Les stimulations fortes sont-elles délétères?
Quand plus c'est mieux

Dominique de Ziegler

Foch-ART Center Suresnes France

Disclosures: *D. de Ziegler, MD*

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- Ferring Pharmaceuticals
- Teva Pharmaceuticals
- *Seventure Partners*
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ART and COS, together by necessity

COS new twists

Vitrification, old technique, new tools

OHSS, a memory of time past

Genetics all over

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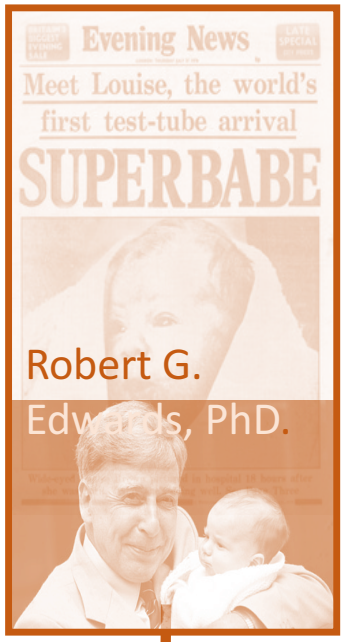

ovulation

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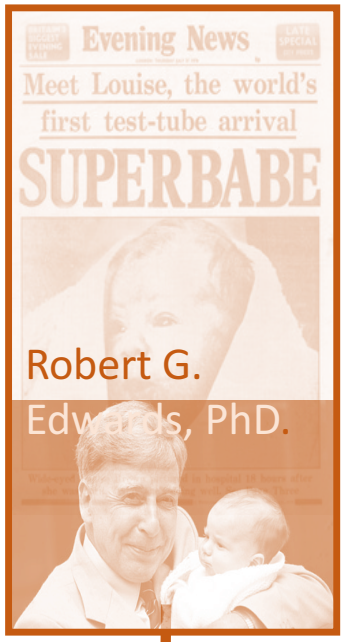

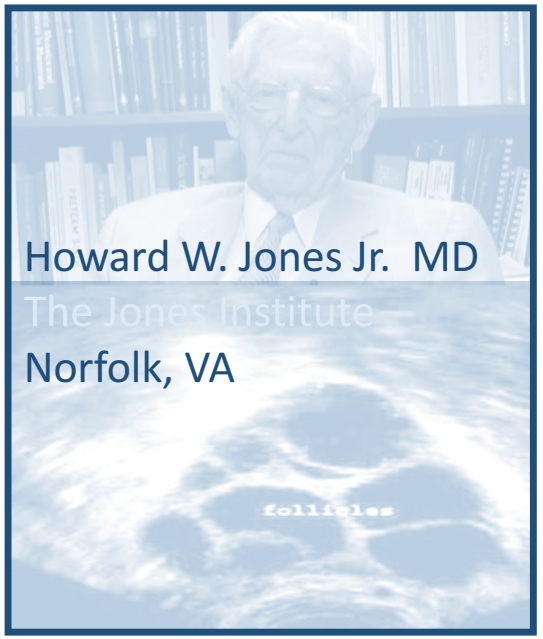

COS

ovulation

Multiple ovulation

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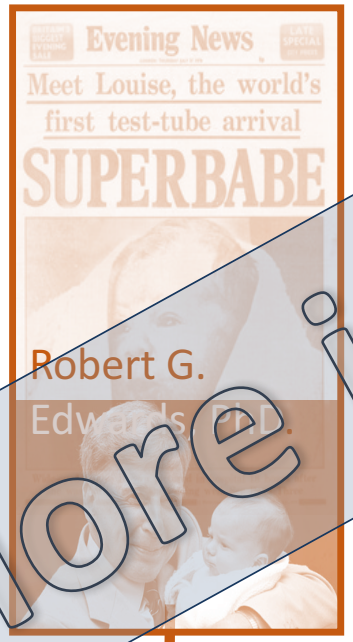
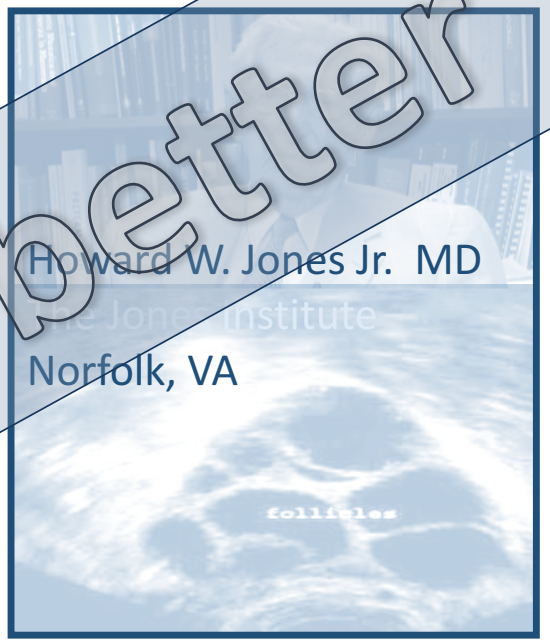


Robert G. Edwards PhD.



Howard W. Jones Jr. MD

The Jones Institute

Norfolk, VA

More is better

COS

ovulation

Multiple ovulation

THE TIMES THEY ARE A-CHANGIN'

CELEBRATING THE SONGS OF

BOB DYLAN

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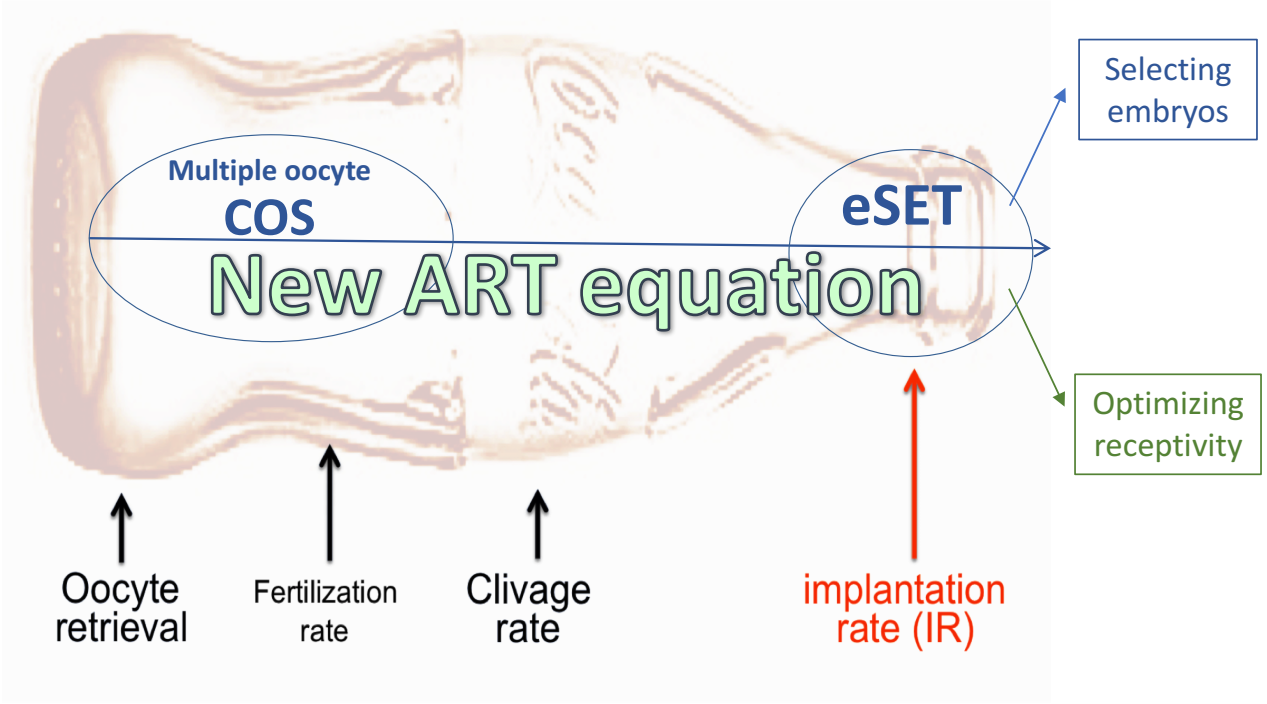

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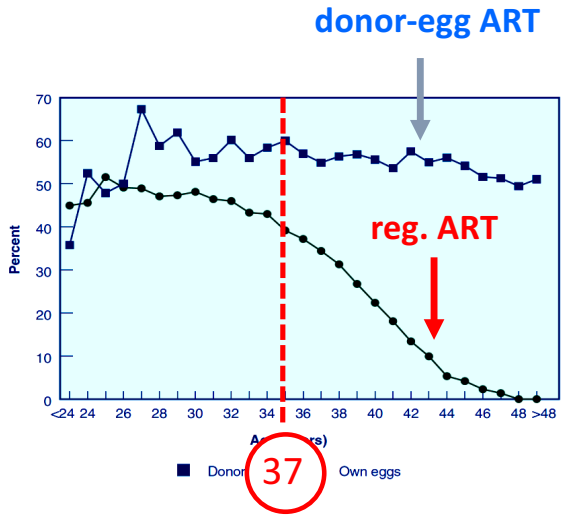
oocyte quality



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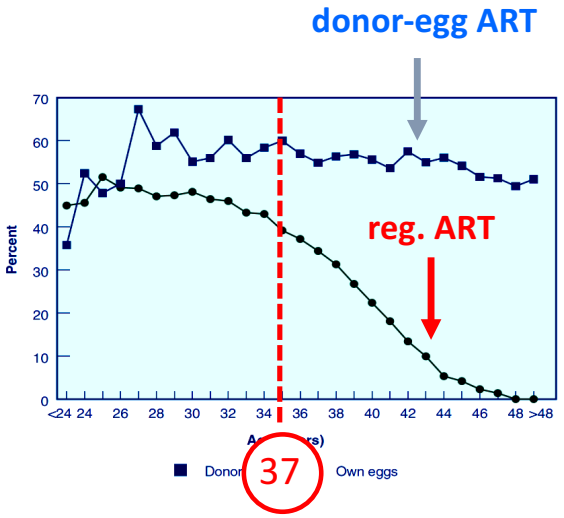
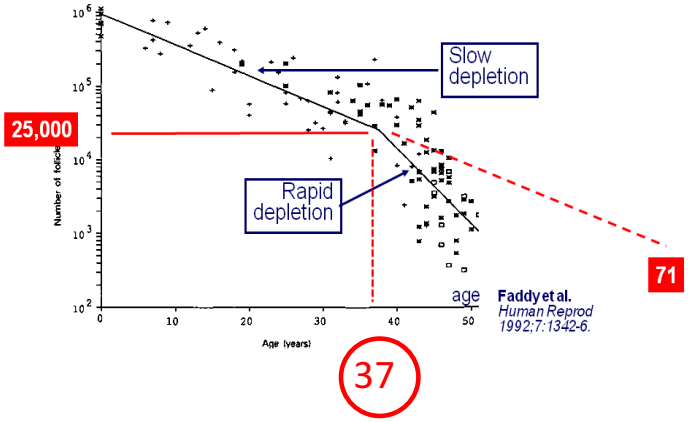
oocyte quality



oocyte quantity



Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

human reproduction

ORIGINAL ARTICLE *Infertility*

Reproductive potential of a metaphase II oocyte retrieved after ovarian stimulation: an analysis of 23 354 ICSI cycles

D. Stoop*, B. Ermini, N.P. Polyzos, P. Haentjens, M. De Vos, G. Verheyen, and P. Devroey

Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium

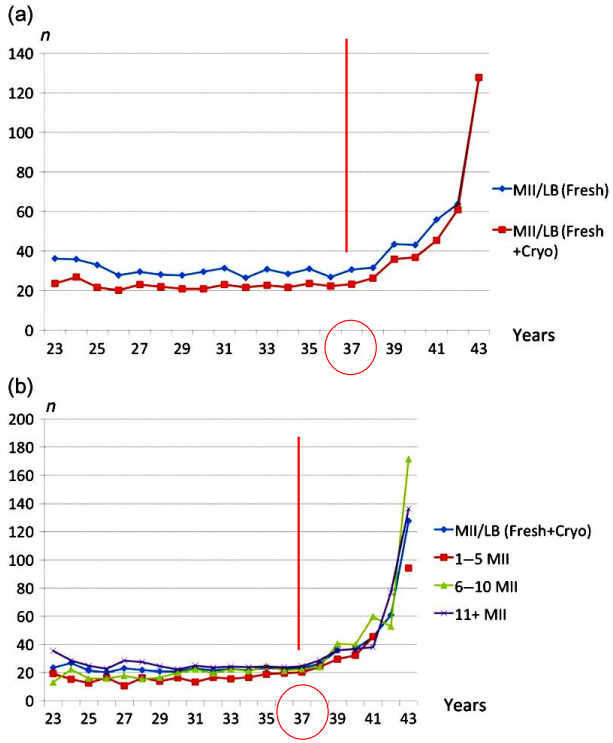
Stoop D et al. Hum. Reprod. 2012;27:2030-2035

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

COS response and ART outcome

Mature oocytes per live birth: (a) fresh cycles and cumulative outcome and (b) cumulative outcome in relation to the oocyte yield.



Stoop D et al. Hum. Reprod. 2012;27:2030-2035

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Human Reproduction, Vol.29, No.6 pp. 1218–1224, 2014
Advanced Access publication on March 20, 2014 doi:10.1093/humrep/deu053

human reproduction ORIGINAL ARTICLE *Infertility*

Association between response to ovarian stimulation and miscarriage following IVF: an analysis of 124 351 IVF pregnancies

Sesh Kamal Sunkara[1,*], Yacoub Khalaf[1], Abha Maheshwari[2], Paul Seed[1], and Arri Coomarasamy[3]

[1]King's College London, London, UK [2]University of Aberdeen, Aberdeen, UK [3]University of Birmingham, Birmingham, UK

*Correspondence address. E-mail: sksunkara@hotmail.com

Les stimulations fortes sont-elles délétères?

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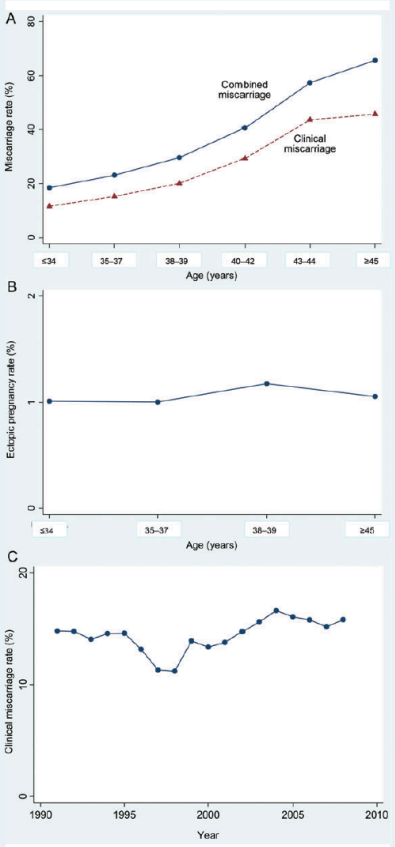


Figure 2 (**A**) Miscarriage rate by age. (**B**) Ectopic pregnancy rate by age. (**C**) Clinical miscarriage rate by time period.

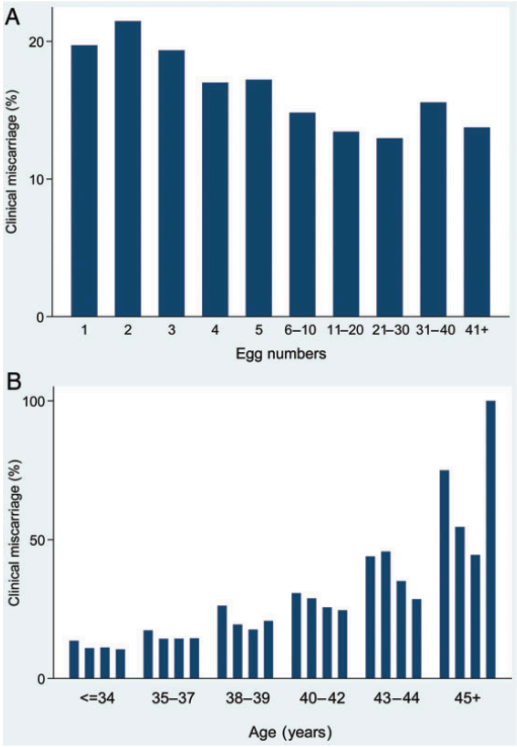


Figure 3 Relationship between oocyte number and clinical miscarriage rate. (**A**) Overall association. (**B**) Stratified by age group. Each age group was divided according to oocyte number; from left to right: 1–3 oocytes, 4–9 oocytes, 10–14 oocytes, ≥15 oocytes.

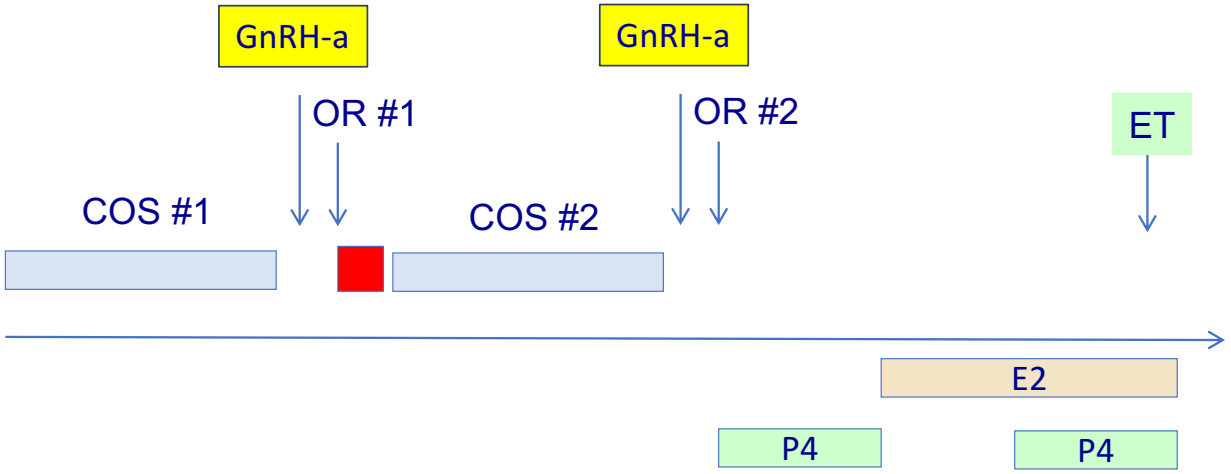
Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Accepted Manuscript

Title: Dual ovarian stimulation is a new viable option for enhancing the oocyte yield when the time for assisted reproductive technnology is limited

Author: Rebecca Moffat, Paul Pirtea, Vanessa Gayet, Jean Philippe Wolf, Charles Chapron, Dominique de Ziegler



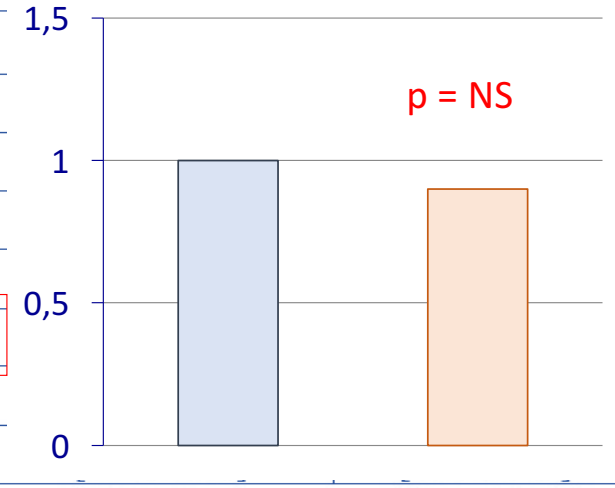
Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Université Paris-Descartes, Hôpital Cochin Paris, France

More oocytes in less time: The Duplex protocol (DPX)

Characteristic	COS 1	COS 2	P value
Estradiol day 6 (pg/ml)	469,8 ± 333,8 [70-1363]	220 ± 138,6 [62-549]	0,002
Progesterone day 6 (ng/ml)	0,6 ± 0,5 [0,1-2,1]	0,6 ± 0,3 [0,1-1,5]	0,137
Estradiol day 8 (pg/ml)	696,6± 493,2 [122-2213]	244 ± 168,8 [55-746,0]	<0.001
Progesterone day 8 (ng/ml)	0,6 ± 0,4	0,6 ± 0,4	0,707
Estradiol day OI (pg/ml)			0,001
Progesterone day OI (ng/ml)			0,234
Oocytes			0,03
Oocytes M2			0,073
2 PN (mean)			0,108
Blastocysts (mean)			0,64
Length of Stimulation (days)			<0.001
Total FSH (IU)			<0.001



Results are expressed as the mean ± SD [min-max]

Les stimulations fortes sont-elles délétères?
Quand plus c'est mieux

Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation

Filippo Maria Ubaldi, M.D., M.Sc.,[a,b,c] Antonio Capalbo, Ph.D.,[a,b,c] Alberto Vaiarelli, M.D., Ph.D.,[a,b]
Danilo Cimadomo, M.Sc.,[a,b,d] Silvia Colamaria, M.D.,[a,b] Carlo Alviggi, M.D., Ph.D.,[d,e]
Elisabetta Trabucco, M.D.,[a,b] Roberta Venturella, M.D.,[a,b,f] Gábor Vajta, Ph.D.,[g,h] and Laura Rienzi, M.Sc.[a,b,c]

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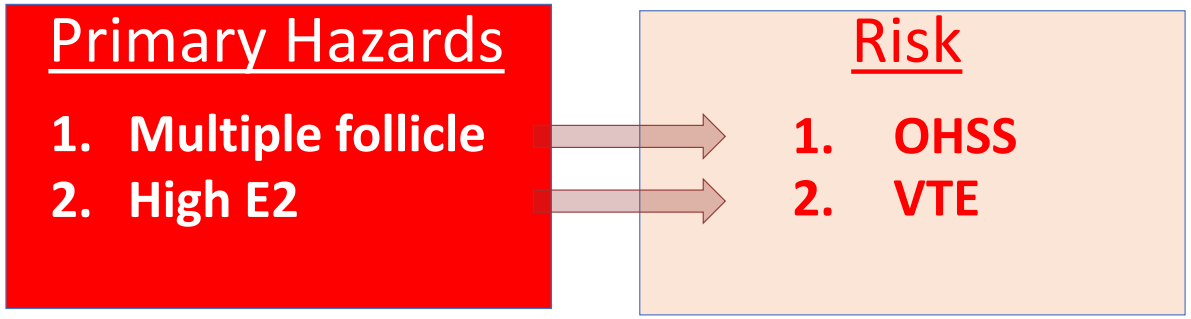
Problem: Hazards different from expected



Les stimulations fortes sont-elles délétères?

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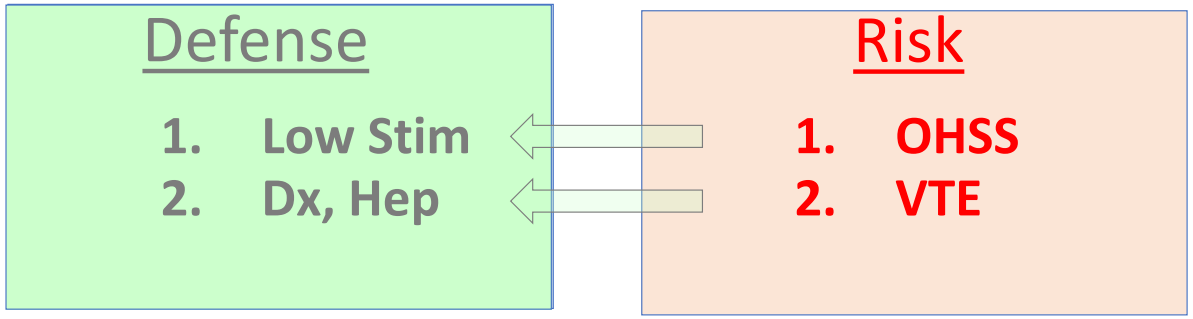

Les stimulations fortes sont-elles délétères?

Human Reproduction vol.14 no.11 pp.2681–2686, 1999

EDITORIAL

Minimal ovarian stimulation for IVF

Minimal ovarian stimulation for IVF: appraisal of potential benefits and drawbacks

Bart C.J.M.Fauser[1,8], Paul Devroey[2], Sam S.C.Yen[3], Roger Gosden[4], William F.Crowley Jr[5], David T.Baird[6] and Philippe Bouchard[7]

[1]Division of Reproductive Medicine, Department of Obstetrics and Gynecology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands, [2]Department of Reproductive Medicine, Dutch speaking Free University Brussels, Brussels, Belgium, [3]Department of Reproductive Medicine, Division of Reproductive Endocrinology, University of California, San Diego, CA, USA, [4]Center for Reproduction Growth and Development, University of Leeds, Leeds, UK, [5]Reproductive Endocrine Service, Center for Hayward Medical School and the Mass. General Hospital, Boston, MA, USA, [6]Department of Obstetrics and Gynecology, Centre for Reproductive Biology, University of Edinburgh, Edinburgh, UK and [7]Service d'Endocrinologie, Hopital St. Antoine, Paris, France

[8]To whom correspondence should be addressed

This Editorial was previously published on Embryo.ca, August 7, 1999

Shortly after the first pregnancy following in-vitro fertilization (IVF) was reported in a spontaneous cycle, evidence accumulated that overall pregnancy chances per IVF attempt increased significantly when more than one embryo was transferred. Subsequently ovarian stimulation protocols have been developed which aim at the ongoing growth of several follicles in normo-ovulatory women to obtain multiple oocytes for fertilization *in vitro* and multiple embryos. The presence of many preovulatory follicles allows for easier oocyte retrieval, and less effective IVF, embryo culture and cryopreservation. Early current ovarian stimulation protocols like many others, are relatively complex and expensive, and are not without danger. New procedures are frequently introduced without proper scientific evaluation (ISLAT working group, 1998) and current IVF strategies have been questioned (Edwards *et al.*, 1996; Olivennes and Frydman, 1996). In 1995, the worldwide number of IVF cycles was ~250 000 (Mouzon and Lansac, 1997). Ovarian birth rates have been reported as 6–25% per cycle. Problems related to stimulation include emotional stress, abdominal discomfort, risks of short-term complications and uncertainties regarding long-term health consequences for both the mother and children of multiple pregnancies. Some observations suggest that even singleton pregnancies resulting from IVF are more frequently complicated by bleeding, pre-eclampsia, diabetes, premature deliveries (Schenker and Ezra, 1994). Thus, the decision to undertake IVF treatment should not be considered lightly. Approximately 25% of patients refrain from a second attempt after a first unsuccessful IVF cycle (P.Devroey, unpublished observations), even where the costs are reimbursed by insurance companies.

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening complication of IVF characterized by enlarged ovaries, extravasation of fluid to the abdominal cavity resulting in ascites, hypovolaemia and haemoconcentration. Eventually, renal failure, thromboembolic complications and respiratory distress may occur. Severe forms of OHSS are associated with pregnancy, and related human chorionic gonadotrophin (HCG) production, which renders its management even more complex. The incidence of moderate OHSS is estimated to be 6% per cycle, with severe cases approaching 2% (Aboulghar and Mansour, 1994; Delvigne and Schenken, 1997). This means an annual worldwide occurrence of at least 5000 cases of serious OHSS. Several patients are hospitalized every year in most major fertility centres. With careful monitoring of ovarian response, the risks of this serious complication can be reduced, but never brought to zero. The number of deaths resulting from OHSS is unknown, but with proper management the incidence should be low.

The health risks of hyperstimulation are easily quantifiable, but discussion continues about the other potential long-term health consequences of ovarian stimulation, especially concerning any association between stimulation and ovarian cancer. Although many epidemiological studies on gonadotrophin therapy published so far report an increased risk (Shoham, 1994; Bristow and Karlan, 1996), it should be realized that experimental hypergonadotrophism and knock-out animal studies have suggested a relationship between long-term exposure to high gonadotrophin concentrations and the development of ovarian stromal tumours (Risma *et al.*, 1995; Kumar *et al.*, 1996; Kanter *et al.*, 1997). Although the situation in women has not yet been clarified, the risk of ovarian cancer is probably very low, if it exists. It should be realized that negative results are not usually published and that many previous reports were retrospective and poorly controlled. However, the reduced risk of ovarian cancer observed in steroid contraceptive pill users suggests a link between ovarian tumours and gonadotrophins (regulation).

It is also too early to exclude the possibility of risks, such as an earlier menopause due to increased follicular expenditure, although this seems highly unlikely because of the limited effects of ovulation stimulation on the number of follicles present at the thousands undergoing atresia. No evidence was obtained in studies on mice undergoing chronic treatment with pregnant mare's serum gonadotrophin (R.Gosden, unpublished observations). Finally, some studies have suggested that pro-

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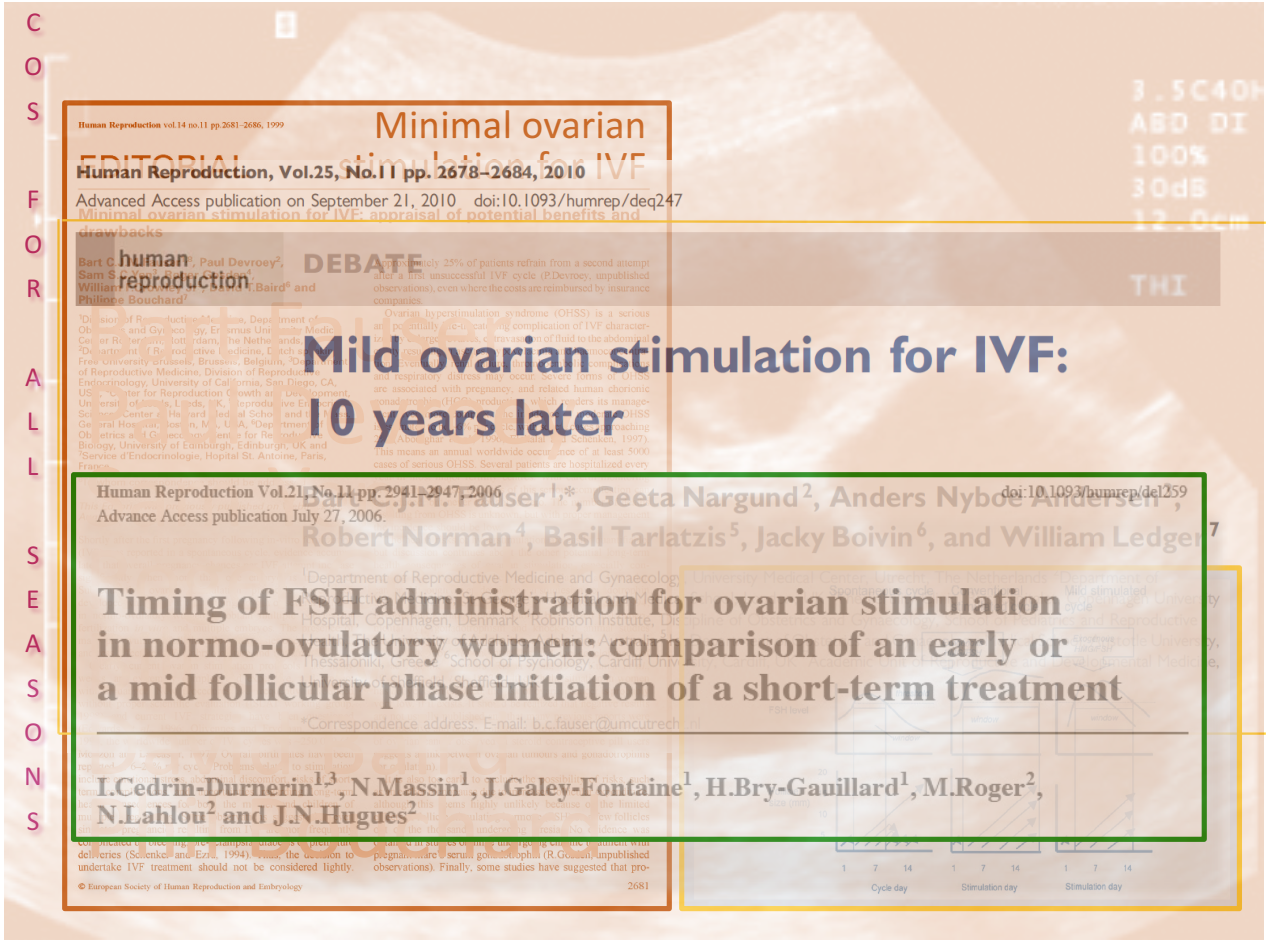

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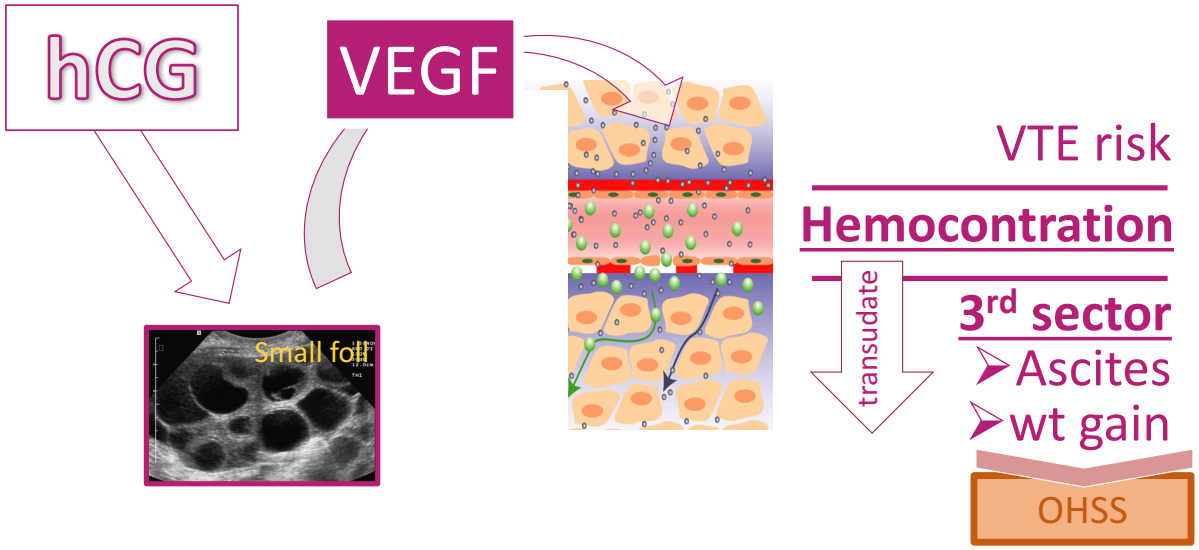
Hazards: different from expected, now redefined: **hCG**



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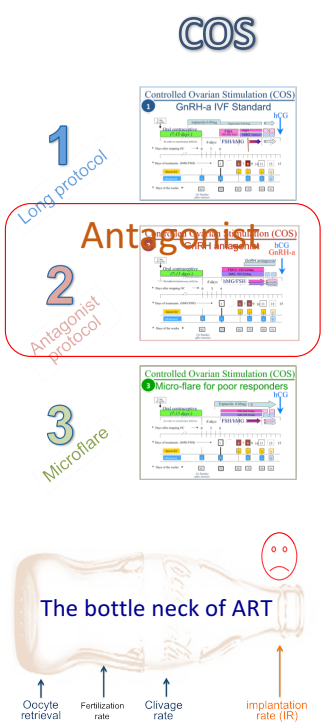
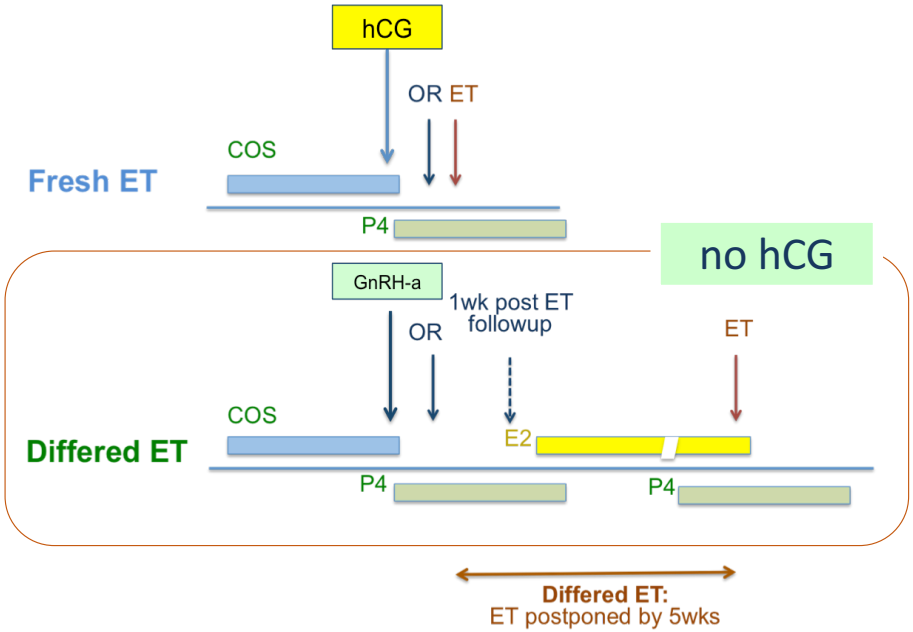


The deferred ET option (Def-*ET*)



The GnRH trigger option

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

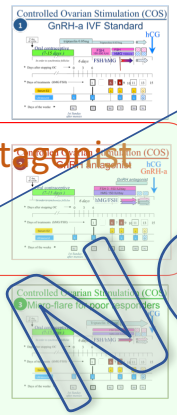
The deferred ET option (Def-*ET*)

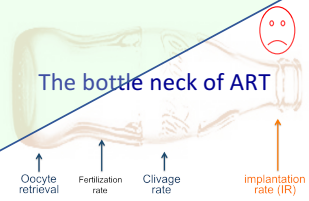
COS

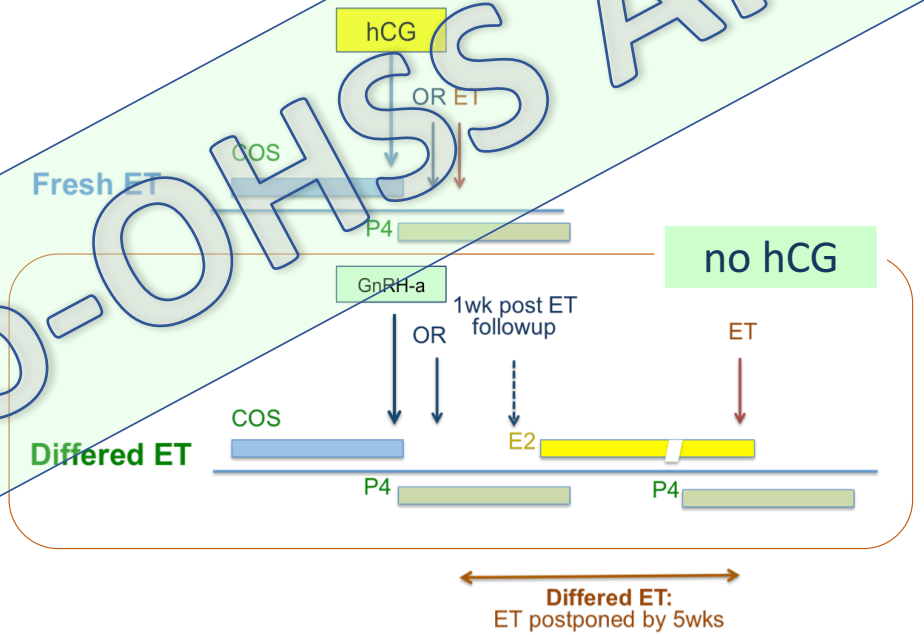
1 Long protocol

2 Antagonist protocol

3 Microflare







The GnRH trigger option

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Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Changing ovarian stimulation parameters in a subsequent cycle does not increase the number of euploid embryos

Brooke Hodes-Wertz, M.D., M.P.H., David H. McCulloh, Ph.D., Alan S. Berkeley, M.D., and Jamie A. Grifo, M.D., Ph.D.

New York University Fertility Center, Langone Medical Center, New York University, New York, New York

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

TABLE 3

Change in no. euploid embryos and secondary outcomes.

		Group 1					Group 0			
Intervention	**n**	**Change in no. oocytes retrieved**	**Change in no. embryos for biopsy**	**Change in no. euploid embryos**	**Change in % of euploid embryos (%)**	**n**	**Change in no. oocytes retrieved**	**Change in no. embryos for biopsy**	**Change in no. euploid embryos**	**Change in % of euploid embryos (%)**
Days of stimulation										
Control: no change, d	20	0.15	0.00	0.60	1.8	16	1.69	1.50	1.00	23.2
1–5 d(s) longer	41	1.51	0.56	0.32	−4.6	39	-0.44	−0.23	0.26[a]	4.7
Lead-follicle size										
Control: same size	18	0.61	−0.50	−0.28	−11.4	16	3.38	0.69	1.00	27.0
≥ 1 mm	42	0.81	0.26	−0.02	−3.8	38	−1.18[a]	0.08	0.26[a]	13.5
IU per day										
Control: <75 increase	46	1.13	0.52	0.41	−6.9	33	0.42	0.30	0.82	25.4
Increased by ≥ 75	15	−1.67	0.20	0.40	−8.0	22	−1.73	−0.95	−0.23[a]	−2.4[a]
Type of cycle										
Control: both GnRH-antagonist cycles	36	1.33	1.00	1.00	10.7	21	0.81	0.33	0.86	22.3
Add CC to GnRH-antagonist cycle	4	0.50	1.25	1.25	−9.5	9	3.11	2.22	1.11	24.5
Switch to microdose GnRH-a	3	1.61	0.83	0.81	1.0	11	−2.36	−0.36	0.64	19.5

Note: Group 1 = group with euploid embryo(s) in the first cycle; Group 0 = group with no euploid embryo(s) in the first cycle; CC = clomiphene citrate; GnRH-antagonist = gonadotropin-releasing hormone antagonist; GnRH-a = gonadotropin-releasing hormone agonist.

[a] Statistically significant difference in outcome between control and intervention groups, $P < .05$.

Hodes-Wertz. Array comparative genomic hybridization to gauge ovarian stimulation. Fertil Steril 2015.

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Aging and the environment affect gamete and embryo potential: can we intervene?

David R. Meldrum, M.D.,[a] Robert F. Casper, M.D.,[b,c,d] Antonio Diez-Juan, Ph.D.,[e] Carlos Simon, M.D., Ph.D.,[f,g] Alice D. Domar, Ph.D.,[h] and Rene Frydman, M.D., Ph.D.[i]

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Obesity

Smoking: The olive tree principle

Exercise

Antioxydants

Diet

Mitochondria, clinical use of CoQ10

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Human Reproduction Update, Vol.22, No.6 pp. 725–743, 2016
Advanced Access publication on August 25, 2016 doi:10.1093/humupd/dmw028

human reproduction update

Ovarian ageing: the role of mitochondria in oocytes and follicles

Pascale May-Panloup[1,2,*], Lisa Boucret[1,2], Juan-Manuel Chao de la Barca[2,3], Valérie Desquiret-Dumas[2,3], Véronique Ferré-L'Hotellier[1], Catherine Morinière[4], Philippe Descamps[4], Vincent Procaccio[2,3], and Pascal Reynier[2,3]

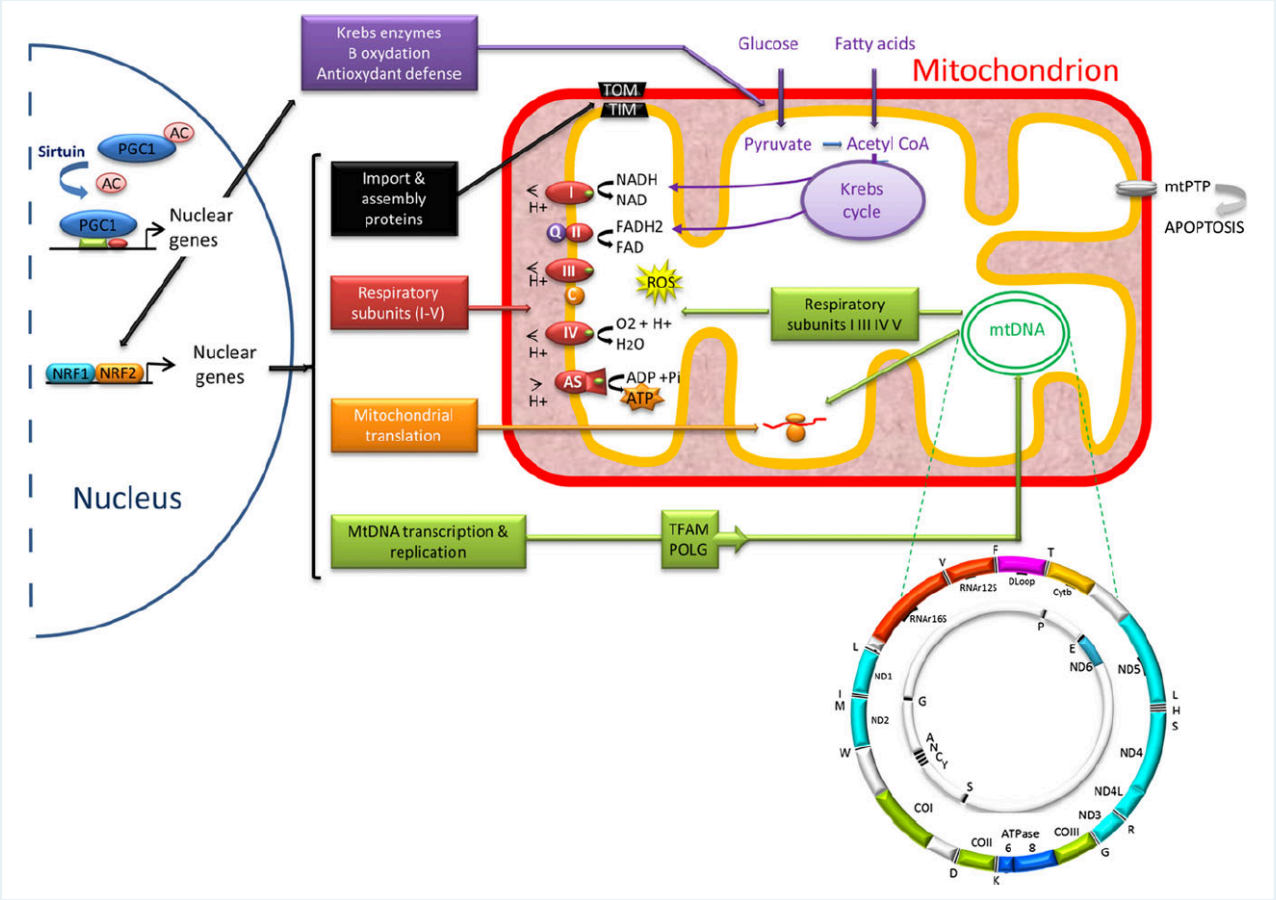


Figure 1 The mitochondrion is the site of the terminal catabolism of energetic molecules. Reduced coenzymes (NADH2 and FADH2) from the Krebs cycle and the oxidation of fatty acids supply electrons to the respiratory chain. OXPHOS is carried out by the five multienzyme complexes I–IV and ATP synthase (AS) embedded in the inner mitochondrial membrane. The production of ATP by the respiratory chain is accompanied by the formation of the toxic ROS. Mitochondrial function is coordinated with the general cell metabolism by PGC1 alpha and the sirtuin family. PGC1 alpha activates nuclear genes involved in fatty acid oxidation, antioxidant defense and the Krebs cycle. In parallel, PGC1 alpha promotes the expression of NRF1 and NRF2, transcription factors of nuclear genes coding for mitochondrial import proteins (TIM and TOM), assembly proteins and respiratory subunits, as well as for factors responsible for mtDNA translation (tRNA and rRNA), transcription and replication (TFAM and POLG). Mitochondria possess their own genome (mtDNA), a double-stranded, circular, 16 569 bp molecule coding for 13 subunits of the respiratory chain complexes (I: ND NADH deshydrogenase (blue), III: Cyt ubiquinone-cytochrome c. reductase (orange), IV CO cytochrome oxydase (green) and ATPase (dark blue), 22 tRNAs and two rRNAs (represented as groups) (red). The organelle also integrates the mitochondrial permeability pore (mtPTP) involved in apoptosis.

Les stimulations fortes sont-elles délétères?
Quand plus c'est mieux

Ooplasmic transfer

Molecular Human Reproduction vol.4 no.3 pp. 269–280, 1998

Ooplasmic transfer in mature human oocytes

Jacques Cohen[1,4], Richard Scott[1], Mina Alikani[1], Tim Schimmel[1], Santiago Munné[1], Jacob Levron[2], Lizi Wu[3], Carol Brenner[1], Carol Warner[3] and Steen Willadsen[1]

[1]The Institute for Reproductive Medicine and Science of Saint Barnabas, Livingston New Jersey, USA, [2]Department of Obstetrics and Gynecology, Tel Hashomer, Tel-Aviv, Israel, and [3]Department of Biology, Northeastern University, Boston, Massachusetts, USA

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Spindle transfer for mitochondrial dysfunction

Pregnancy derived from human zygote pronuclear transfer in a patient who had arrested embryos after IVF

John Zhang [a,b,*], Guanglun Zhuang [c], Yong Zeng [c], Jamie Grifo [d], Carlo Acosta [c], Yimin Shu [c], Hui Liu [a,b]

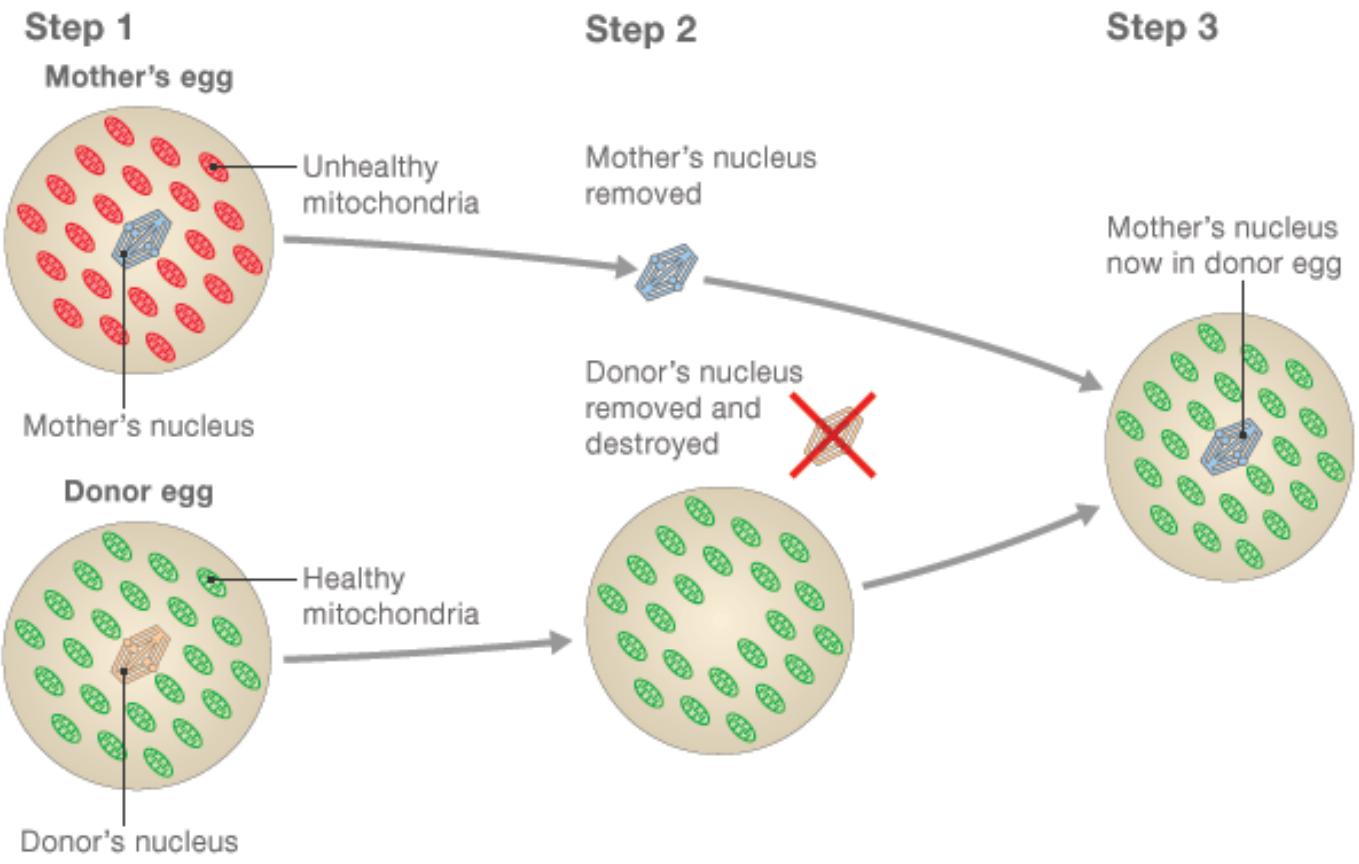
[a] *Reproductive Endocrinology and Infertility, Beijing, China;* [b] *New Hope Fertility Center, New York, NY, USA;* [c] *Sun Yat-Sen University of Medical Science, Guangzhou, China;* [d] *New York University School of Medicine, Division of Reproductive Endocrinology and Infertility, New York, NY, USA*

* Corresponding author. *E-mail address:* johnzhang211@gmail.com (J Zhang).

Dr Zhang completed his medical degree in at the Zhejiang University School of Medicine, and subsequently received his Master's Degree at Birmingham University in the UK. In 1991, Dr Zhang earned his PhD in IVF, and, after studying and researching the biology of mammalian reproduction and human embryology for nearly 10 years, became the first Fellow in the Division of Reproductive Endocrinology and Infertility of New York University's School of Medicine in 2001. Dr. Zhang continues his research in minimal stimulation IVF, non-embryonic stem cell research, long-term cryopreservation of oocytes, and oocyte reconstruction by nuclear transfer.

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux



Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Spindle transfer for mitochondrial dysfunction

ASRM 2016, Salt Lake City

O-267 Wednesday, October 19, 2016 11:45 AM

FIRST LIVE BIRTH USING HUMAN OOCYTES RECONSTITUTED BY SPINDLE NUCLEAR TRANSFER FOR MITOCHONDRIAL DNA MUTATION CAUSING LEIGH SYNDROME. J. Zhang,[a] H. Liu,[a] S. Luo,[b] A. Chavez-Badiola,[c] Z. Liu,[a] m. yang,[a] S. Munne,[d] M. Konstantinidis,[d] D. Wells,[e] T. Huang.[f] [a]New Hope Fertility Center, New York, NY; [b]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [c]New Hope Fertility Center, Guadalajara, Mexico; [d]Reprogenetics, Livingston, NJ; [e]Reprogenetics, Oxford, United Kingdom; [f]Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

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KEY MESSAGE

Conventional IVF stimulation protocols aim to maximize oocyte yields; mild stimulation protocols address the need for reduced patient discomfort and risk of ovarian hyperstimulation syndrome; both are associated with benefits and disadvantages. Physicians should consider individual patient clinical characteristics, medical history and IVF goals when determining the best treatment options.

ELSEVIER

Ovarian stimulation protocols for IVF: is more better than less?

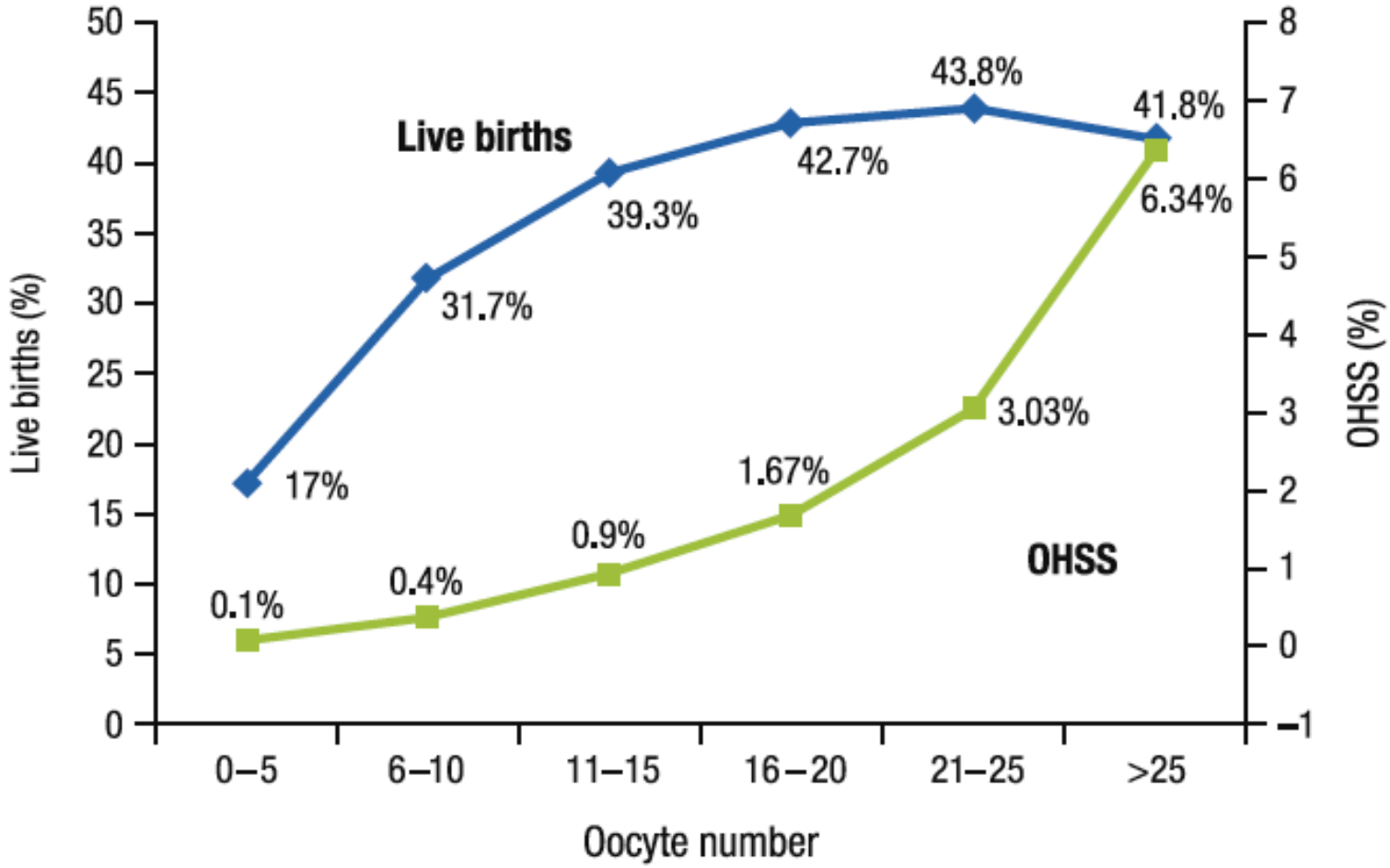
Michael M Alper [a,*], ***Bart C Fauser*** [b]

[a] *Boston IVF, 130 2nd Avenue, Waltham, MA 02451, USA*

[b] *Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands*

Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux



Les stimulations fortes sont-elles délétères?

Quand plus c'est mieux

Too often, COS responses and ART outcome are confused. COS response does not reflect fecundity, but affects the efficacy of ART.

Antagonists protocols are as efficient as classic 'long' agonist protocols and, eradicate OHSS.

Deferred ET indicated in endometriosis, repeated failure and as low-risk option for high risk patients.

LH effects needed when OC used for synchronization. Combining FSH and hMG is good option.

COS regimen does not impact on euploidy rate.

Les stimulations fortes sont-elles délétères?
Quand plus c'est mieux

Dominique de Ziegler

Foch-ART Center Suresnes France

Pr Jean Marc Ayoubi
Pr Renato Fanchin
Pr Rene Frydman
Pr Philippe Bouchard
Dr Paul Pirtea
Dr Marine Poulain