Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates

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Agent to trigger ovulation

- hCG
- GnRH agonist:
  - A useful strategy to prevent ovarian hyperstimulation syndrome (OHSS)
  - No difference in # of MII oocytes, fertilization rates, or embryo development in IVF-ET cycles
  - Significant ↓ in pregnancy rates

GnRHa-induced ↓ in pregnancy rates

- Mainly due to irreversible luteolysis
  - Negative feedback that suppress pituitary LH release
  - Ovary is a target of GnRH receptor and action
  - Ovary possesses intrinsic GnRH axis
  - GnRHa can mobilize Ca+ , activates mitogen protein kinases, ↑ c-fos mRNA expression, ↓ steroidogenic capacity → *GnRHa initiated intracellular cascade to drive programmed cell death or apoptosis*
- Direct impact on oocyte quality → influence the capacity of the embryo to be implanted

- *Objective*: to evaluate **the implant capacity of embryos** derived from oocytes matured with a bolus of GnRHa
  - **Ovarian compartment** (folliculogenesis, oocyte maturation and corpusl uteum activity)
  - Endometrial compartment (implantation)

  ➔ Oocyte donor program

Methods

- Donors: *recruited following the guidelines set by Spanish Committee of Assisted Reproductive Techniques*
  - 18~35 y/o healthy female with normal MC cycle
  - Donation is anonymous and altruistic
  - Exclusion: PCO, endometriosis, hydrosalpinges, and severe male factor (total # < 5x 10^6)
- n= 60, all received OCPs before stimulation to synchronized oocyte donation
- Recipients (n=89)

Protocol

GnRH antagonist - FSH/LH step-down protocol

D1	2	3	4	5	6	7	8	9			
		150 IU/d rFSH (Puregon)					GnRH antagonist				
or											
			150 IU/d rFSH (Puregon)					GnRH antagonist			

GnRH antagonist (Orgalutran) 0.25 mg/d SC
Menopur (75 IU rFSH + 75 IU LH)

Timing: follicles > 18 mm and E_2 < 5,000 pg/mL

- hCG 250 ug sc (30)
- GnRHa 0.2 mg sc (30)

- TVOR → 32-34 hrs later after hCG or GnRHa
- ICSI (intracytoplasmatic sperm injection)
- Fertilization: *2 pronuclei*
- ET at day 3 of fertilization → any embryo with multinucleated blastomeres excluded
- 60 recipients (34-47 y/o):
  - Ovarian failure (63%), 4 unsuccessful IVF cycles (32%), Genetic (2%), Others (3%)
  - **E_2** → EM > 8mm (mature)
  - **P (600mg/d)** → for at least 3 days before ET

- A pregnancy test performed 15 days after ET → (+) → ultrasound scan 2 wks later to determine # and status of embryos
- Clinical pregnancy: PPT(+) + FHB(+)
- Biochemical pregnancy: PPT(+) + FHB(-)
- Implantation rate: # of sacs / # of embryos transferred

- Analysis of variance, student t test, Fisher exact test

- The donor's corpus luteum activity was indirectly evaluated by luteal phase duration.
  - From day of triggering to presence of bleeding (EM shading)
- Ovarian hyperstimulation syndrome: *(Rizk and Aboulghar's criteria)*
  - 5/30 donors in hCG group developed mild OHSS (ovarian enlargement (5-7cm), bloating, and minimal abdominal pain) → hospitalization not required

Results

TABLE 1

Triggering ovulation with GnRH agonist does not compromise embryo implantation rates.

	GnRH agonist	hCG	*P*
No. donors	30	30	
Age (yrs)	21.56 ± 2.8	24.77 ± 1.4	ns
Serum levels day 3			
FSH (mIU/mL)	5.2 ± 1.2	4.4 ± 1.3	ns
LH (mIU/mL)	2.8 ± 0.3	2.3 ± 1.9	ns
E_2 (pg/mL)	44.1 ± 9.3	32.5 ± 20.7	ns
GnRH antagonist (ampules)	4.46 ± 2.12	4.63 ± 1.41	ns
FSH (IU)	1,612.5 ± 103	1,605 ± 225	ns
LH (IU)	337.5 ± 174.2	441 ± 213	ns
E_2 (pg/mL) day hCG	2,261.2 ± 195	1,726.33 ± 354	ns
After day 5 of COH			
Follicles >12 mm	5.2 ± 1.2	3.1 ± 2.2	ns
Follicles <12 mm	8.2 ± 1.9	9.2 ± 1.2	ns
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Folicles day hCG	11.56 ± 2.5	7.11 ± 3.4	ns
COH (days)	10.4 ± 2.12	10.8 ± 1.89	
Luteal phase (days)	4.16 ± 0.70	13.63 ± 2.12	<.05
OHSS rate (n)	(0/30)	(5/30)	
%	0	16.6	<.05

Note: ns = not significant; COH = controlled ovarian hyperstimulation.

Acevedo. GnRH agonists do not alter embryo implantation. Fertil Steril 2006.

TABLE 2

Triggering ovulation with GnRH agonist does not compromise embryo implantation rates.

	GnRH agonist	hCG	*P*
Oocytes (n)	327	288	ns
Oocytes (x)	9.1 ± 4.01	10.3 ± 6.3	ns
Fertilization rate (%)	80	65	ns
Oocytes MI (%)	6	8	ns
Oocytes MII (%)	70	76	ns
Embryo quality (%)			
Grade 1	35	50	ns
Grade 2	52	41	ns
Grade 3	72	8	ns
Multinucleated	4	1	ns
Embryos with >8 blastomeres (x)	1.5 ± 1.2	1.9 ± 1.3	ns

Note: ns = not significant; x = mean ± SD.

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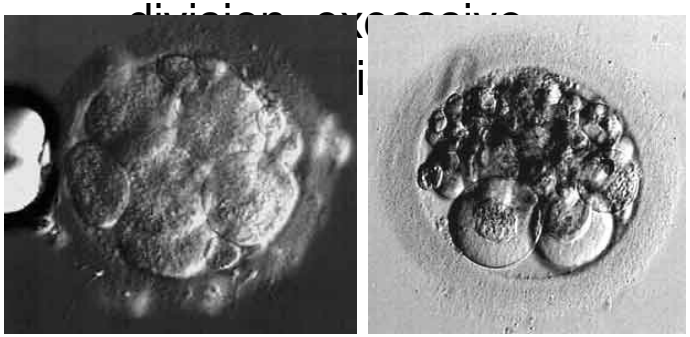

Grade 1: even cell division, no fragmentation

Grade 2: even cell division, small fragmentation

Grade 3: uneven cell division, moderate fragmentation

Grade 4: uneven cell

TABLE 3

Triggering ovulation with GnRH agonists does not compromise embryo implantation rates.

	GnRH agonist	hCG	*P*
No. recipients	30	30	
Oocytes donated	5.9 ± 2.4	5.4 ± 3.1	ns
Pregnancies/transfer (%)	55	59	ns
Biochemical pregnancy (%)	5	9	ns
Clinical pregnancy (%)	84	90	ns
Implantation rate (%)	29	32	ns

Note: ns = not significant.

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summary

- No significant difference in # of retrieved oocytes, MII oocytes, fertilization, pregnancy / transfer, and implantation rates
- Significant difference ***in luteal phase length*** and in ***OHSS***
  - Shorter luteal phase and fewer OHSS in GnRHa triggered group

Discussion

- ↑ early pregnancy losses in IVF-ET cycles when ovulation induction with GnRHa
  - Mostly related to GnRHa dependent luteolysis
  - Still unknown whether it could also be due to some alteration to some extent in developmental program of embryo
- **Oocyte donor cycle model**
  - Ovary would be the sole receptor of GnRHa action → excluding corpus luteum and endometrium as factors in implantation failure

- GnRHa can induce a physiologic release of LH that is sufficient to promote oocyte maturation to the same level as that generated by hCG
  - acute release of LH and FSH (flare effect)
- Embryo is **NOT** the factor for decrease in early implantation → luteinized granulosa cells of ovary as the main target for GnRHa reception and action
  - Corpus luteum performance is seriously affected when ovulation induced with GnRHa

- COS protocols based on GnRH antagonist to prevent premature LH rise and GnRH agonist for ovulation triggering provide a safe and OHSS-free clinical environment.
  - Loner half-life of hCG → sustained luteotrophic effect → OHSS

Fetil Steril 2004;81:1–5

- GnRHa to induce final oocyte maturation can be a good alternative to avoid OHSS in ART

Conclusion

- In controlled ovarian stimulation IVF donor cycles, GnRHa trigger ovulation and induce luteolysis but do not compromise embryo implantation capacity.

Thank You !