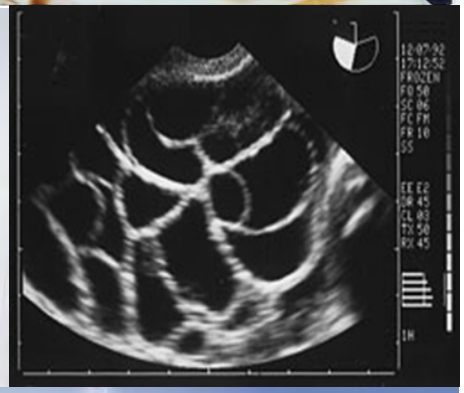
Problems and Complications During the Treatment of Infertility in Women with PCOS : How to Prevent and Manage ?

Timur Gürgan MD



RISKY BUSINESS?

Do infertility treatments damage babies' genes? Doctors used to think not. Now they are not so sure

By MICHAEL D. LEMONICK

THE OLD WAY
A study finds birth defects in 4.2% of naturally conceived babies

IN THE 24 YEARS SINCE THE BIRTH OF Louise Brown, the world's first test-tube baby, thousands of would-be parents have been assured that as far as scientists knew there was no extra risk of genetic damage associated with in-vitro fertilization, or IVF. No matter how sperm meets egg—whether in a woman's body or in a Petri dish (and even if the sperm needs some help getting inside the egg)—nature is equally vigilant about preventing serious genetic mishaps from coming to term. With those assurances, test-tube births have soared from a few hundred a year in the early 1980s to tens of thousands today.

But according to a pair of reports in last week's *New England Journal of Medicine*, that conventional wisdom may be wrong. In the first study, doctors in Britain and Australia found that infants conceived with both straightforward test-tube methods and a more invasive technique called intracytoplasmic sperm injection, in which sperm is injected directly into the egg, have an 8.6% risk of major birth defects—including heart and kidney abnormalities, cleft palate and undescended testicles—compared with the 4.2% rate in babies made the old-fashioned way.

The second study, conducted by the U.S. Centers for Disease Control and Prevention (CDC), reported that babies conceived through what doctors call assisted reproductive technologies (ART) have 2.6 times the risk of low or very low birth weight—a significant risk factor for cardiac and cognitive problems. "Our findings are controversial," concedes Dr. Jennifer Kurinczuk, a perinatal epidemiologist at the Uni-

BOTTOM LINE:

PCOS

(Endocrin disorder and metabolic disfunction lifelong)

-Oligo-anovulation

-Hyperandrogenism

-PCO in USG

(The Rotterdam ESHRE/ ASRM-Sponsored PCOS Consensus Workshop Group 2003)

Adolescence: Menstrual disorders

Hirsutism, acne, obesity

Psychologic problems

Reproductive age: **Infertility**

Older age: Diabetes

Cardiovascular disease

Cancer

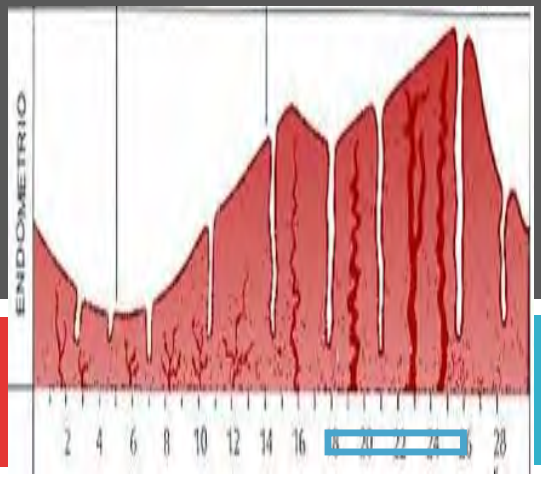
BALANCING Paradigm

Maximize beneficial effects of treatment

Minimize complications and risks

Individualization of ovarian stimulation

High-quality gametes and embryos



Optimal endometrial receptivity

PCOS

- Increased gonadotropin secretion
  - High LH levels
  - Increased LH receptor response
  - LH βsubunit genetic variation
- Insulin resistance (%50-70)
  - Increased theca cell response
- Obesity (%60)
- Increased androgen production
- Hyperprolactinemia
- Tyroid gland anomalies

Complications of infertility treatment,pregnancy,and perinatal period women with PCOS

Infertility treatment

- **Multiple prenancy**
- **OHSS**
- **IVF cancelation**
- **During IVF procedure**

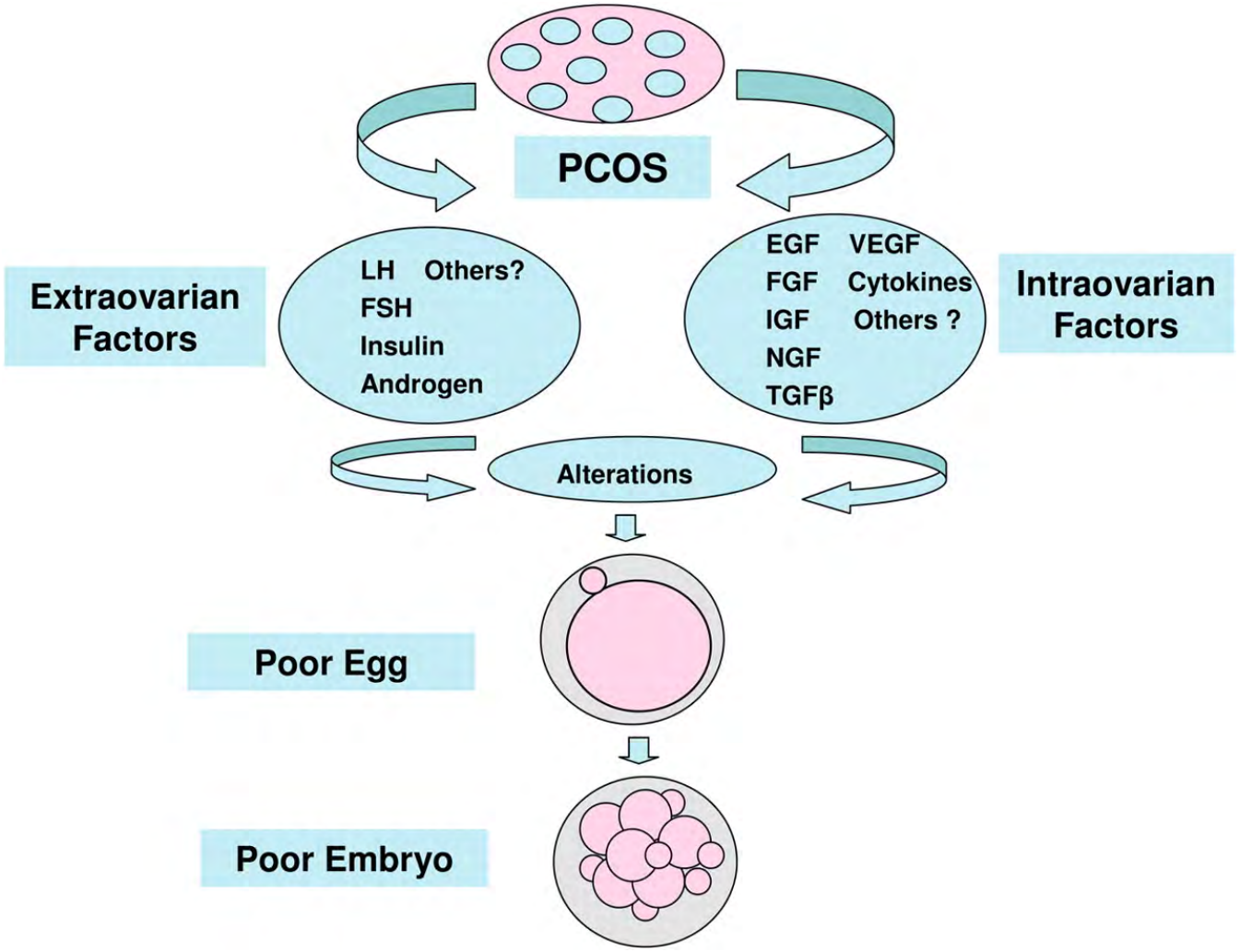
Pregnancy

- **Early pregnancy loss**
- **Gestational diabetes**
- **PIH**
- **Pre-eclampsia**
- **Delivery by caesarean section**

Perinatal period

- **Admission to neonatal intensive care unit**
- **Perinatal mortality**
- **Premature delivery**

Intra-and extra-ovarian factors associated with the PCOS pathology that negatively affect oocyte and subsequent embryo quality.



Jie Qiao, and Huai L. Feng Hum. Reprod. Update 2011;17:17-33

human reproduction update

Impact of PCOS on early embryo cleavage kinetics

ML Wissing *, MR Bjerge, AIG Olesen, T Hoest, AL Mikkelsen

Table 2 t_8 Embryo kinetics in the study of PCOS patients with ICSI.

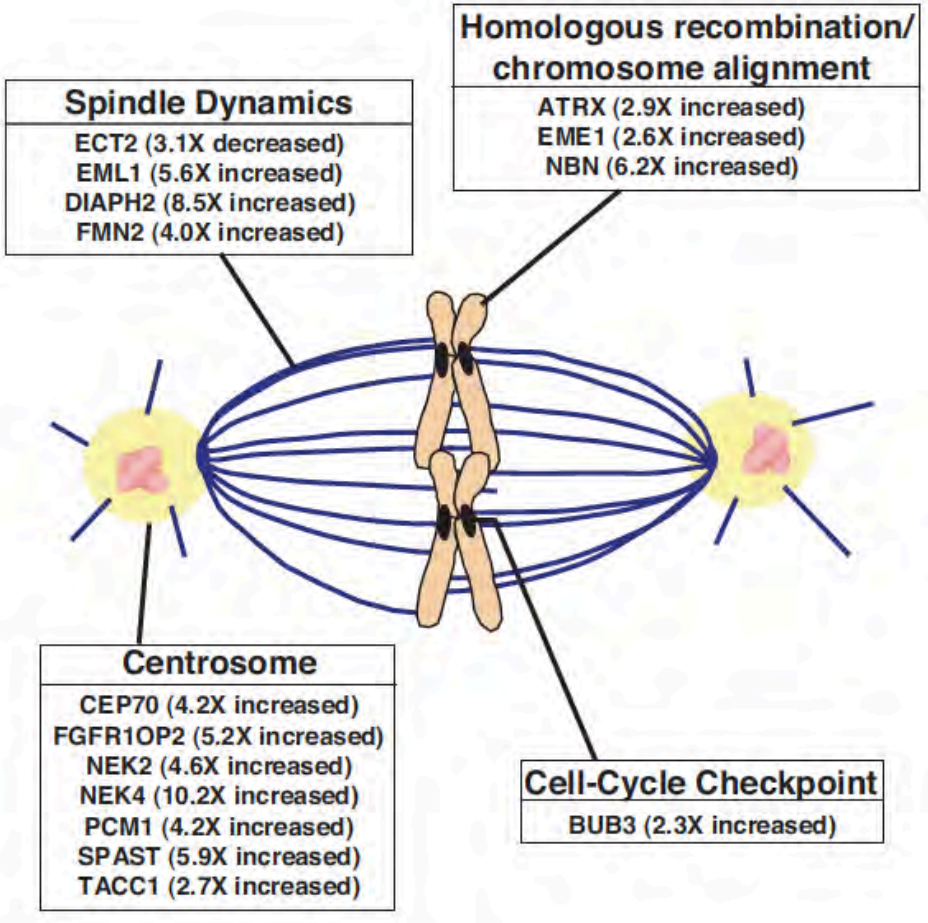
	Controls (n = 20)	*Hyperandrogenic PCOS (n = 25)*	*Normoandrogenic PCOS (n = 26)*	*P-value*
No. of embryos	97	110	140	
2PN breakdown	23.6 (23.1–24.1)[a]	26.8 (25.8–27.9)[a]	24.8 (23.8–25.8)	0.0128
First cleavage (t_2)	26.4 (25.9–27)[a]	30.8 (28.8–31.3)[a]	27.6 (26.4–28.8)	0.0061
3 cells (t_3)	35.4 (34.1–36.7)[a]	39.6 (37.8–41.3)[a]	36.7 (35.6–37.9)	0.0171
4 cells (t_4)	38.9 (37.7–40.1)[a]	43.8 (41.9–45.6)[a,b]	39.3 (38.1–40.6)[b]	0.0017[a] 0.0063[b]
5 cells (t_5)	47.5 (45.2–49.8)	51.4 (48.3–54.6)	47.5 (45.7–49.3)	NS
6 cells (t_6)	50.9 (48.8–53.0)[a]	56 (53.8–58.2)[a]	51.4 (49.4–53.8)	NS
7 cells (t_7)	55.3 (52.8–57.7)[a]	61.6 (58.8–64.5)[a]	56.0 (53.5–58.9)	0.04
8 cells (t_8)	56.7 (54.3–59.0)[a]	64.8 (61.3–68.3)[a]	61.7 (58.8–64.7)	NS
Morula (t_M)	89.0 (86.1–91.9)	92.9 (89.3–96.5)	92.3 (89.4–95.1)	NS
Blastocyst (t_B)	102.7 (99.3–106.1)	108.4 (104.6–112.3)	103.8 (100.3–107.4)	NS
$t_3 - t_2$	9.0 (7.9–10.2)	10.2 (9.0–11.3)	9.8 (8.9–10.7)	NS
$t_4 - t_3$	3.2 (2.3–4.2)	4.8 (3.3–6.6)	2.8 (2.0–3.7)	NS
t_4 before 46 h (day 2)	91 (83–96)[a]	60 (50–71)[a]	78 (71–85)	<0.0001
t_8 before 69 h (day 3)	61 (50–73)[a]	36 (25–48)[a]	35 (20–51)	0.0086

Fertilisation and cleavage rates decreased and / or delayed in Hyperandrogenic PCOS

Wissing et al 2015

Molecular Abnormalities in Oocytes from Women with Polycystic Ovary Syndrome Revealed by Microarray Analysis

Jennifer R. Wood, Daniel A. Dumesic,* David H. Abbott, and Jerome F. Strauss III*



There are different transcriptomes in pcos oocytes due to different mRNA syntesis.

Wood et al 2007

Hum. Reprod. Advance Access published September 4, 2012

Human Reproduction, Vol.0, No.0 pp. 1–8, 2012

doi:10.1093/humrep/des325

human reproduction ORIGINAL ARTICLE Reproductive biology

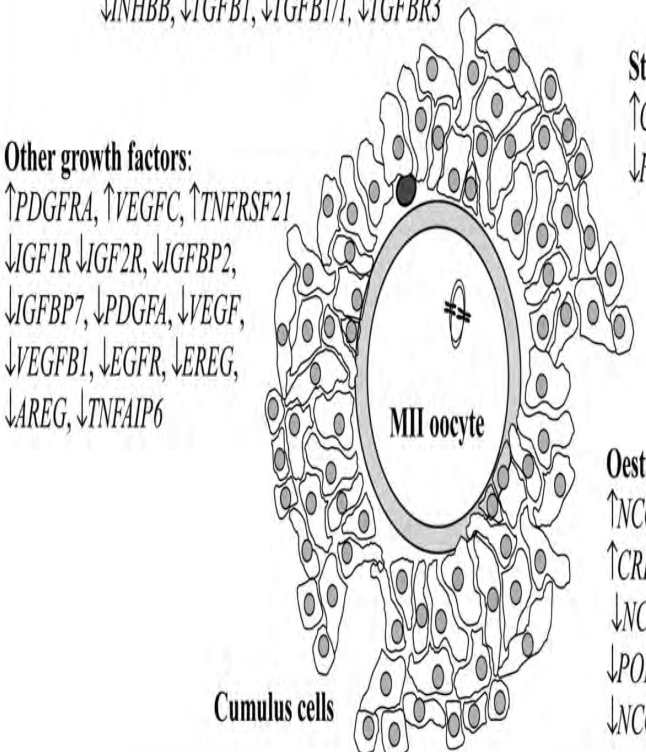
Altered gene expression profile in cumulus cells of mature MII oocytes from patients with polycystic ovary syndrome

D. Haouzi[1,2,3,4], S. Assou[1,2,3,4], C. Monzo[1,2,3,4], C. Vincens[2], H. Dechaud[1,2,3,4], and S. Hamamah[1,2,3,4,*]

[1]CHU Montpellier, Institut de Recherche en Biothérapie, Hôpital Saint-Eloi, Montpellier F-34295, France [2]CHU Montpellier, ART/PGD Division, Département de Biologie de la Reproduction, Hôpital Arnaud de Villeneuve, Montpellier F-34295, France [3]INSERM U1040, Hôpital Saint-Eloi, Montpellier F-34295, France [4]Université Montpellier1, UFR de Médecine, Equipe 'Développement embryonnaire précoce et cellules souches embryonnaires humaines', Montpellier F-34000, France

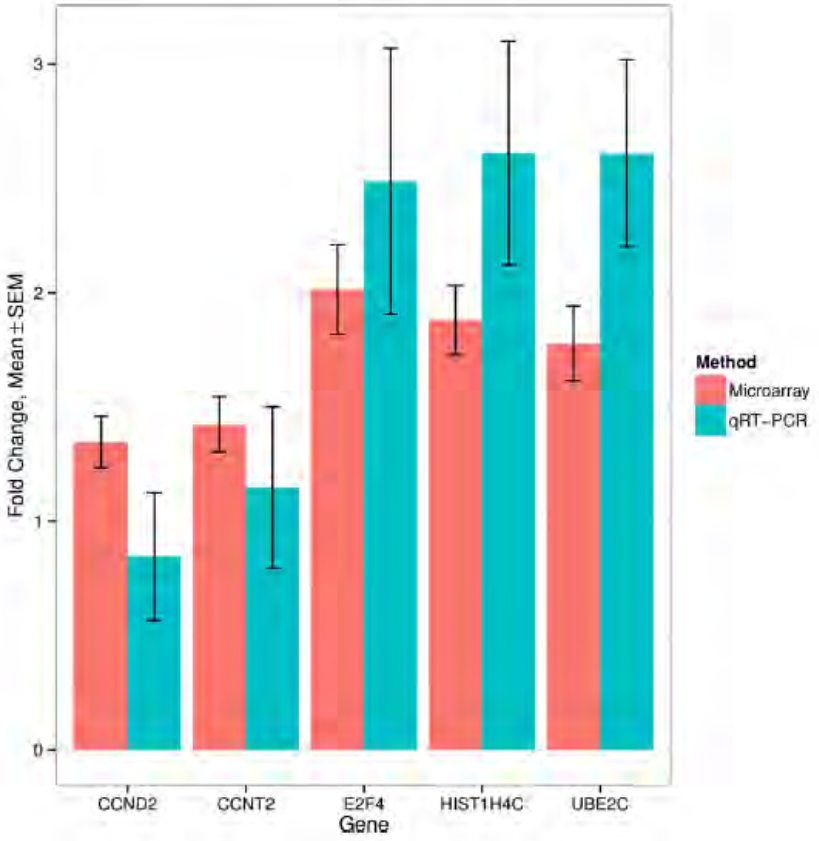
*Correspondence address. Tel: +33-04-67-33-64-04; Fax: +33-04-67-33-62-90; E-mail: s-hamamah@chu-montpellier.fr

The abnormal expression of many mRNAs in PCOS CCs might affect both oocyte competence and follicular microenvironment



The transcriptome of corona radiata cells from individual MII oocytes that after ICSI developed to embryos selected for transfer: PCOS women compared to healthy women

Marie Louise Wissing[1*], Si Brask Sonne[2], David Westergaard[3], Kho do Nguyen[4], Kirstine Belling[3], Thomas Høst[1] and Anne Lis Mikkelsen[1]



Delayed corona radiata cells maturation in PCOS

Wissing et al 2014

PCOS and IVF

FSH deficiency

LH hypersecretion

Hyperandrogenemia

Hyperinsulinemia

Impaired folliculogenesis

Low oocyte quality

Low cleavage rate

Low blastocyst formation

Low fertilization rate

Increased embryonic fragmentation

Low embryo quality

İmpaired endometrial receptivity

Low implantation rate

Increased miscarriage rate

Oocyte and Embryo Quality in PCOS

- Myoinositol and chiroinositol
- L-carnitin
- Electroacupuncture
- Melatonin
- **Oocyte activation**
- **PGS (D3 vs D5)**
- **Otolog/Heterolog cumulus cell co-culture**

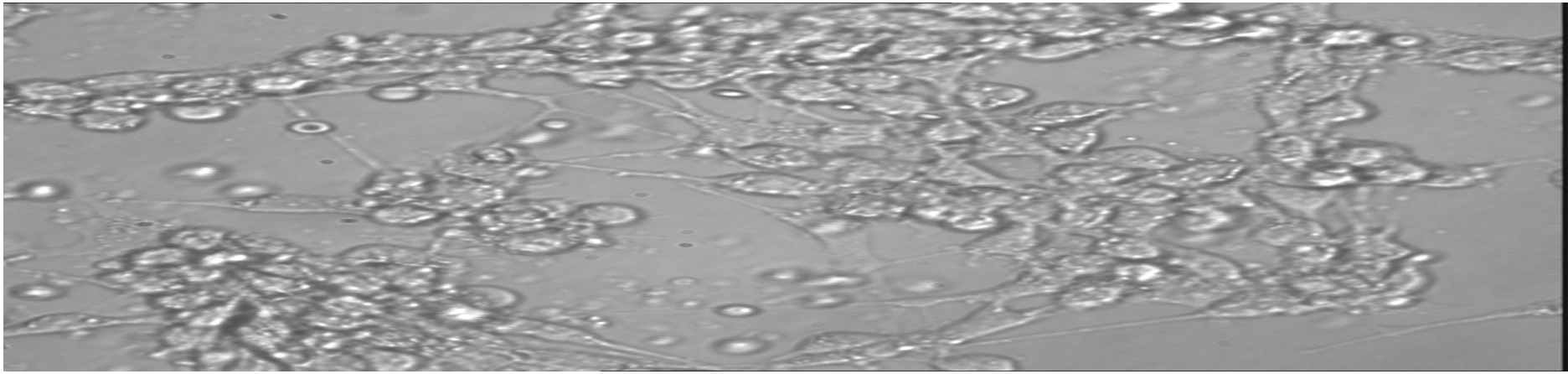
Benefit of autologous embryo-cumulus cells coculture and blastocyst transfer in repeated implantation failures: a collaborative prospective randomised study.

Benkhalifa M , Demirol A , Sari T , Balashova E , Giakoumakis Y , Gurgan T

- **In this study a total of 432 patients with a minimum of 3 repeated implantation failures were accepted for a prospective randomised study with or without autologous cumulus cell embryo coculture and transfer at day 3 or day 5-6.**

- **We also investigate the expression of Leukaemia Inhibitor factor (LIF) and Platelet Activating Factor Receptor (PAF-R) on day 3 confluent cumulus cells.**

- **The data reported clearly the positive effect on clinical pregnancy rate of coculture and blastocyst transfer in repeated implantation failure. The molecular analysis showed that cumulus cells are expressing the LIF and the PAF receptor genes.** **Zygote,2008**



Impaired endometrial receptivity and implantation failure in PCOS

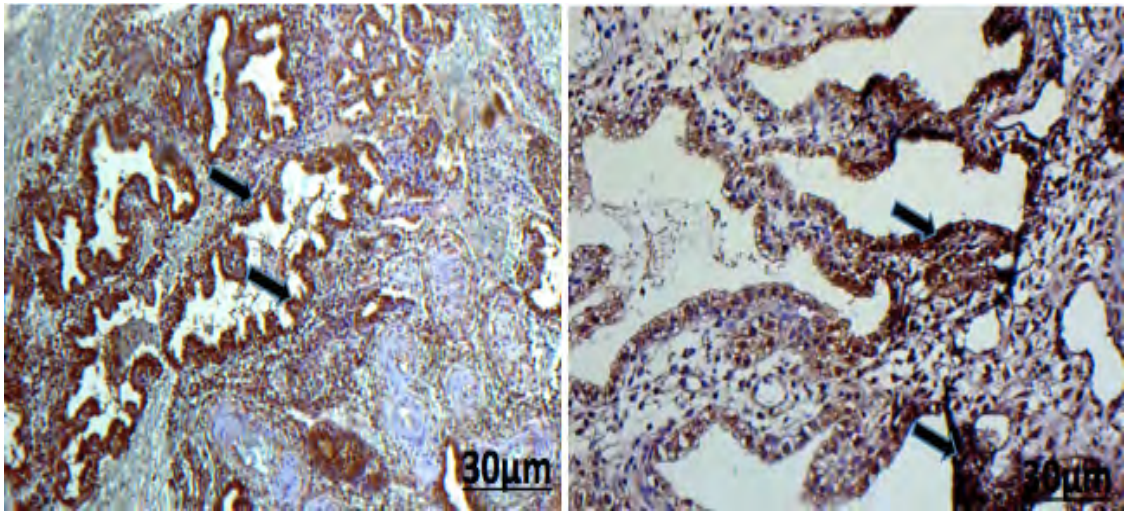
Endometrium in PCOS

- Low progesterone
- High estrogen
- High androgen

Impaired endometrial receptivity and implantation failure in PCOS

Endometrium in PCOS

Atypical decidualization



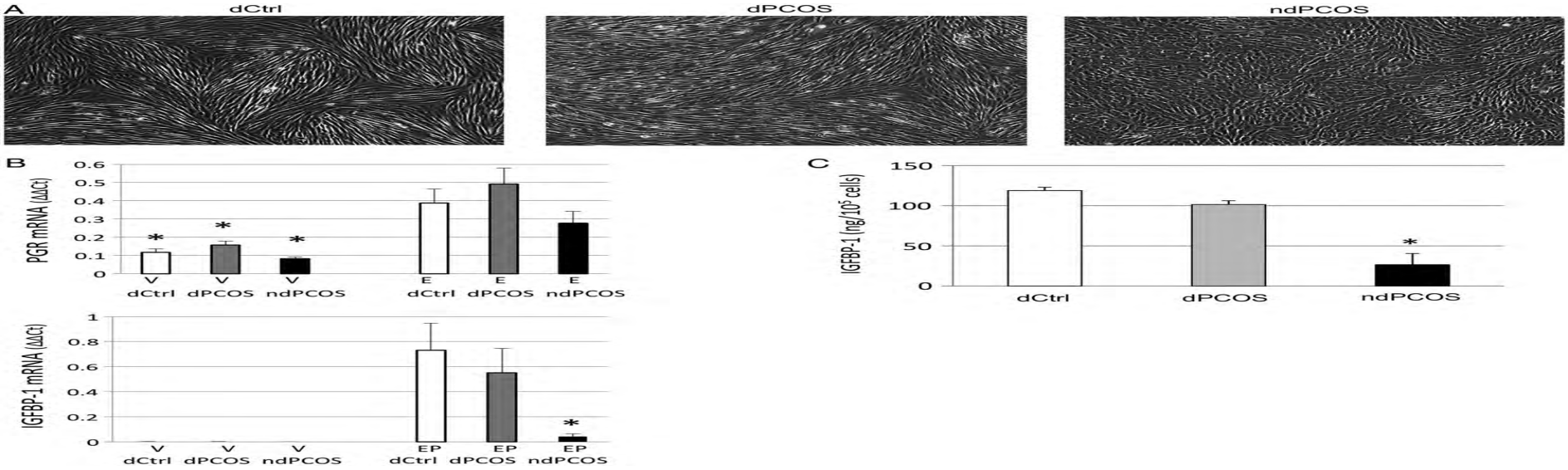
Hum. Reprod. Advance Access published March 6, 2015
Human Reproduction, Vol.0, No.0 pp. 1–13, 2015
doi:10.1093/humrep/dev055

human reproduction ORIGINAL ARTICLE Reproductive endocrinology

Endometrial stromal fibroblasts from women with polycystic ovary syndrome have impaired progesterone-mediated decidualization, aberrant cytokine profiles and promote enhanced immune cell migration *in vitro*

T.T. Piltonen[1,2,†], J.C. Chen[1,†], M. Khatun[2], M. Kangasniemi[2], A. Liakka[3], T. Spitzer[1], N. Tran[1], H. Huddleston[1], J.C. Irwin[1], and L.C. Giudice[1,*]

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA, USA [2]Department of Obstetrics and Gynecology, Medical Research Center, University of Oulu, Oulu University Hospital, Oulu, Finland [3]Department of Pathology, Medical Research Center, University of Oulu, Oulu University Hospital, Oulu, Finland



Impaired endometrial receptivity and implantation failure in PCOS

Immunity in endometrium

- Implantation needs a local immunosupresive microenvironment in endometrium.

(Cooper et al 2001)

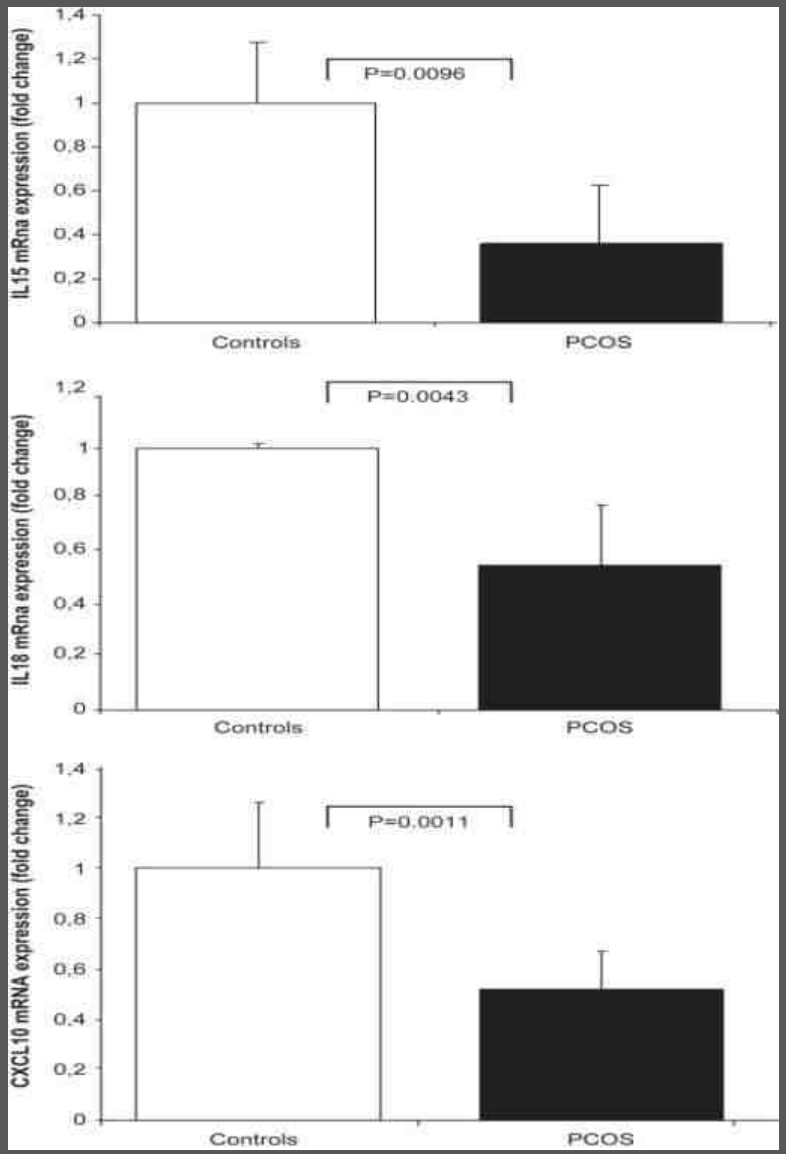
- The poor reproductive potential observed in PCOS patients could be partly related to a local dysregulation in the endometrial immune network during implantation.

(Matteo et al 2010)

Reduced percentage of natural killer cells associated with impaired cytokine network in the secretory endometrium of infertile women with polycystic ovary syndrome

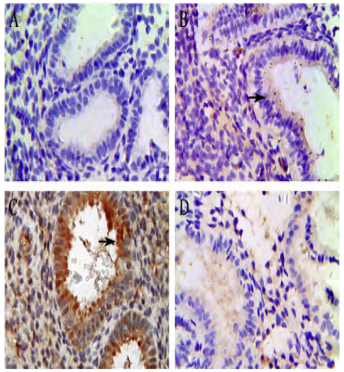
Maria Matteo, M.D., Ph.D., Gaetano Serviddio, M.D., Francesca Massenzio, Ph.D., Giuseppina Scillitani, M.D., Laura Castellana, Ph.D., Giuseppe Picca, M.D., Francesca Sanguedolce, M.D., Mauro Cignarelli, M.D., Emanuele Altomare, M.D., Pantaleo Bufo, M.D., Pantaleo Greco, M.D., Arcangelo Liso, M.D., Ph.D.

Fertility and Sterility
Volume 94, Issue 6, Pages 2222-2227.e3 (November 2010)
DOI: 10.1016/j.fertnstert.2010.01.049



Impaired endometrial receptivity and implantation failure in PCOS

Changing apoptosis in endometrium



Cell apoptosis in the endometrium during the window of implantation is lower in PCOS patients than in the control group, resulting in decreased endometrial receptivity during the window of implantation. This finding may account for the abnormal hormone secretion in serum during the ovulation-stimulating process. Thus, a suitable ovulation-stimulating scheme can be clinically adopted to regulate the hormone level in serum as well as improve the apoptosis of endometrial cells and endometrial receptivity.

Ling Yan , Aiming Wang , Lei Chen , Wei Shang , Min Li , Yong Zhao

Expression of apoptosis-related genes in the endometrium of polycystic ovary syndrome patients during the window of implantation

Gene, Volume 506, Issue 2, 2012, 350 - 354

Reproductive BioMedicine Online (2012) **25**, 345– 354

ELSEVIER

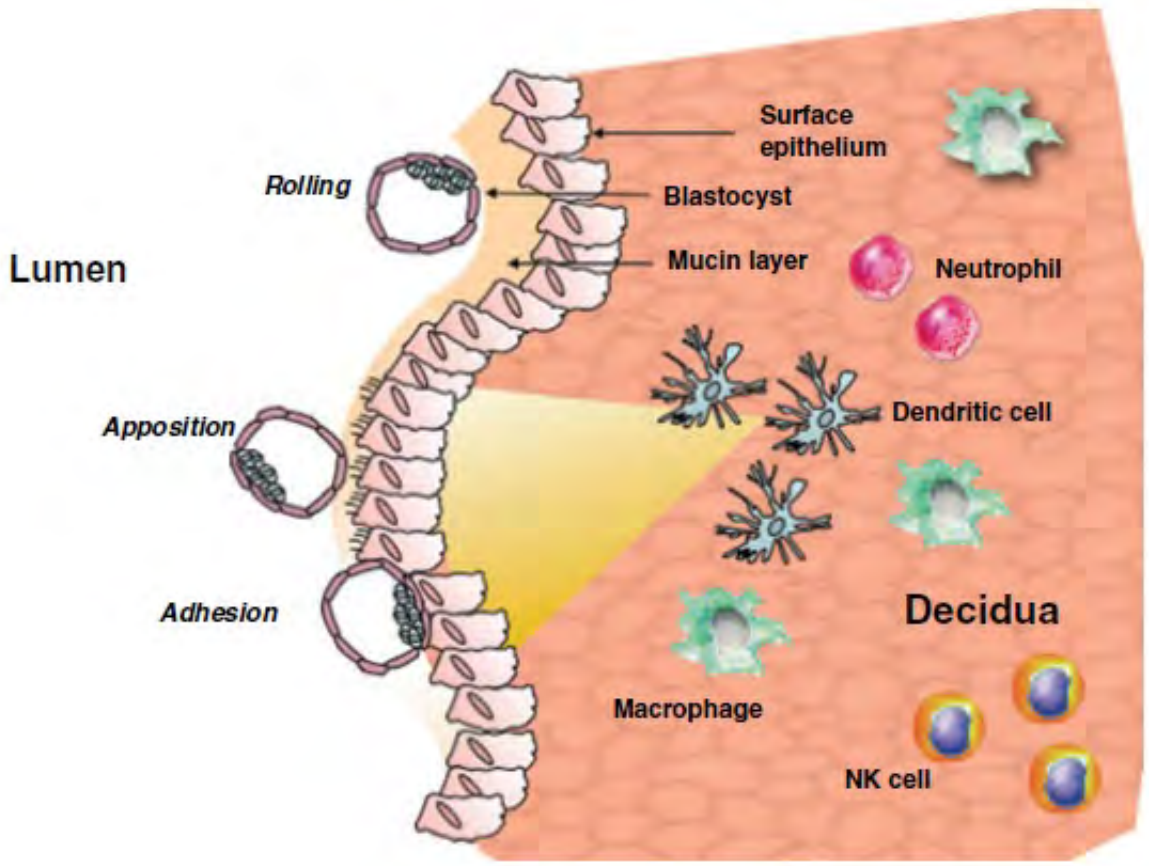
www.sciencedirect.com
www.rbmonline.com

ARTICLE

Local endometrial injury and IVF outcome: a systematic review and meta-analysis

Tarek El-Toukhy *, SeshKamal Sunkara, Yakoub Khalaf

Up-regulation of dendritic cells, local inflammation and injury



Dendritic cells & macrophages increase in local injury

& during the window of implantation

Dekel et al. Am J Reprod Immunol 2010;63:17

DOI: 10.1111/eci.12417

ORIGINAL ARTICLE

Repeated implantation failure: a new potential treatment option

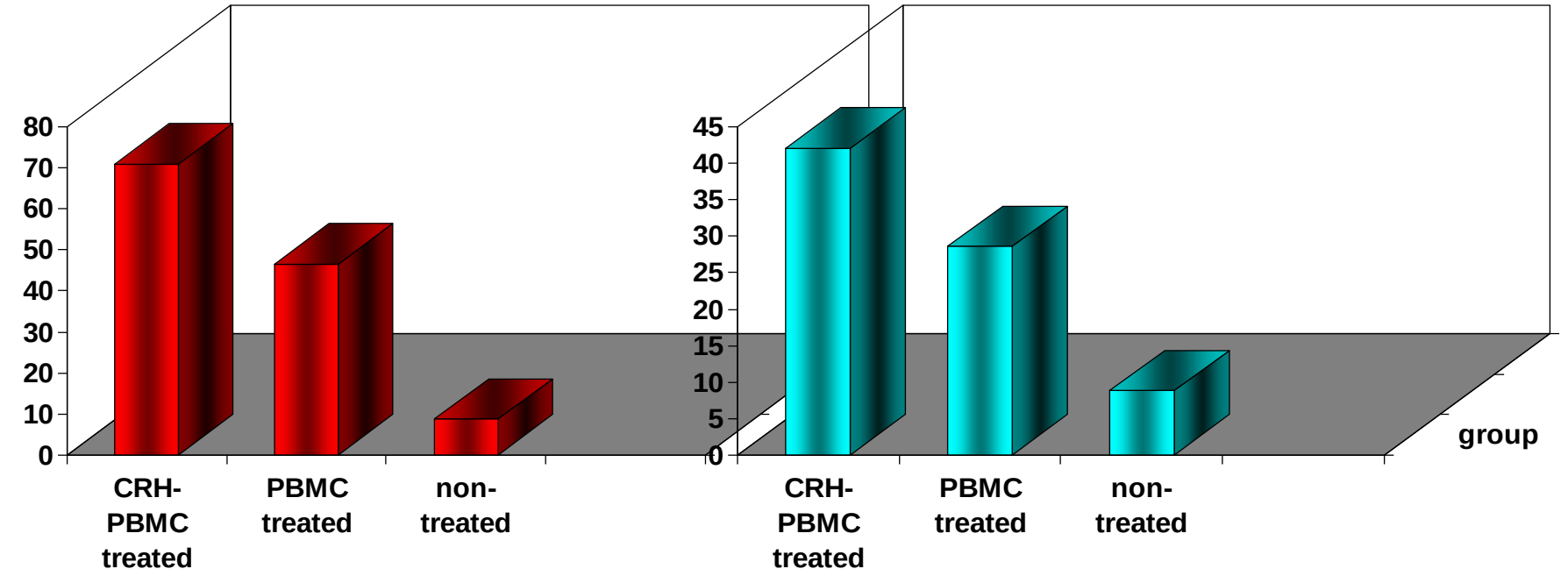
Antonis Makrigiannakis*, Moncef BenKhalifa†, Thomas Vrekoussis‡, Sami Mahjub§, Sophia N. Kalantaridou‡ and Timur Gurgan¶

*Department of Obstetrics and Gynecology, Medical School, University of Crete, Heraklion, Greece, †Reproductive Medicine & Medical Cytogenetics, Regional University Hospital & Medical School, Picardie University Jules Verne, Amiens, France, ‡Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Ioannina, Greece, §Elyssa IVF Center, Tunis, Tunisia, ¶Department of Obstetrics and Gynecology, Medical School, Hacettepe University, Ankara, Turkey

Eur J Clin Invest 2015; 45 (4): 380–384

Clinical outcome of the patients under 38

	CRH-PBMC treated	PBMC treated	Non-treated
Clinical pregnancy rate	44,8	22,3	2,5
Implantation rate	21,4	12,4	1,6
Live birth rate			



Problems of ART in PCOS

Problems other than IVF

- definition
- Before IVF

PCOS IVF

- Poor response
- Overresponse/OHSS
- Low fertilisation and implantation rate
- Early pregnancy loss
- High order pregnancy

Embryology

- Immature oocytes
- Low cleavage
- Low quality embryos

PCOS: Early Pregnancy Loss

1. Infertility treatment
   - Effect of estrogen receptors on endometrium
   - LH induction
   - Inadequacy of pinopod formation

Creus et al. Hum Reprod 2003
Shoham et al. Clin Endocrinol 1990
Hamilton-Fairley BJOG 1992
Homburg Fertil Steril 1993

2. Obesity

Wang et al. Human Reproduction 2001
Wang et al. Obesity Research 2002

3. Hyperinsulinemia (increased PAI, obesity)

Palomba et al. Fertil Steril 2005

PCOS: Early Pregnancy Loss

4. High LH levels

Homburg et al Fertil Steril 1993

5. Decreased receptivity and disfunction of endometrium
   - hyperinsulinemia
   - low serum gylicodelin
   - low IGFBP1
   - increased plasma Endothelin 1

Jakubowicz et al. J Clin Endocrnol Met 2001
Diamantis-Kandarakis et al. Eur J Endocrinol 2005
Orio et al. J Clin Endocrnol Met 2005

6. Low quality of oocytes

Preventing early pregnancy losses

- Metformin
  - Decreases serum PAI levels
  - Decreases plasma Endothelin 1levels
  - Decreases androjen and LH serum levels
  - İncreases serum Glycodelin levels

Glueck et al. Hum Reprod 2002
Glueck et al. Hum Reprod 2004
Palomba et al. J Clin Endocrinol Met 2004
Palomba et al. J Clin Endocrinol Met 2005

- Weight loss

Wang et al. Hum Reprod

- Decreasing LH levels
  - GnRH Agonist
  - GnRH Agonist + Low Dose FSH
  - Dual Supression OC+GnRH Agonist

Homburg et al Hum Reprod 1996
Damario et al. Hum Reprod 1997
Urman et al J Reprod Med 1997

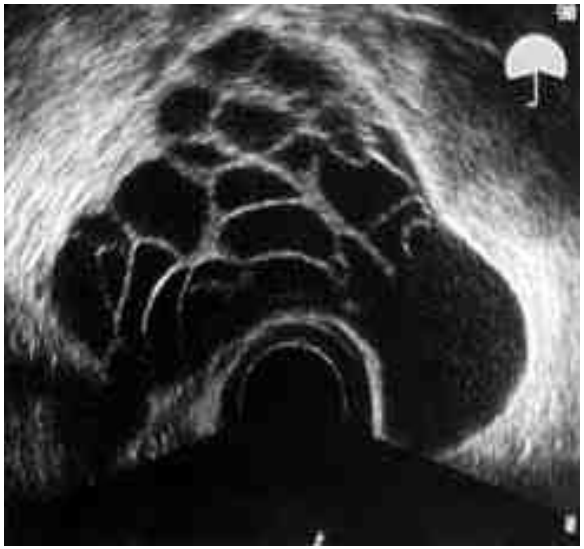
A step-by-step approach to ovulation induction in PCOS

Step	Approach
1	Weight loss if BMI ie elevated
2	Clomiphene citrate ± glucocorticoids
3	Insulin sensitizer as a single agent
4	Insulin sensitizer & clomiphene citrate
5(3)	Gonadotropin treatment
6	Insulin sensitizer & gonadotropin treat.
7(4)	Ovarian surgery
8	IVF/ICSI & IVM

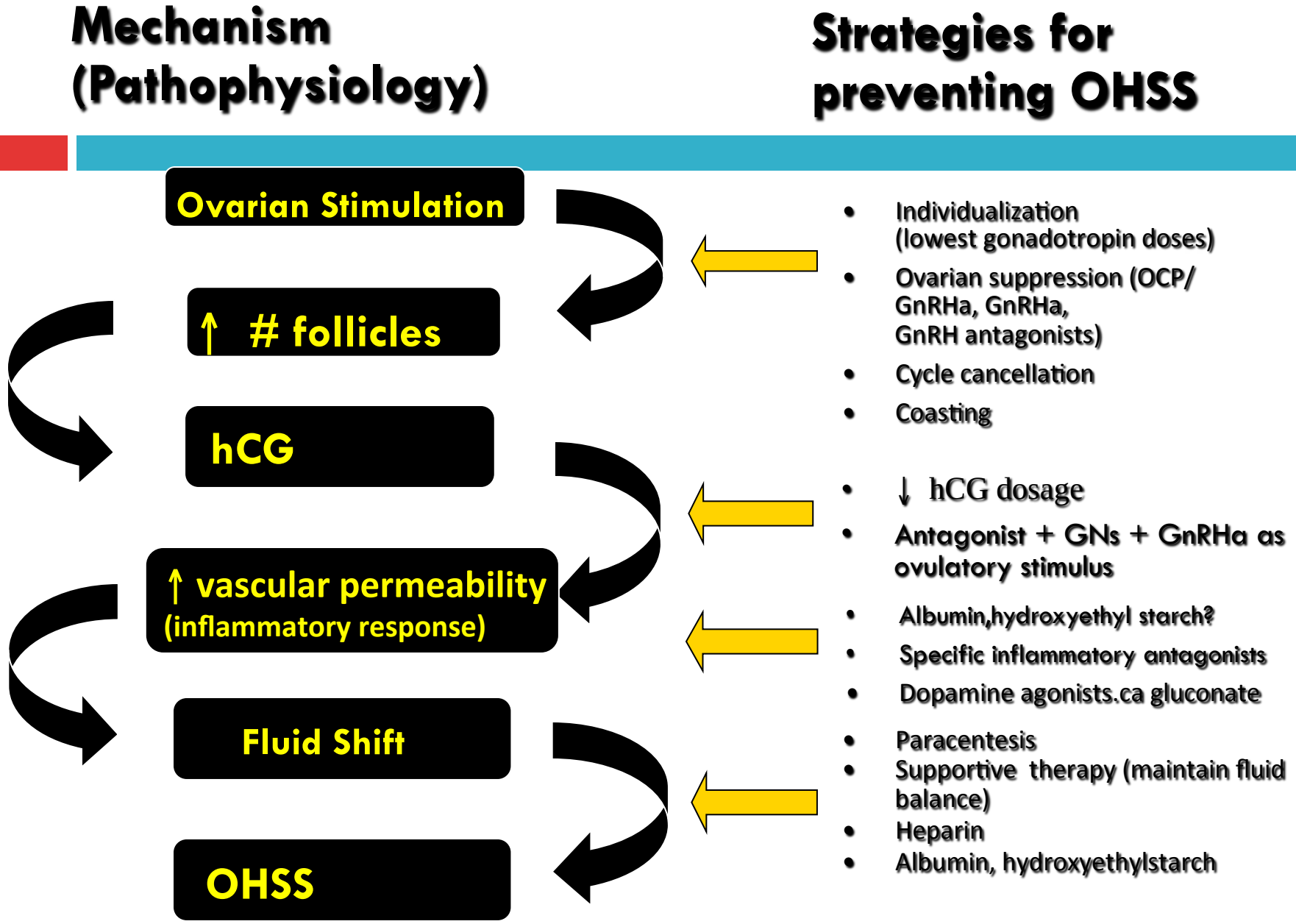
Kim LH, Taylor AE, Barbieri RL. Fertil Steril 73: 1097-8, 2000, ASRM/ESHRE 2007

PCOS and IVF

OHSS & Multiples



OHSS: Strategies for Prevention



PCOS: How to manage problems ovarian stimulation

- OC pre-treatment (Dual suppression)
- Agonist vs antagonist
- **Triggering ovulation with GnRH agonist**
- Metformin
- Coasting
- Embryo freezing
- **IVM**

Damario et al, Hum Reprod 1997
Mancini et al. Gynecol Endocrinol 2010
Engmann et al. Fertil Steril 2008
Humaidan et al. Hum Reprod 2009
Greisinger et al. Fertil Steril 2007
Siristadidis et al. Cochrane Reviews 2009

Agonist trigger: what is the best approach? Agonist trigger and low dose hCG

Peter Humaidan, M.D., D.M.Sc.

1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study

Peter Humaidan, M.D.,[a] *Helle Ejdrup Bredkjær, M.D., Ph.D.,*[b] *Lars Grabow Westergaard, M.D., D.M.Sc.,*[c] *and Claus Yding Andersen, D.M.Sc.*[d]

Pregnancy outcome in GnRHa vs. hCG-group.

Variable	GnRHa	hCG	OR (95% CI)	*P* Value
Patients, n	152	150		
Rate of transfer, n (%)	130/152 (86)	138/150 (92)	0.5 (0.4–0.7)	.054
Embryos transferred, median (range)	2 (1–2)	2 (1–2)		
Positive hCG per ET, n (%)	63/130 (48)	66/138 (48)	1.0 (0.9–1.2)	.36
Clinical pregnancy per patient, n (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	.29
Ongoing pregnancy per patient, n (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	.16
Early pregnancy loss, n (% of positive hCG)	13/63 (21)	11/66 (17)	1.3 (0.7–1.9)	.36

GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients

P. Humaidan[1,2,*], N.P. Polyzos[3], B. Alsbjerg[1], K. Erb[4], A.L. Mikkelsen[5], H.O. Elbaek[6], E.G. Papanikolaou[7], and C.Y. Andersen[8]

Management

1. Moderate OHSS → conservative treatment and follow-up

2. Severe OHSS:

Admission for monitoring

1. Strict fluid chart
2. Plasma and urine osmolarity
3. Urea and electrolytes
4. Clotting parameters
5. Liver function tests
6. Pregnancy test
7. Pelvic sonography
8. Invasive hemodynamic monitoring

Medical treatment

1. Correction of circulatory and electrolyte imbalance
   - correction of electrolyte imbalance
   - plasma expanders
2. Anticoagulants: clinical or laboratory evidence of thromboembolism
3. Prostaglandin synthetase inhibitors could be hazardous to renal perfusion
4. Antihistamines: not effective
5. Danazol: not effective
6. Diuretics: deplete intravascular volume
7. Dopamine: in oliguric patients

Surgical treatment

Laparotomy
1. Experienced surgeon
2. Only if hemorrhage
   - torsion
   - rupture
   - ectopic
3. Only hemostatic

Laparoscopy
Unwinding of twisted ovarian cyst

Aspiration of ascitic fluid
1. Abdominal paracentesis
2. Transvaginal aspiration

Advantages:
1. Improves symptoms
2. Improves renal function and urine output
3. Shortens venous return and cardiac output
4. Improves venous return and cardiac output

Precautions:
1. Sonographic guidance
2. Replacement of plasma protein
3. Repeat aspiration may be required

Balancing Technique

- Simple
- Effective
- Safe
- Reproducable
- Economic


Thank you for your attention