New Developments in GnRH Antagonist Co-treatment

Professor Basil C. Tarlatzis, MD PhD

Unit for Human Reproduction
1st Department of Obstetrics and Gynaecology
Aristotle University of Thessaloniki, Greece

Rationale for using GnRH antagonists

The premature LH surge

Cycle cancellation

20%

Loumaye 1990 Hum Reprod

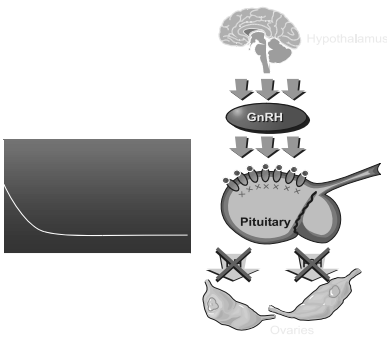
Rationale for using GnRH antagonists

The need both to control LH surge
as well as to avoid complex, high cost stimulation regimens
involving prolonged agonist treatment,

led to the development of newer antagonistic analogues
(Albano et al 2000, Borm and Mannaerts 2000, Olivennes et al 2000, Fluker et al 2001, European and Middle East Orgalutran Study Group 2001)

MECHANISM
OF GnRH ANTAGONIST ACTION

Mechanism of GnRH antagonist action



MECHANISM
OF GnRH ANTAGONIST ACTION

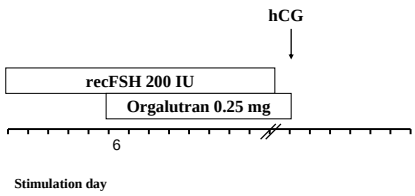
Antagonist treatment is highly dose dependent,
relying on the balance between
endogenous GnRH present and antagonist administered
(Felberbaum et al 1995)

Almost directly after GnRH antagonists enter circulation
any growing follicle or corpus luteum present will be adversely affected,
while uterine bleeding is expected to occur within 48h

Within 6-8 hours of administration, any imminent LH surge is blocked
(Klingmuler at al 1993)

SCHEMES
OF GnRH ANTAGONIST ADMINISTRATION

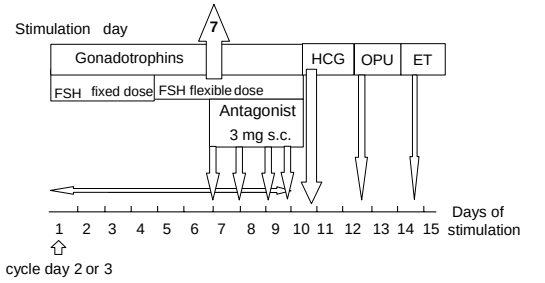
Multiple dose scheme



Diedrich et al 1994

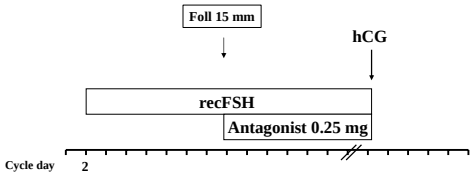
Single dose scheme

Olivennes et al Fertil Steril 1994

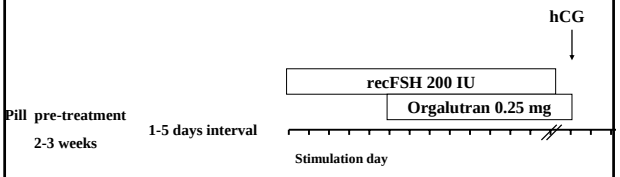


Flexible antagonist administration

Ludwig et al Hum Reprod 2002

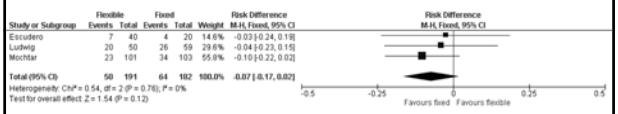


Oral contraceptive pill pre-treatment



Fischl et al 2001

Fixed vs. flexible antagonist administration



RD = -7% (95% CI:-17 to + 2)

Kolibianakis et al unpublished

Probability of pregnancy

GnRH agonists vs. GnRH antagonists


Arch Gynecol Obstet (2001) 265:175–182 © Springer-Verlag 2001

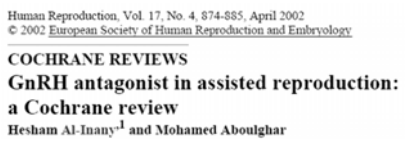
ORIGINAL ARTICLE

M. Ludwig · A. Katalinic · K. Diedrich

Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol

Meta-analysis

No difference in PR


Human Reproduction, Vol. 17, No. 4, 874-885, April 2002
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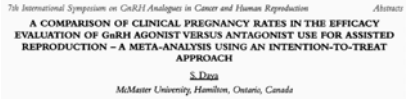
COCHRANE REVIEWS

GnRH antagonist in assisted reproduction: a Cochrane review

Hesham Al-Inany[1] and Mohamed Aboulghar

5% lower PR with antagonists


7th International Symposium on GnRH Analogues in Cancer and Human Reproduction Abstracts

A COMPARISON OF CLINICAL PREGNANCY RATES IN THE EFFICACY EVALUATION OF GnRH AGONIST VERSUS ANTAGONIST USE FOR ASSISTED REPRODUCTION – A META-ANALYSIS USING AN INTENTION-TO-TREAT APPROACH

S. Daya

McMaster University, Hamilton, Ontario, Canada

No difference in PR

Gonadotrophin-releasing hormone antagonists for assisted conception (Review)

Al-Inany HG, Abou-Setta AM, Aboulghar M

This record should be cited as:
Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001750. DOI: 10.1002/14651858.CD001750.pub2.

This version first published online: 19 July 2006 in Issue 3, 2006.
Date of most recent substantive amendment: 19 May 2006

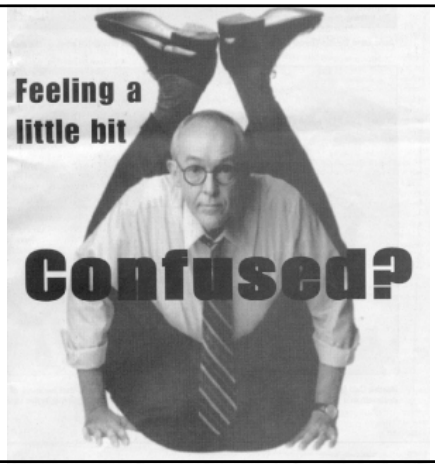
3.7% lower ongoing/live birth rate with antagonists

Human Reproduction Update, Vol.12, No.4 pp. 451–471, 2006 doi:10.1093/humupd/dml018
Advance Access publication August 18, 2006

Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis

E.M.Kolibianakis[1,5], J.Collins[2], B.C.Tarlatzis[1], P.Devroey[3], K.Diedrich[4] and G.Griesinger[4]

No difference in live birth rate



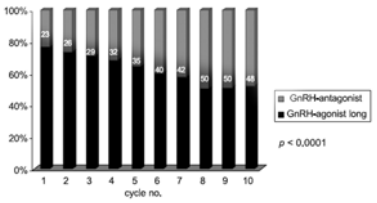
GnRH antagonists in ovarian stimulation: a treatment regimen of clinicians' second choice?

Data from the German national IVF registry. Griesinger et al. 2005 Hum Reprod

Age categories (years)	GnRH agonist (%)	GnRH antagonist (%)	*P*
18–30	28.5	25.4	
31–35	41.1	36.6	<0.0001
36–40	26.3	30.1	
41–55	3.8	7.9	

GnRH antagonists in ovarian stimulation: a treatment regimen of clinicians' second choice?

Data from the German national IVF registry. Griesinger et al. 2005 Hum Reprod

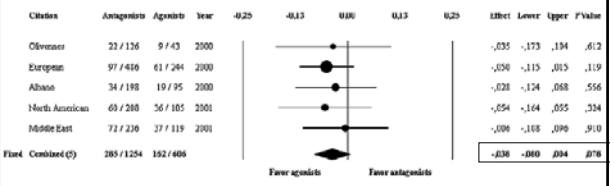


Proportion of long GnRH agonist and GnRH antagonist cycles stratified by cycle rank

In 2003, 1 in 4 cycles was performed with GnRH antagonists

Odds ratio for live birth
in the studies included in the Cochrane meta-analysis

(Al-Inany and Aboulghar. Cochrane 2001)



35% power to detect a difference of 5% in LB

Kolibianakis et al. Hum Reprod Update 2006

Evidence based approach

Meta-analysis

What is the question of interest?

Is live birth rate

different

between patients randomized to receive

GnRH agonists or GnRH antagonists?

LBR:

How different?

What magnitude of difference we accept as clinically important?

5%

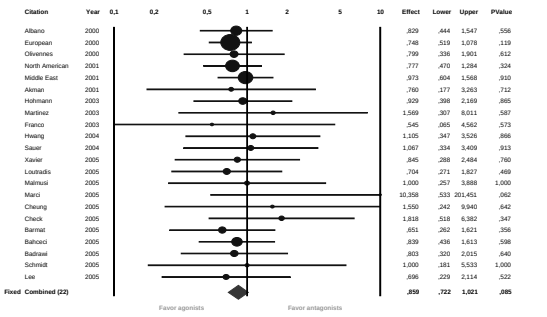
Agonists vs. Antagonists in IVF

Kolibianakis et al. Hum Reprod Update 2006

Probability of live birth

LIVE BIRTH

Kolibianakis et al. Hum Reprod Update 2006



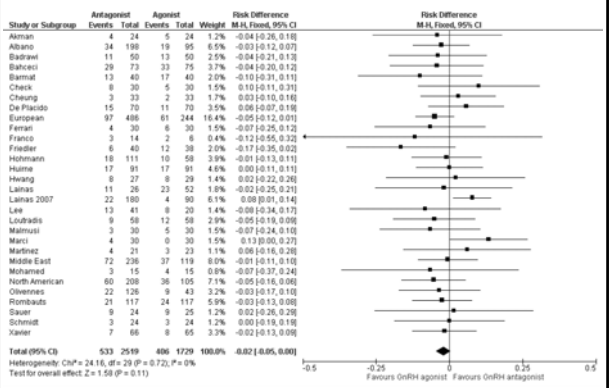
Odds ratio:0.859

p=0.085

Rate difference

2.7%

LIVE BIRTH



RD= 2%

95% CI -5% to+ 0%

Kolibianakis and Griesinger unpublished

ODDS RATIO= 0.88

95% CI : 0.76 to 1.03

The probability of live birth

does not depend

on the type of analogue used

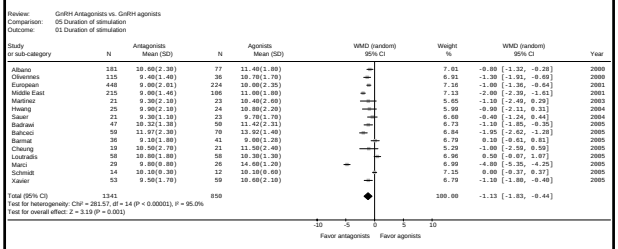
for inhibition of premature LH surge

Agonists vs. Antagonists in IVF

Kolibianakis et al. Hum Reprod Update 2006

Duration of FSH treatment

Duration of FSH treatment



1.1 less days with antagonists
p<0.001

Kolibianakis et al. Hum Reprod Update 2006

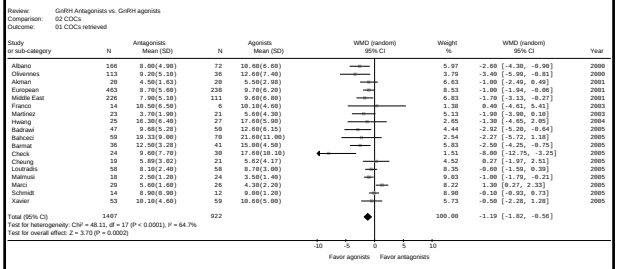
Agonists vs. Antagonists in IVF

Kolibianakis et al 2006 (23)

COCs retrieved

Embryos cryopreserved

COCs retrieved

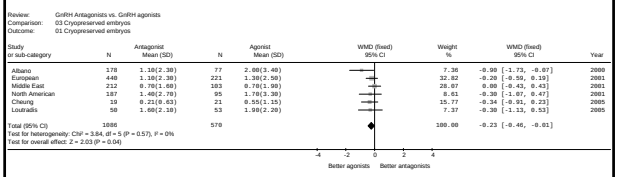


1.2 COCs more with GnRH agonists

p<0.001

Kolibianakis et al. Hum Reprod Update 2006

Cryopreserved embryos



0.23 cryopreserved embryos more with GnRH agonists

p<0.001

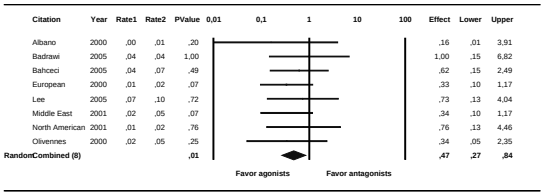
Kolibianakis et al. Hum Reprod Update 2006

Agonists vs. Antagonists in IVF

Kolibianakis et al. Hum Reprod Update 2006

Hospital admission due to OHSS

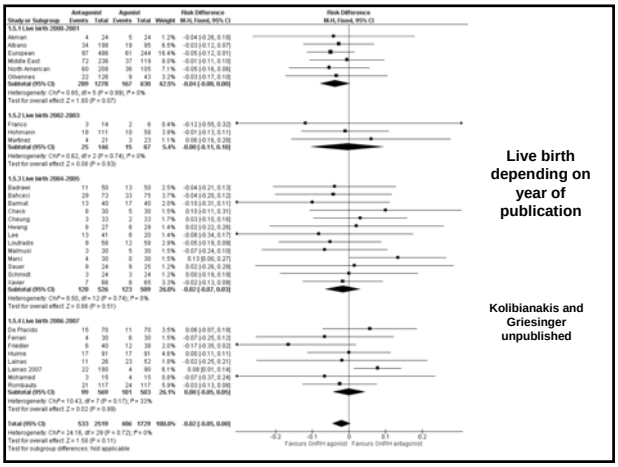
Hospital admission due to OHSS



RR : 0.47

~ 2 times less risk for hospital admission due to OHSS with GnRH antagonists

Kolibianakis et al. Hum Reprod Update 2006



Live birth in PCOS patients and poor responders

Kolibianakis and Griesinger unpublished

Study or Subgroup	Antagonist Events	Antagonist Total	Agonist Events	Agonist Total	Weight	Risk Difference M-H, Fixed, 95% CI
1.4.1 PCOS						
Bahceci	29	73	33	75	19.4%	-0.04 [-0.20, 0.12]
Hwang	8	27	8	29	7.3%	0.02 [-0.22, 0.26]
Lainas	11	26	13	52	9.1%	0.17 [-0.05, 0.40]
Subtotal (95% CI)	48	126	54	156	35.9%	0.02 [-0.09, 0.14]
Heterogeneity: Chi² = 2.39, df = 2 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.4.2 Poor responders						
Akman	4	24	5	24	6.3%	-0.04 [-0.26, 0.18]
Cheung	3	33	2	33	8.7%	0.03 [-0.10, 0.16]
De Placido	15	66	11	67	17.4%	0.06 [-0.07, 0.20]
Lainas 2007	0	0	0	0		Not estimable
Malmusi	3	30	5	30	7.9%	-0.07 [-0.24, 0.10]
Marci	4	30	0	30	7.9%	0.13 [0.00, 0.27]
Martinez	4	21	3	23	5.8%	0.06 [-0.16, 0.28]
Mohamed	3	15	4	15	3.9%	-0.07 [-0.37, 0.24]
Schmidt	3	24	3	24	6.3%	0.00 [-0.19, 0.19]
Subtotal (95% CI)	39	243	33	246	64.1%	0.03 [-0.04, 0.09]
Heterogeneity: Chi² = 4.85, df = 7 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)	87	369	87	402	100.0%	0.03 [-0.03, 0.08]
Heterogeneity: Chi² = 7.25, df = 10 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Not applicable						

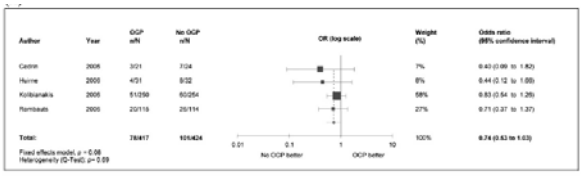
Risk Difference M-H, Fixed, 95% CI

-0.2 -0.1 0 0.1 0.2

Favours OnRH agonist Favours OnRH antagonist

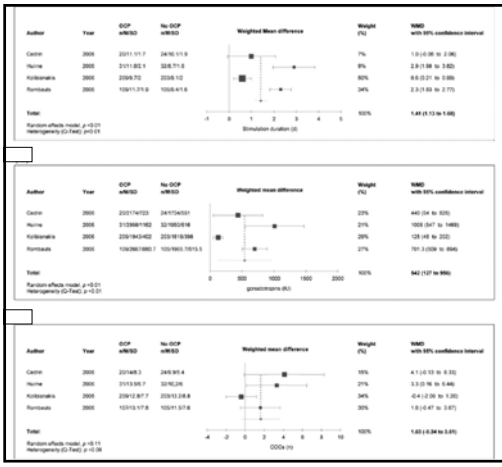
Modifications of the GnRH antagonist protocol

OCP in antagonist cycles



Clinical/ongoing pregnancy RD -5% (-10 to +0.4), p=0.07

Griesinger et al 2007 FS

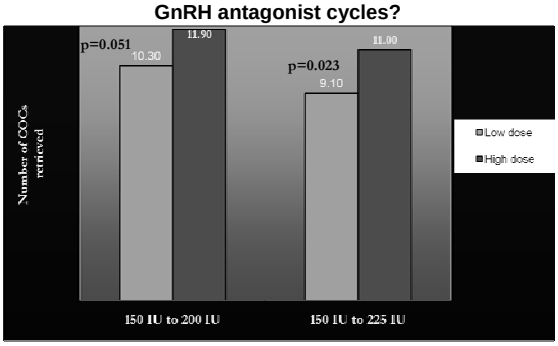


OCP in antagonist cycles

Griesinger et al 2007 FS

Starting dose of FSH

Should we increase the starting dose of gonadotropins in GnRH antagonist cycles?



Wikland et al 2001 Hum Reprod, Out et al 2004 Hum Reprod

Starting dose of FSH

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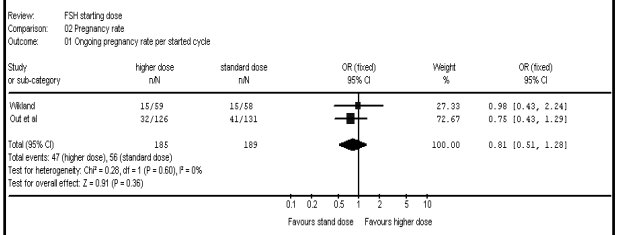
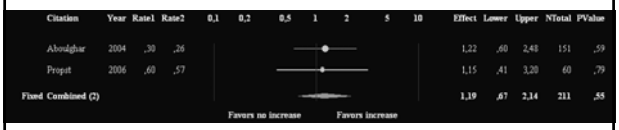


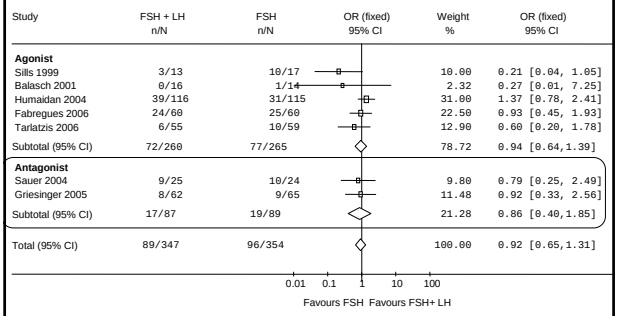
Wikland et al 2001 Hum Reprod, Out et al 2004 Hum Reprod

Should we increase the gonadotrophin dose when antagonist is started?



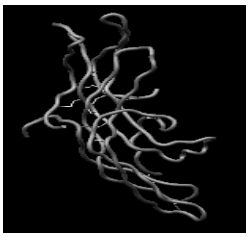
Kolibianakis et al unpublished

Should we add LH in antagonist cycles?

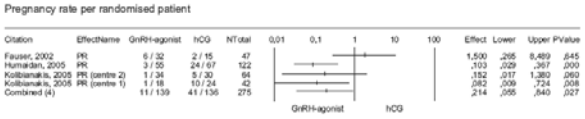


Kolibianakis et al. Hum Reprod Update 2007

Replacement of hCG



Replacement of hCG by GnRH agonist



The use of GnRH agonist to trigger final oocyte maturation should be performed with caution and only within the context of a randomized controlled trial

Griesinger et al. Hum Reprod Update 2005

Is luteal support necessary in GnRH antagonist cycles?

Fixed dose of rec FSH 150 IU, daily antagonist by a follicle of 14mm

By a follicle of 18mm patients were randomized to receive rec hCG, rec LH, GnRH agonist

No luteal support

Beckers et al. JCEM 2004

Is luteal support necessary in GnRH antagonist cycles?

	r-hCG (n = 11)	r-LH (n = 13)	GnRH agonist (n = 15)
Duration follicular phase (d)	11 (9–14)	12 (10–14)	12 (9–16)
No. days GnRH antagonist	4 (3–8)	4 (3–6)	4 (2–7)
No. follicles ≥ 11 mm	7 (5–16)	8 (2–18)	9 (3–13)
No. oocytes retrieved	7 (3–23)	7 (1–26)	10 (1–17)
No. patients achieving embryo transfer[b]	9	11	14
Pregnancy[b]	2 (18%)	1 (8%)	2 (13%)
Ongoing pregnancy[b]	2 (18%)	0 (0%)	1 (7%)

The study was canceled prematurely because of observed premature luteal phase bleeding and extremely low pregnancy rates.

Beckers et al. JCEM 2004

Conclusions

Flexible antagonist administration by a follicle of 14-15 mm appears to decrease the probability of pregnancy

Increasing the starting dose of gonadotrophins in GnRH antagonist cycles does not appear to be necessary

Increasing the dose of gonadotrophins when GnRH antagonist is started does not appear to be necessary

Addition of recombinant LH after antagonist initiation does not appear to be necessary

Conclusions

Replacing hCG with GnRH agonist is associated with a decreased probability of pregnancy in antagonist cycles

Luteal support is necessary in GnRH antagonist cycles

Conclusions

The probability of live birth rate does not depend on the type of analogue used for suppression of premature LH surge

A shorter duration of FSH stimulation (~1 day less) is expected with the use of GnRH antagonists and is accompanied by a lower number of COCs retrieved (1.2 less) as compared to GnRH agonists

The use of GnRH antagonists is associated with a significantly lower risk of hospital admission due to OHSS (RR 0.47)

What beyond meta-analysis?

Patient friendliness

Rational use

Safety

Flexibility

Thank you !