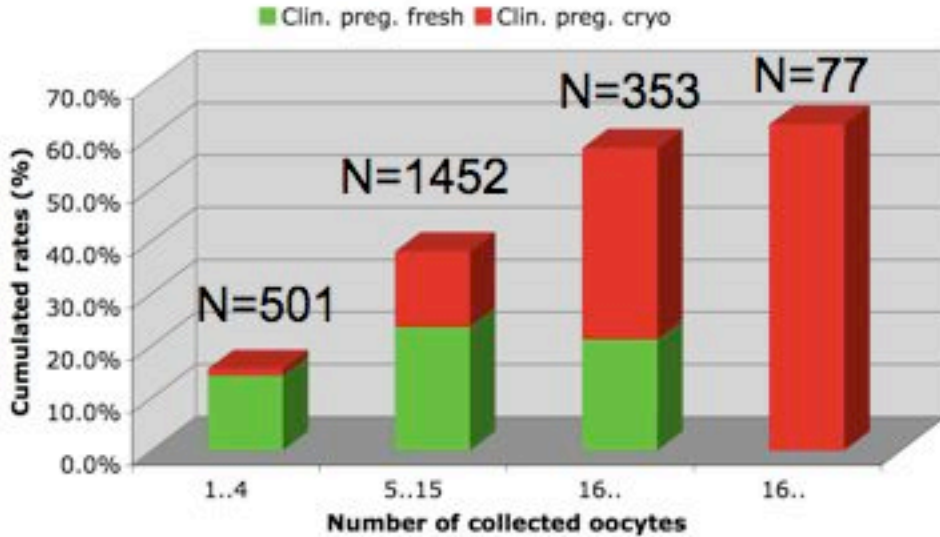


<35 years

Cumulated delivery rates (<35 ans)

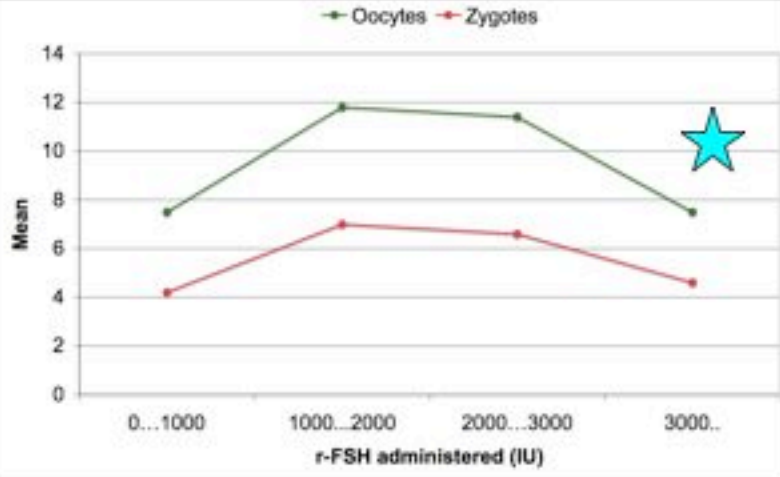
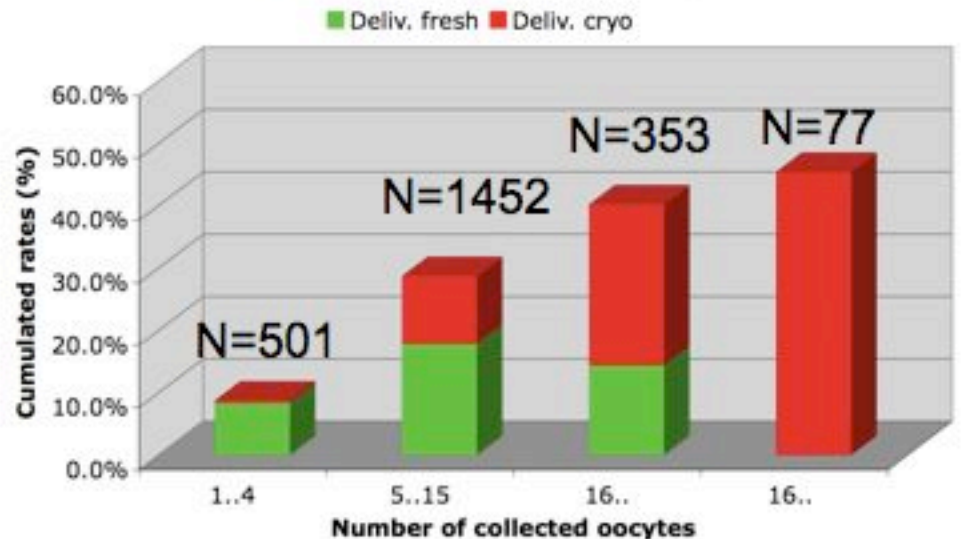


Cumulated pregnancy rates (35-39 years)

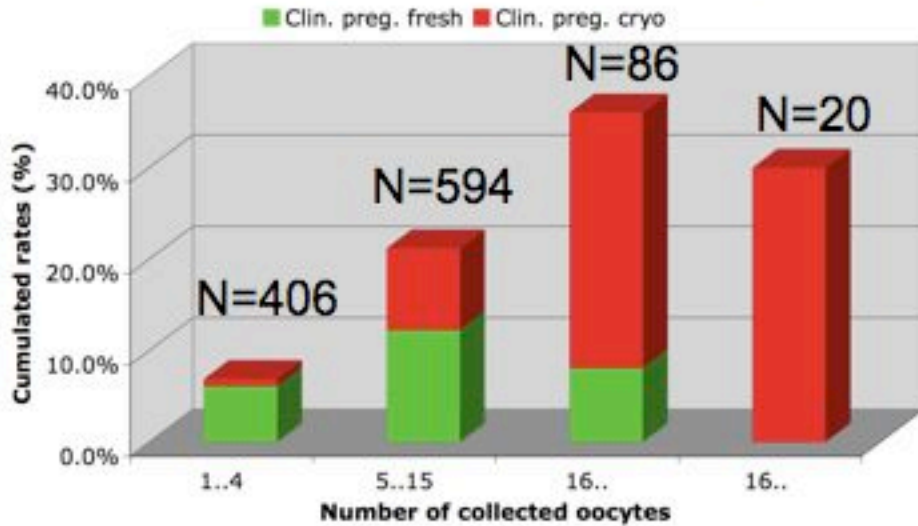


35 -39 years

Cumulated delivery rates (35-39 years)

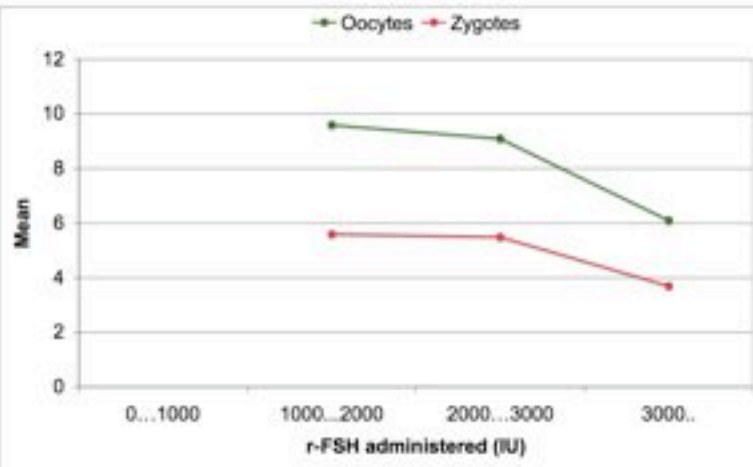
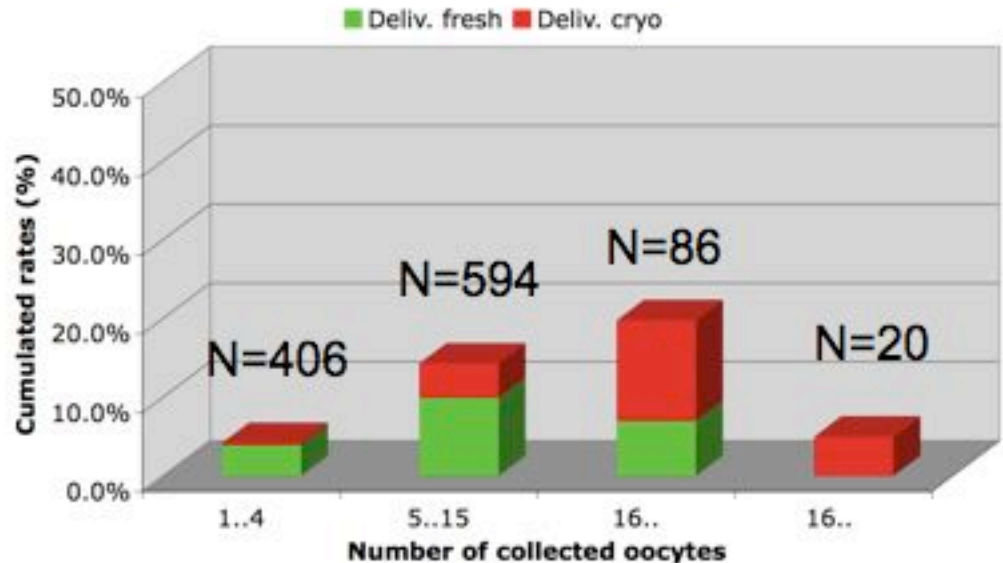


Cumulated pregnancy rates (≥40 years)



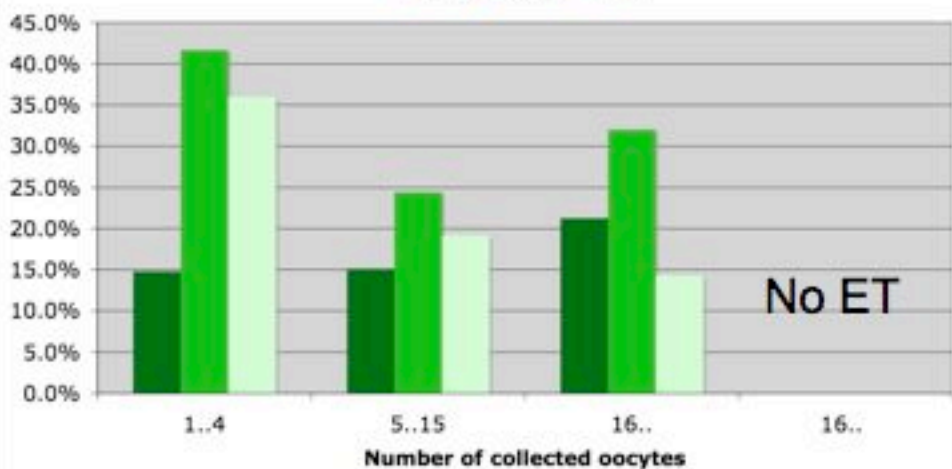
> 40 years

Cumulated delivery rates (≥40 years)



Abortion rates fresh (%)

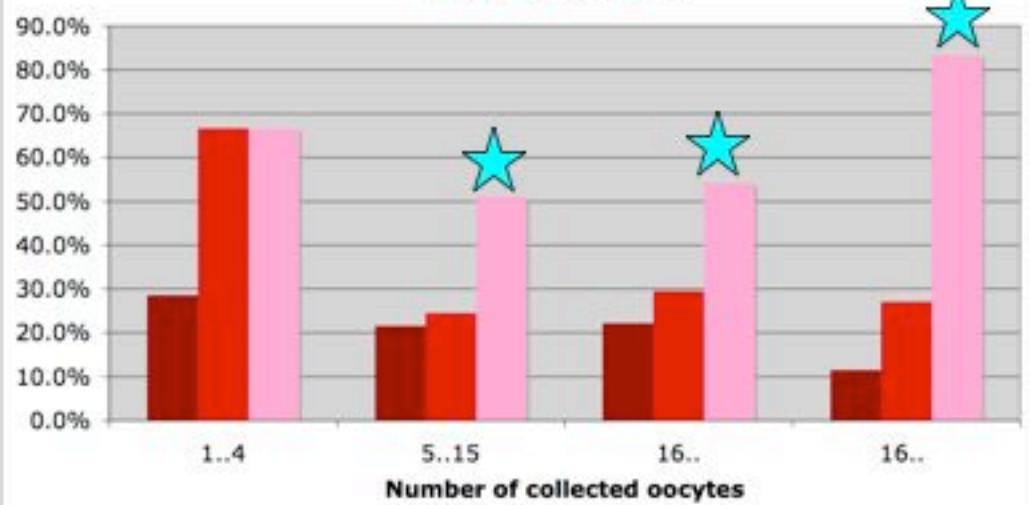
■ <35 ■ 35..39 ■ ≥40



Related to:
 Fresh embryos
 Frozen embryos

Abortion rates cryo (%)

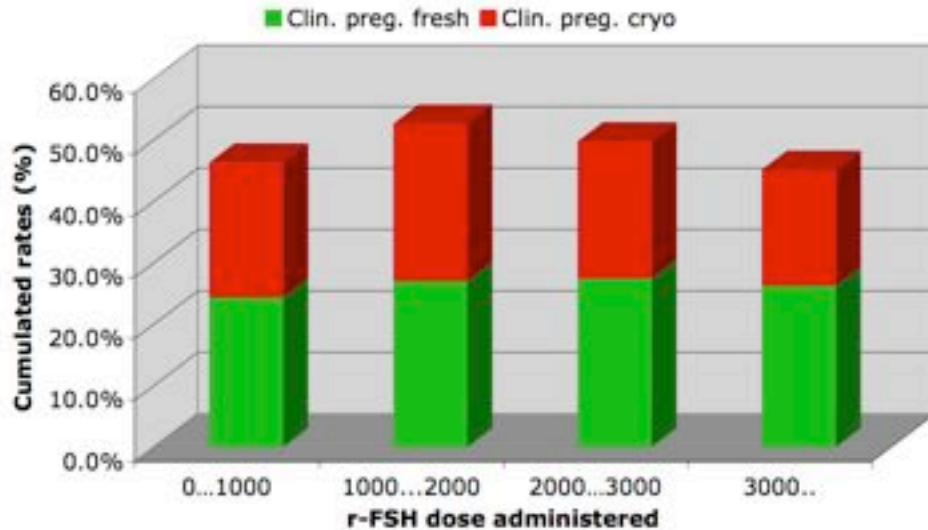
■ <35 ■ 35..39 ■ ≥40



	CUDERA / oocytes retrieved			
AGE	≤ 4	5 - 15	≥ 16	≥ 16 Fr
< 35	21	36.7	44.5	47.2
35-39	8.8	28.7	40.2	45.5
≥ 40	4.1	14.3	19.8	5

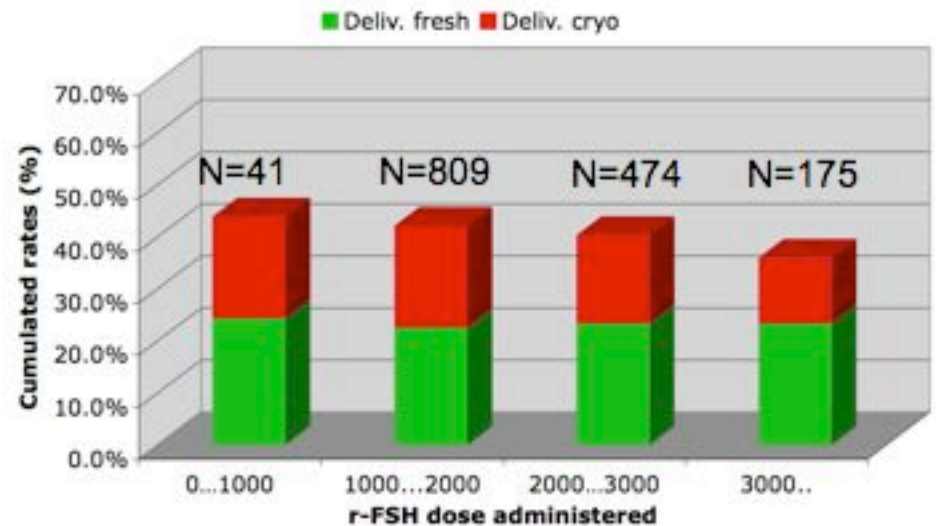
- 2-3 times less deliveries
- Mostly related to frozen zygotes
 - >40: only 4.1 % of the patients deliver
 - >35: Abortion rate > in low responders

Cumulated pregnancy rates (<35 years)

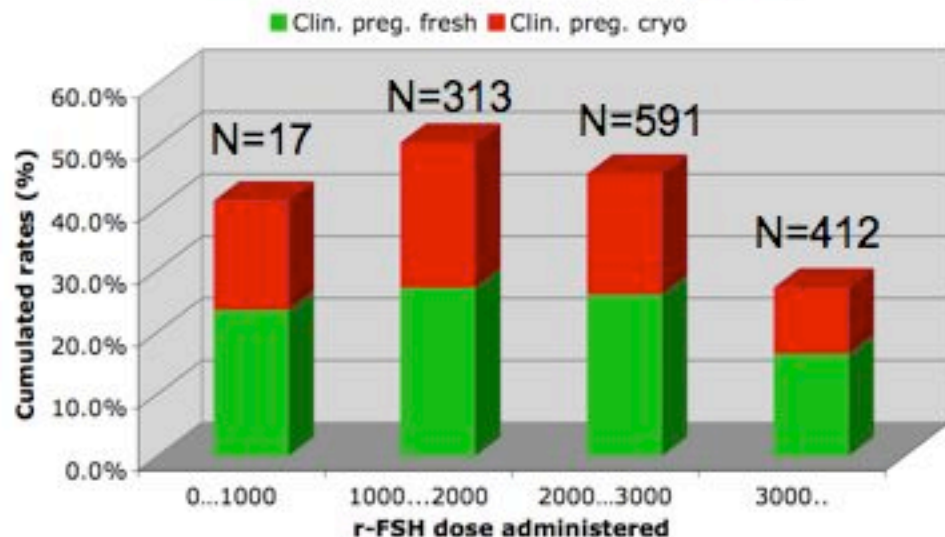


<35 years

Cumulated delivery rates (<35 years)

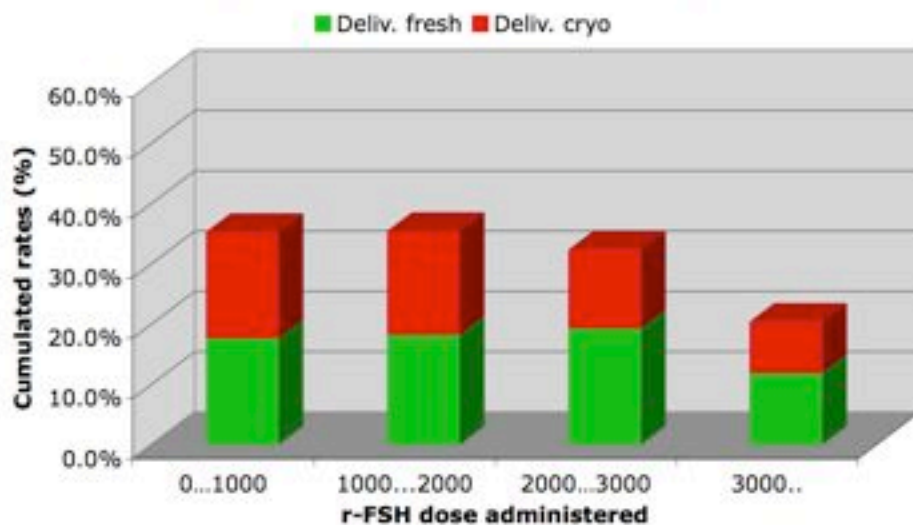


Cumulated pregnancy rates (35-39 years)

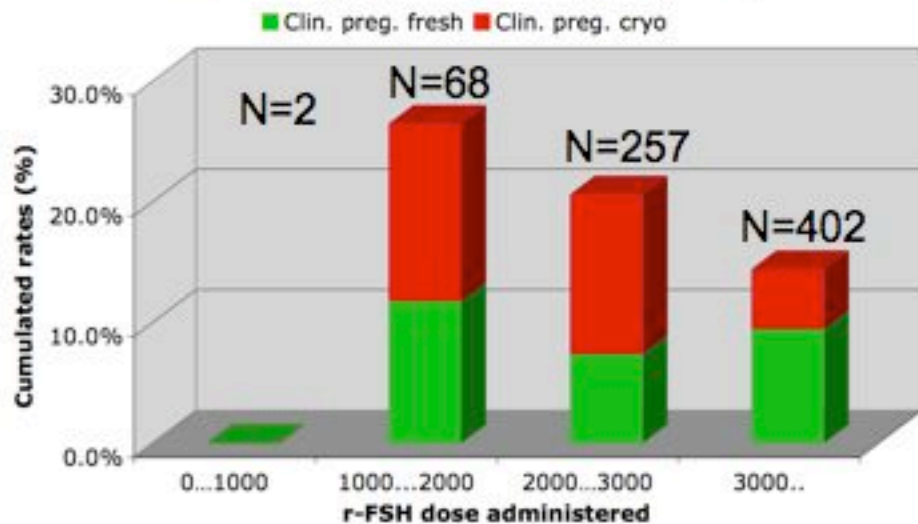


35 -39 years

Cumulated delivery rates (35-39 years)

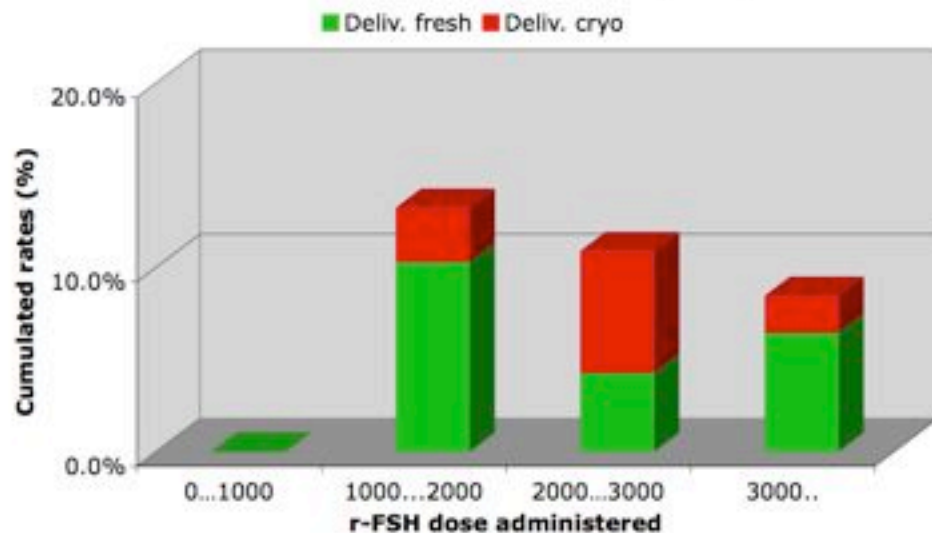


Cumulated pregnancy rates (≥ 40 years)



> 40 years

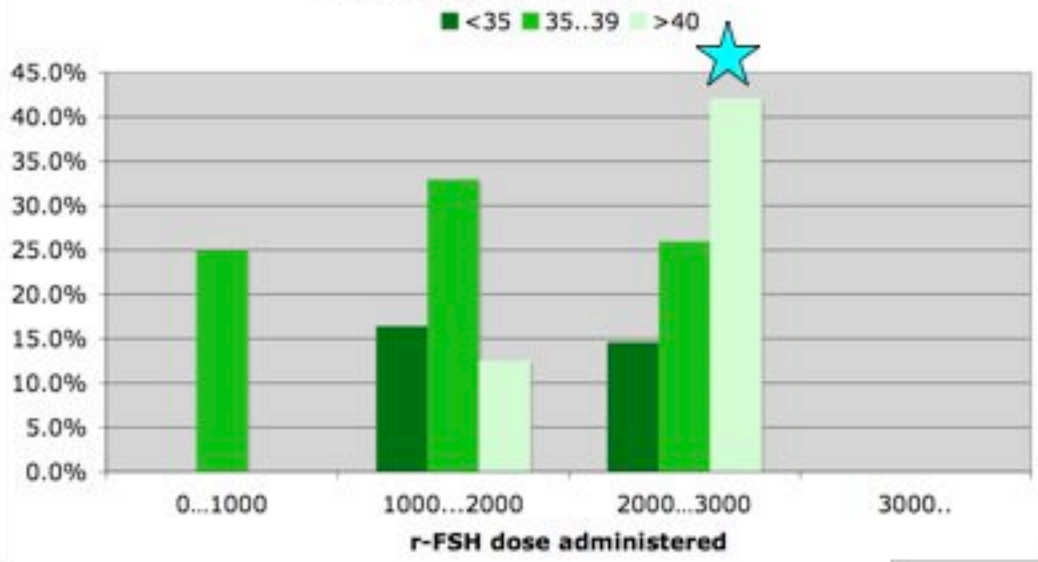
Cumulated delivery rates (≥ 40 years)



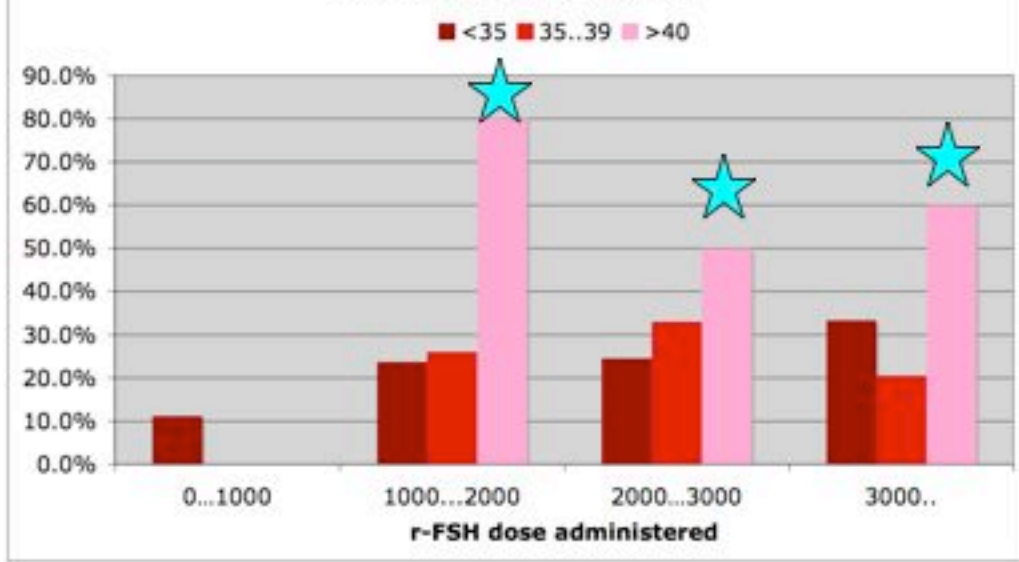
Cumulated Abortion rates

Related to:
 Fresh embryos
 Frozen embryos

Abortion rates fresh (%)



Abortion rates cryo (%)



	CUDERA / total rFSH dose			
AGE	<1000	1000-2000	2000-3000	>3000
< 35	34.9	31.1	40.3	26
35-39	35.2	35.5	32.3	20.4
≥ 40	0	13.2	10.9	8.5

- <40: deliveries related with dose <3000
- <40: 50% related with frozen zygotes
 - ≥40: no delivery when < 1000 IU
 - ≥40: abortion rate > in low responders

- 2-3 times less deliveries than in normal response
- Mostly related to frozen zygotes
- Implantation rates similar than in normal response
- >40: only 4.1 % of the patients deliver
- >35: Abortion rate > in low responders
- <40: deliveries related with dose <3000
- <40:50% related with frozen zygotes
- >40: no delivery when < 1000 IU
- Abortion rate is related more with the age than with the dose

- The therapeutic response remains the best prognostic tool
- Allows to decide whether the cost efficiency of a treatment is adequate or not
- The objective of such an attitude is to start or to abandon treatment

- The end point of the treatment is a child.
- Appropriate counselling allows to optimise the medical care.
- Patients may be offered other alternatives, such as oocyte donation or adoption, in case the parental project is not abandoned.



<http://www.cpma.ch>

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