HOW TO DEFINE POOR OVARIAN RESPONSE?

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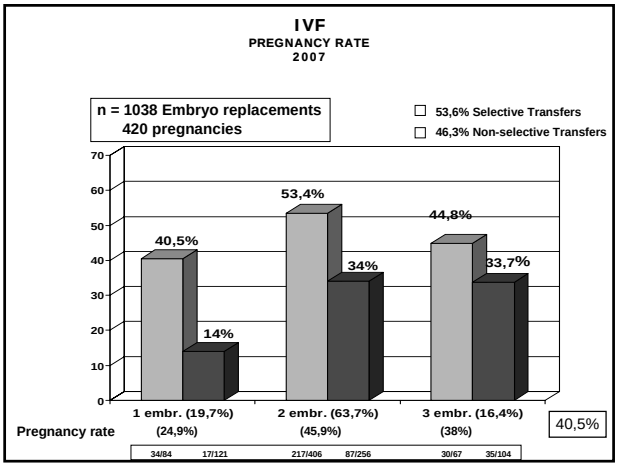
OVARIAN RESPONSE

The term ovarian response is used in clinical research and practice, both qualitatively (ovulation induction protocols) and quantitatively (ovarian stimulation for IVF)

FAUSER et al 2008
HUM.REPROD.UPDATE 14-1: 1-14



WHAT IS A BAD RESPONDER ?

POOR RESPONSE

Can be defined as a failure to produce an adequate number of mature follicles and/or peak estradiol concentrations less than a defined minimum. The cut-off values vary between centers and each center should define their own criteria

LASHEN et al 1999
HUM.REPROD. 14-4: 964-9

POOR RESPONSE DEFINITION

There were no uniform criteria for the definition of poor ovarian response. In this analysis poor ovarian response encompassed insufficient follicular growth and / or cycle cancellation

VERHAGEN et al 2008
HUM.REPROD.UPDATE 14-21: 95-100

POOR RESPONSE DEFINITION

- A universally accepted definition is still lacking *Fasouliotis et al 2000.*
- There is no universal definition for the poor responder *Loutradis et al. 2008*
- Poor response. The devil is in the definition *Turhan N.O. 2006*

POOR RESPONSE DEFINITION

Low response in:

- **Diagnosis → CANCELLATION**
- **Treatment → PREGNANCY**

POOR RESPONSE DEFINITION

Low response in:

- **Diagnosis → CANCELLATION**
- **Treatment → PREGNANCY**

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Fratarelli et al 2008
Schoolcraft et al 2008
Kwee et al 2008
Barreto et al 2008
Loutradis et al 2008

LOW RESPONSE

MULTIVARIATE LOGISTIC REGRESSION ANALYSIS (n= 6000 IVF cycles)

		B	E.T	Wald	sig.	OR	CI 95% OR	
Age								
	>=40	-	-	-	-	1	-	-
	<40	1,015	0,093	120,1	<0,001	2,8	2,3	3,3
FSH								
	>=11	-	-	-	-	1	-	-
	<11	0,269	0,102	7	<0,001	1,3	1,1	1,5
GNS								
	>3800	-	-	-	-	1	-	-
	<3800	0,459	0,086	28,4	<0,001	1,6	1,3	1,9
Oocytes Pick-Up								
	<=5	-	-	-	-	1	-	-
	>5	0,729	0,089	67,8	<0,001	2,1	1,7	2,4

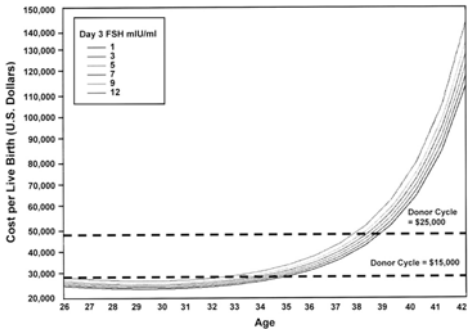
POOR RESPONSE DEFINITION

	Mean	Range	I.U. Dexeus
Age (yrs)	39	38-40	40
FSH basal (IU/l)	11,8	10,5-14	11
AFC (n)	8	5-12	5
GNS (IU)	3350	3000-3800	3800
Follicles > 14 HCG	3,2	2-5	6
Estradiol HCG (pg/ml)	670	500-1000	1100
Oocytes (n)	3,8	3-5	5

LOW RESPONSE

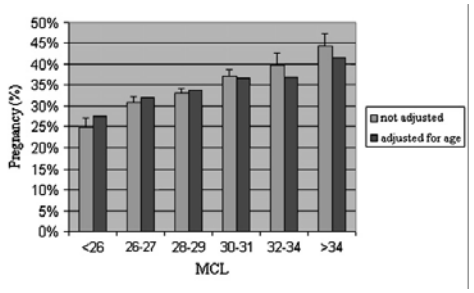
DIAGNOSIS

COST PER LIVE BIRTH BY FSH AND AGE



HENNE et al.
FERTIL. STERIL. 2008

PREGNANCY RATE PER ET IN RELATION TO STRATIFIED MCL, UNADJUSTED AND ADJUSTED FOR AGE. MEAN VALUES ± SEM (SEM NOT FOR ADJUSTED VALUES). P_{trend} <.0001 FOR BOTH



BRODIN ET AL
FERTIL. STERIL. 2007

Gynecological Endocrinology, April 2007; 23(4): 206–212 informa

ORIGINAL ARTICLE

Sonographic assessment of ovarian reserve. Its correlation with outcome of *in vitro* fertilization cycles

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Abstract

Ovarian reserve is a crucial factor for normal ovarian response and the achievement of pregnancy after *in vitro* fertilization (IVF). Recently, the study of morphological markers by means of ultrasonographic counting of antral follicles (AFC) has proved useful. The present prospective study included 327 consecutive IVF patients who had a basal ultrasound scan of their ovarian reserve during the early follicular phase and had a first IVF cycle between 1 and 3 months later. We performed 313 ovum pick-ups with a mean of 11.1 ± 7.9 oocytes retrieved. The pregnancy rate per aspiration was 34.5%. Clear and significant differences were observed between normal and low response with respect to AFC, follicle-stimulating hormone (FSH) level and age. We also found that AFC correlated negatively and significantly with age, FSH and LH, and positively and also significantly with the total number of follicles, estradiol level and the number of oocytes retrieved. Using receiver operating characteristic curves, the cut-off value of AFC for poor response was 7 follicles. The value of AFC for predicting pregnancy was lowest, although patients with AFC of 8 or more follicles obtained significantly higher pregnancy rates. We consider that AFC should be included in the study of the infertile patient.

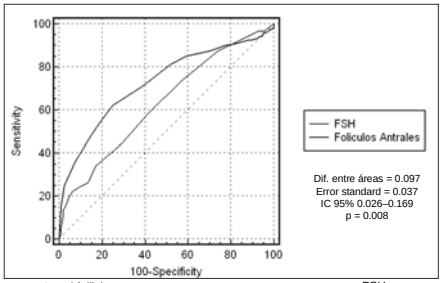
Keywords: *Antral follicle counts, sonographic assessment of IVF of ovarian reserve, IVF*

AFC: Multivariate Logistic Regression Analysis

NON CANCELLATION

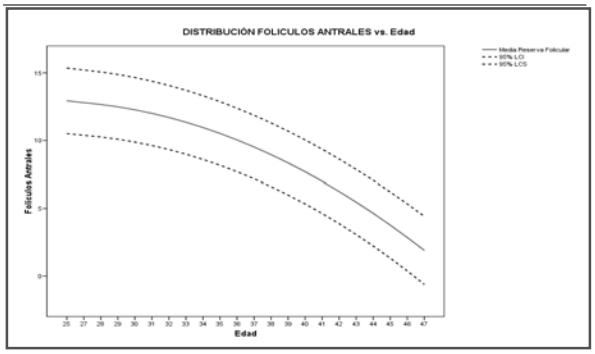
		B	ET	P	OR	IC OR 95%
AGE						
	≤33	-0.433	0.293	0.139	0.64	(0.36-1.15)
	34-36	-0.177	0.310	0.567	0.83	(0.45-1.53)
	37-39	-0.336	0.294	0.254	0.71	(0.40-1.27)
	≥40	-	-	-	1	-
AFC						
	≤5	-	-	-	1	-
	6-8	0.809	0.269	0.003	2.24	(1.32-3.80)
	9-11	1.384	0.313	<0.001	3.99	(2.15-7.37)
	≥12	1.730	0.355	<0.001	5.64	(2.81-11.32)

AFC
PREDICTIVE VALUE FOR LOW RESPONSE



	Antral follicles	FSH
	AUDC = 0.726 (0.67-0.77)	AUDC = 0.629 (0.57-0.68)
≤ 7	S = 62.0% (52.7-70.7) E = 74.8% (68.3-80.5) PPV = 59.1% NPV = 77.0%	S = 33.9% (25.5-43.0) E = 83.0% (77.2-87.9) PPV = 53.9% NPV = 68.1%

AFC and AGE
RESULTS



C.C. TEST
Multivariate Logistic Regression Analysis

CANCELLATION

		B	ET	P	OR	IC OR 95%
E_2 D3						
	≤25	-	-	-	1	-
	26-40	0.620	0.378	0.101	1'85	(0'88-3'89)
	41-60	0.589	0.390	0.131	1'80	(0'83-3'87)
	>60	1.070	0.354	0.003	2'91	(1'44-5'88)
FSH TOTAL						
	≤14	-	-	-	1	-
	15-18	-0.380	0.499	0.442	0'68	(0'25-1'80)
	19-25	1.05	0.378	0.006	2'85	(1'36-5'99)
	>26	1.46	0.372	<0.001	4'30	(2'07-8'92)

LOGISTIC REGRESSION ANALYSIS FOR AGE, CYCLE DAY 3 FSH AND PREVIOUS CANCELLED CYCLE AND ALL POSSIBLE COMBINATIONS AS PROGNOSTIC INDICATORS OF OVARIAN RESPONSE IN ART CYCLES IN THE WHOLE POPULATION STUDIED

	ODDS RATIO	95% CI
Age alone	0.842	0.772-0.918
FSH alone	0.999	0.998-1
Previous cancelled cycle alone	7.58	4.13-13.81

PEÑARRUBIA et al 2005
Hum. Reprod. 20:3: 622-628

LOW RESPONDERS CLASSIFICATION

1) Elderly patients with an abnormal endocrinological profile.

2) Young patients with an altered endocrinological profile.

3) Young patients with a normal basal hormonal profile.

LOW RESPONSE

RESULTS OF TREATMENT

PREGNANCY RATE / OPU IN LOW VS NORMAL RESPONDERS

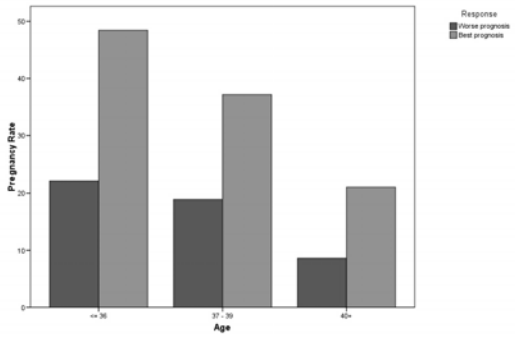
	LOW	NORMAL	P
AGE (<40 yrs)	15.6%	39.4%	*
FOLLICLES >14 mm. (> 6)	19.2%	39.4%	*
ESTRADIOL (>1200 pg/ml)	22.9%	37.8%	*
GNS CONSUMPTION (<3800 IU)	20.4%	38.8%	*
OOCYTES (>5)	17.6%	39.8%	*

* p< 0.001

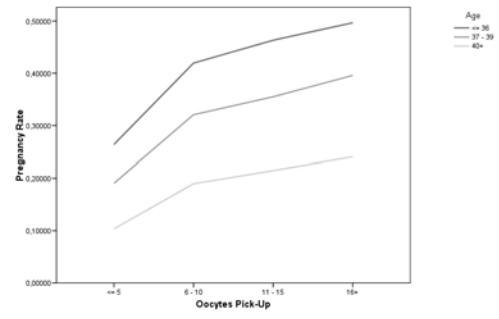
LOW RESPONSE

AGE INFLUENCE ON IVF RESULTS

PREGNANCY RATE ACCORDING TO THE PRESENCE OF FACTORS OF POOR RESPONSE



PREGNANCY RATE ACCORDING TO AGE AND NUMBER OF OOCYTES RETRIEVED



AFC: Multivariate Logistic Regression Analysis

PREGNANCY

		B	ET	P	OR	IC OR 95%
AFC						
	≤5	-	-	-	1	-
	6-8	-0.632	0.236	0.007	1.88	(1.18-2.99)
	9-11	-0.859	0.232	<0.001	2.36	(1.50-3.72)
	≥12	-1.379	0.233	<0.001	3.97	(2.51-6.25)
AGE						
	≤33	-0.685	0.230	0.003	1.98	(1.26-3.12)
	34-36	-0.786	0.234	0.001	2.19	(1.39-3.47)
	37-39	-0.634	0.242	0.009	1.88	(1.17-3'03)
	≥40	-	-	-	1	-

C.C. TEST
Multivariate Logistic Regression Analysis

PREGNANCY

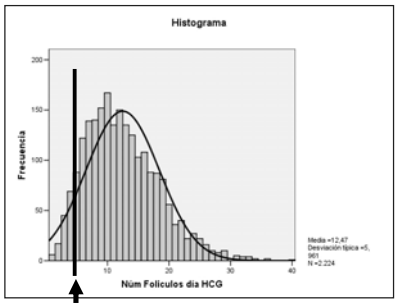
		B	ET	P	OR	IC OR 95%
AGE						
	≤33	1.073	0.266	<0.001	2.94	(1.75-5)
	34-36	0.955	0.244	<0.001	2.63	(2.61-4.3)
	37-39	0.442	0.254	0.081	1.56	(0.95-2.56)
	≥40	-	-	-	1	-
FSH TOTAL						
	≤14	1.05	0.285	<0.001	2.88	(1.65-5.03)
	15-18	0.83	0.294	0.004	2.31	(1.3-4.1)
	19-25	0.63	0.247	0.032	1.89	(1.05-3.38)
	>26	-	-	-	1	-

LOW RESPONSE

INFLUENCE OF NUMBER OF OOCYTES RETRIEVED

LOW RESPONSE

Number of follicles hCG day / IVF pregnancy (1st.IVF)



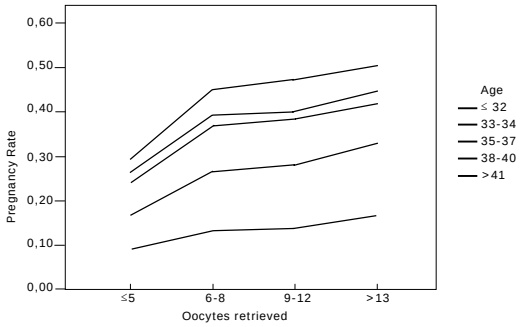
≤ 5 follicles (≥ 14 mm) day of HCG administration

MULTIVARIATE LOGISTIC REGRESSION. INFLUENCE OF THE NUMBER OF OOCYTES RETRIEVED ON PREGNANCY RATE (n=5476 OPU)

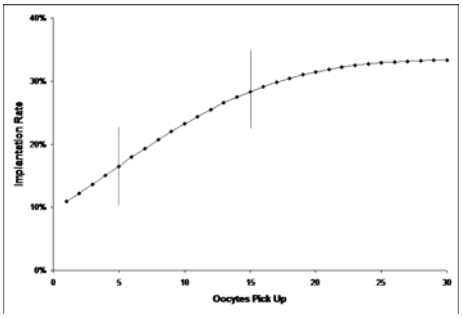
Oocytes retrieved	OR	Sig	95% C.I.
≤ 5	0,57	<0.001	0.46-0.70
6-8	1	-	-
9-12	1,01	0.9	0.83-1.23
≥ 13	1,13	0.2	0.94-1.36

Adjusted for age, basal FSH and Gns consumption

INFLUENCE OF THE NUMBER OF OOCYTES RETRIEVED ON PREGNANCY RATE n= 5476 OPU



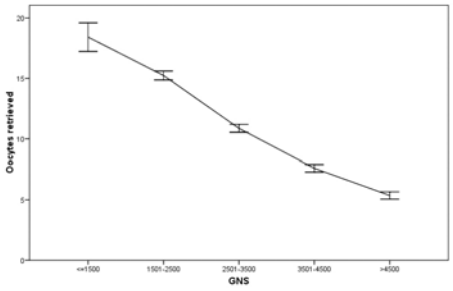
INFLUENCE OF THE NUMBER OF OOCYTES RETRIEVED ON IMPLANTATION RATE
n= 5476 OPU



LOW RESPONSE

INFLUENCE OF GNS CONSUMPTION

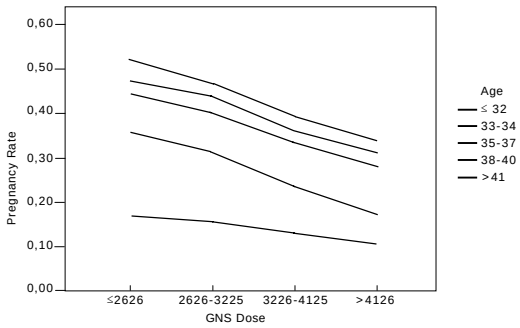
INFLUENCE OF GNS CONSUMPTION ON NUMBER OF OOCYTES RETRIEVED
n= 5476 OPU



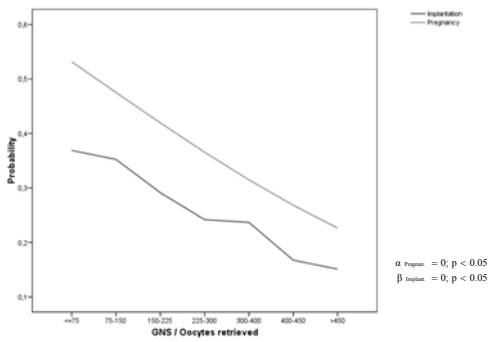
MULTIVARIATE LOGISTIC REGRESSION. INFLUENCE OF GONADOTROPHIN CONSUMPTION ON PREGNANCY RATE (n=5476 OPU)

GNS dose	OR	Sig	95% C.I.
≤ 2626 IU	1	-	-
2627-3225 IU	0.9	0.23	0.76-1.07
3226-4125 IU	0.6	<0.001	0.57-0.81
≥ 4126 IU	0.5	<0.001	0.43-0.67

INFLUENCE OF GONADOTROPHIN CONSUMPTION ON PREGNANCY RATE n= 5476 OPU



PREGNANCY AND IMPLANTATION RATES AND GNS CONSUMPTION PER OOCYTE RETRIEVED



LOW RESPONSE

INFLUENCE OF STIMULATION PROTOCOLS

LOW RESPONSE

- First IVF attempts:
  - Cycles analyzed 3683
- Ovarian stimulation protocol:
  - Long protocol GnRH-agonists
    - 2777 cycles
  - Short protocol GnRH-agonists
    - 906 cycles

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LOW RESPONSE

	N	Cancelled	Low response	Normal response
TOTAL	3683	230 (6.2%)	277 (7.6%)	3176 (86.2%)
Pregnancies	1876 (34.8%)	0	22 (10%)	1854 (37.5%)
LONG	2777 (75.4%)	114 (4.1%)	59 (2.1%)	2604 (93.8%)
Pregnancies	1207 (43.5%)	0	6 (30%)	1012 (49.2%)
SHORT	906 (24.6%)	116 (12.8%)	218 (24.1%)	572 (63.1%)
Pregnancies	152 (16.8%)	0	20 (9.2%)	119 (20.8%)

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LOW RESPONSE

Group A: Good prognosis
Age: <38 yrs & FSH: ≤ 10.5 UI/L
Group B: Young and poor prognosis
Age: <38 yrs & FSH: >10.5 UI/L
Group C: Old and good prognosis
Age: ≥ 38 yrs & FSH: ≤ 10.5 UI/L
Group D: Poor prognosis
Age: ≥ 38 yrs & FSH: > 10.5 UI/L

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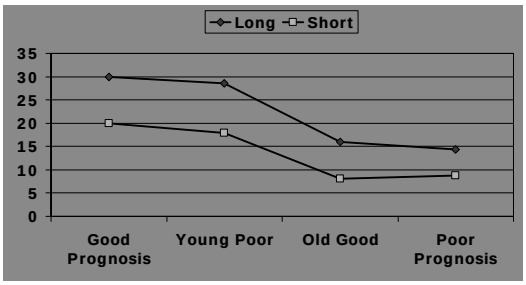
LOW RESPONSE
PREGNANCY RATE IN DIFFERENT PROGNOSIS GROUP



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WHEN SHOULD A BAD RESPONDER BE CANCELLED?

RÉSULTATS DU 2e CYCLE APRÈS UNES ANNULATION LORS DU 1er CYCLE

	Annulation cycle 1			
	Non	Mauvaise réponse	Hyper-stimulation	Déprogram-mation
Cycle 1 n	50 709	4 984	389	730
Cycle 2 n (%)	26.8	51.0	49.6	57.8
Annulation %	1.4	22.2	16.6	21.6
Grossesse %	18.3	12.1	21.2	12.3

B. ROSSIN-AMAR
J.GYNECOL.OBSTET.BIOL.REPROD. 2005; 34:5S14-5S17

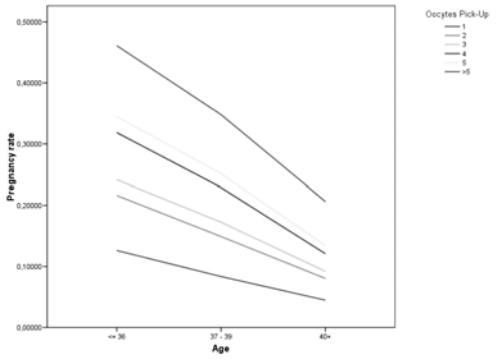
CLINICAL PREGNANCY RATES FOR PATIENTS WITH TRANSFER OF TWO GOOD OR EXCELLENT-QUALITY EMBRYOS, BY NUMBER OF OOCYTES RETRIEVED AND PATIENT AGE

	Age			
	< 37 years		≥ 36 years	
Oocytes retrieved	Cycles	Pregnant (%)	Cycles	Pregnant (%)
< 5	208	80 (38)[a,b]	142	37 (26)[b,d]
≥ 5	3532	1525 (43)[a,c]	426	123 (29)[c,d]

[a,d] Not significant
[b] p<.05
[c] p<.0001

DE SUTTER AND DHONT 2003

PREGNANCY RATE IN LOW RESPONDERS ACCORDING TO OOCYTES RETRIEVED



LOW RESPONDERS
CONCLUSIONS 1

1) Oocyte quality is not impaired in “normal” low responders (= Fertilization rates)

2) Different situation in older patients with low ovarian sensitivity and difficult response.

LOW RESPONDERS
CONCLUSIONS 2

1) Low efficacy of alternative protocols

2) Use of natural cycle for young low responders.

3) Oocyte donation is the last hope for these patients.

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Gracias por su atención
Thank you for your attention

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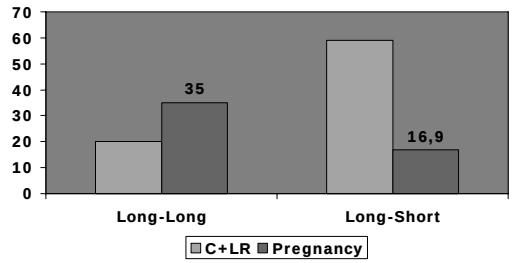
FUNDACIÓN SANTIAGO DEXEUS FONT

RESULTS OF THE ROC ANALYSIS FOR DIFFERENT PARAMETERS DEPENDING ON AFC

PARAMETER	OPTIMUM CUTOFF (number)	AUC	95% CI	Sn, %	Sp, %	PPV, %	NPV, %
Cycles canceled	12	0.578	0.548-0.608	47.7	66.7	39.0	74.1
Cancellation by poor and/or insufficient response	12	0.747	0.696-0.793	71.1	69.2	83.3	52.6
Oocyte pick-up	12	0.578	0.548-0.608	66.7	47.7	74.1	39.0
No donation	10	0.792	0.766-0.817	57.7	90.3	13.8	98.8
No transfer	12	0.534	0.502-0.566	55.1	56.9	15.1	90.1
Pregnancy per cycle started	14	0.521	0.487-0.555	56.6	50.0	60.7	45.7

BARRETO MELO ET AL FERTIL. STERIL. 2008

INFLUENCE OF THE STIMULATION PROTOCOL ON CANCELLATION, LOW RESPONSE AND PREGNANCY RATES (1st and 2nd cycle)



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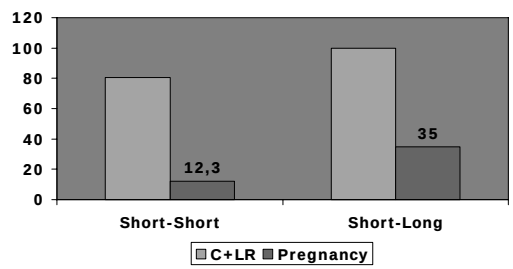
INFLUENCE OF THE STIMULATION PROTOCOL ON CANCELLATION, LOW RESPONSE AND PREGNANCY RATES (1st and 2nd cycle)



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