PRE-CONGRESS COURSE 11

The contribution of endocrinology & early pregnancy management to the success of an ART center

Special Interest Groups Early Pregnancy
and Reproductive Endocrinology
Munich - Germany, 29 June 2014

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

The contribution of endocrinology & early pregnancy management to the success of an ART center

Munich, Germany
29 June 2014

Organised by
The ESHRE Special Interest Groups Early Pregnancy & Reproductive Endocrinology

Contents

Course coordinators

Mariëtte Goddijn (SIG Early Pregnancy) and Georg Griesinger (SIG Reproductive Endocrinology)

Course description

This pre-congress course will provide an update of clinically important research areas of reproductive endocrinology at the intersection with routine fertility treatment with a special focus on reproductive success/failure and recurrent pregnancy loss.

Target audience

Reproductive endocrinologists, fertility specialists, psychologists, gynaecologists & reproductive nurses

Scientific programme

Chairman: Efstratios Kolibianakis - Greece

08:50 - 09:00 Introduction
Mariette Goddijn - The Netherlands
08:50 - 09:00 Introduction
Georg Griesinger - Germany
09:00 - 09:30 Gut and adipose hormones and reproduction in the human
Waljit Dhillo - United Kingdom
09:30 - 09:45 Discussion
09:45 - 10:15 The endocrinology of obesity: impact on fertility, pregnancy, risk of miscarriage and child health
Lesley Regan - United Kingdom
10:15 - 10:30 Discussion

10:30 - 11:00 Coffee break

Chairman: Mariette Goddijn - The Netherlands

11:00 - 11:30 Strategies and benefits of periconceptional lifestyle interventions
Régine P.M. Steegers-Theunissen - The Netherlands
11:30 - 11:45 Discussion
11:45 - 12:30 Debate: Treat subclinical hypothyroidism preconceptionally to foster fecundability, prevent early pregnancy loss and optimize child health?
Yes
Robin Peeters - The Netherlands
No
Kris Poppe - Belgium

12:30 - 13:30 Lunch

Chairman: Frank J. Broekmans - The Netherlands

13:30 - 14:00 Immunological and endocrine aspects of implantation
Thomas Strowitzki - Germany
14:00 - 14:15 Discussion
14:15 - 14:45 The endocrinology of pregnancy
Cornelis B. Lambalk - The Netherlands
14:45 - 15:00 Discussion

15:00 - 15:30 Coffee break

Chairman: Siobhan Quenby - United Kingdom

15:30 - 16:00 Genetic aspects of early pregnancy success
Tina Buchholz - Germany
16:00 - 16:15 Discussion
16:15 - 17:00 Debate: Is there a need for early pregnancy progesterone supplementation?
No
Anders Nyboe Andersen - Denmark
Yes

	Georg Griesinger - Germany
16:45 - 17:00	Discussion & closing of the meeting
17:00 - 18:00	Business meeting SIG Early Pregnancy

ESHRE GUIDELINE:

// MANAGEMENT OF WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY

GET INFORMED

The draft of the guideline will be presented at the ESHRE Annual Meeting 2014 by Dr. Melanie Davies

Be there!
Wednesday 2 July
at 11:30, Room 14

GIVE YOUR OPNION!

The guideline will be open for external review after the annual meeting.

Take this opportunity to review the guideline and submit your comments!

For more information
check www.eshre.eu/guidelines
or email nathalie@eshre.eu

GUIDELINE GROUP

Melanie Davies (Chair), Lisa Webber (Chair), Richard Anderson, Jane Bartlett (Patient representative), Didi Braat, Beth Cartwright, Renata Cifkova, Sabine de Muinck Keizer-Schrama, Eef Hogervorst, Femi Janse, Lih-Mei Liao, Anette Tonnes Pedersen, Veljko Vlaisavljevic and Carola Zillikens

Relationship between gut / adipose hormones and reproduction

Professor Waljit S Dhillo

No conflict of Interest

Learning Objectives

- **Reproductive function is regulated by nutritional status**
- **Orexigenic factors e.g. ghrelin released in food deprivation and inhibit reproductive function**
- **Anorexigenic factors e.g. leptin are released when food available and stimulate reproductive function**
- **Ghrelin and leptin mediate their effects on appetite and reproductive activity via common hypothalamic pathways**

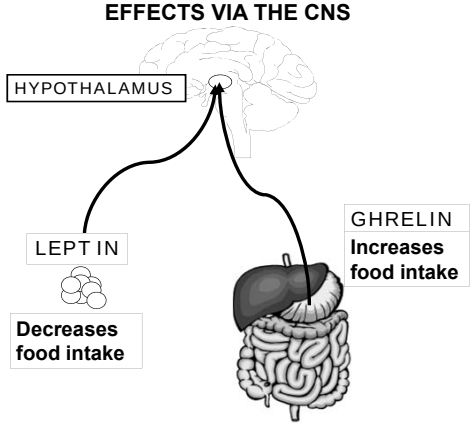
Reproductive function is regulated by nutritional status

The Venus of Willendorf

Reproductive function is regulated by nutritional status

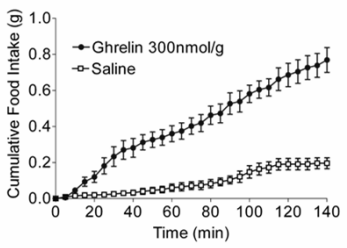
- Body weight at menarche is tightly regulated
- Under nutrition leads to infertility in males and females
- Obesity also leads to sub fertility in males and females
- Common regulatory pathways which control energy homeostasis and reproductive function – poorly understood

GUT & ADIPOSE HORMONES MEDIATE THEIR EFFECTS VIA THE CNS



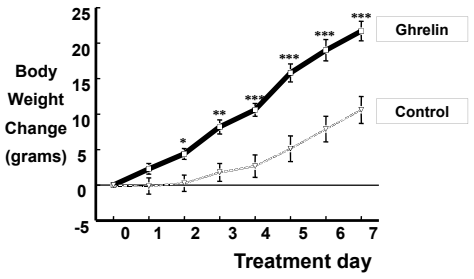
Ghrelin

Ghrelin increases food intake

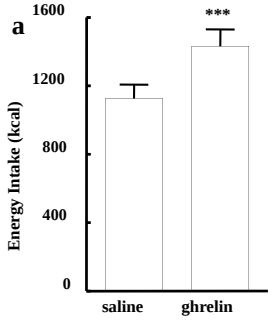


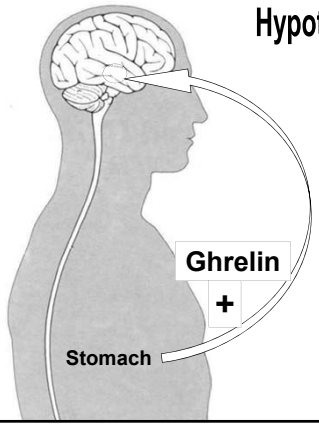
1min food intake data

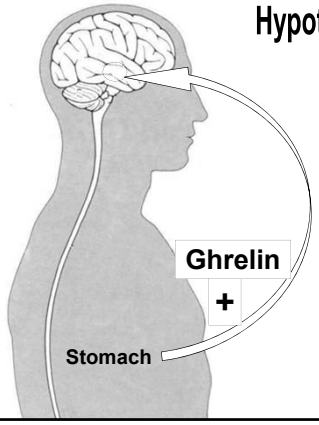
Ghrelin makes you fat



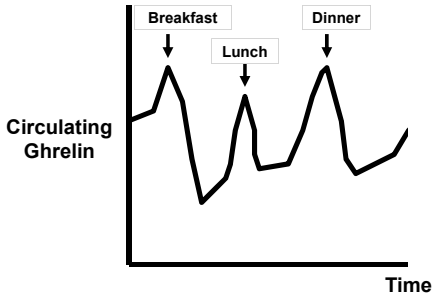
Ghrelin is the only identified hunger hormone in man



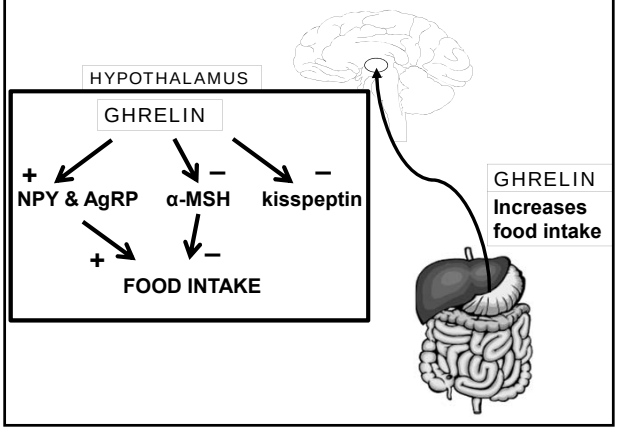




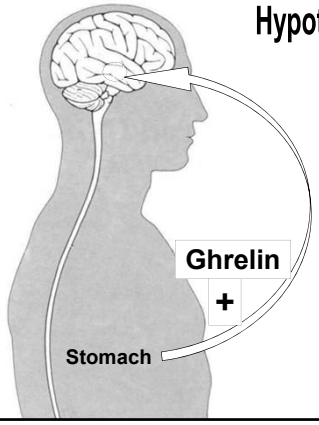
Ghrelin as a meal initiator



HOW DOES GHRELIN INCREASE FOOD INTAKE ?



Hypothalamus

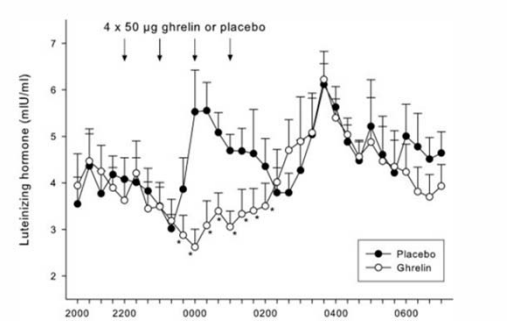


Ghrelin hunger signal

Ghrelin increases when food deprived

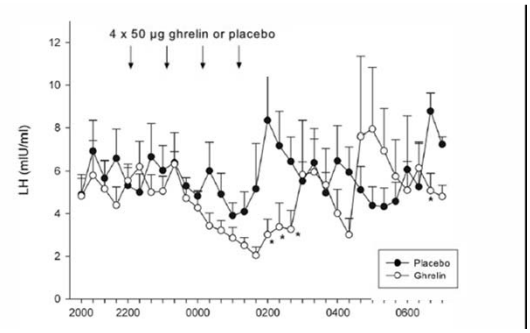
Ghrelin inhibits reproductive function

Ghrelin suppresses gonadotrophins in men



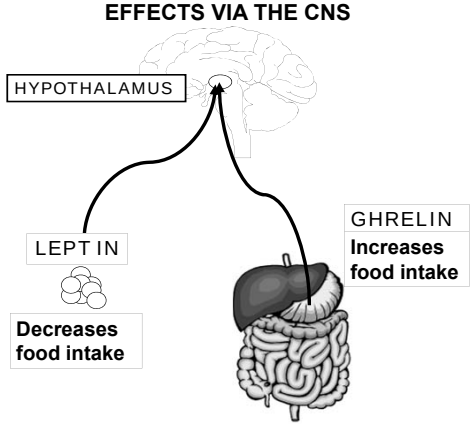
Kluge JCEM 2007

Ghrelin suppresses gonadotrophins in women



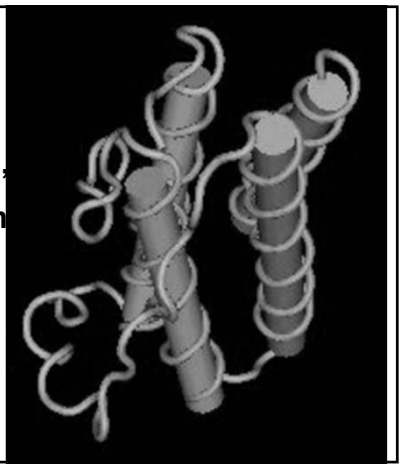
Kluge JCEM 2012

GUT & ADIPOSE HORMONES MEDIATE THEIR EFFECTS VIA THE CNS



Leptin

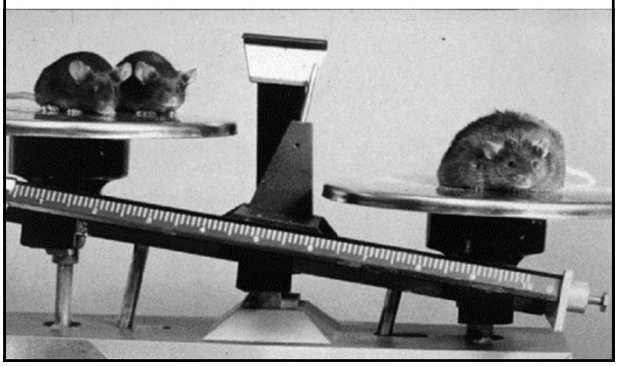
From 'leptos'
meaning 'thin



Leptin

- **Discovered in 1994**
- **Ob/ob gene codes for 167 amino acid hormone**
- **Missing in the *ob/ob* mouse.**

The *ob/ob* Mouse



Leptin is a long term signal of body weight

- **Made by adipocytes in white adipose tissue**
- **Circulates in plasma in proportion to amount of adipose tissue**

Leptin

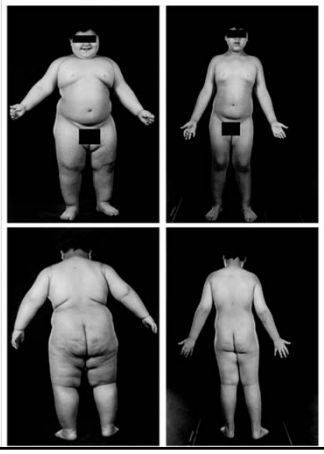
- **Acts upon the hypothalamus to inhibit appetite**
- **Low when low body fat**
- **High when high body fat**

Leptin

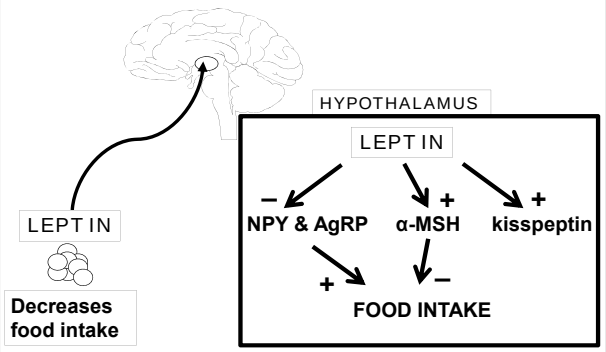
- **Leptin replacement in the *ob/ob* mouse decreases weight**

Congenital leptin deficiency in humans

- **Small number of cases identified**
- **Mutation in *ob* gene- homologous to *ob/ob* mouse**
- **Severely hyperphagic and obese**
- **In these children leptin has been effective in**
  - **reducing body weight**

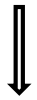


HOW DOES LEPTIN INHIBIT FOOD INTAKE ?



Leptin signalling is required for fertility

Inactivating mutation in leptin gene (ob/ob)
Inactivating mutation in leptin receptor (db/db)



HYPOGONADOTROPHIC HYPOGONADISM

- **low GnRH**
- **low LH / FSH**
- **low testosterone / oestradiol**

Leptin

- **Leptin replacement in the *ob/ob* mouse decreases weight AND stimulates reproductive function**

Congenital leptin deficiency in humans

- **Small number of cases identified**
- **Mutation in *ob* gene- homologous to *ob/ob* mouse**
- **Severely hyperphagic and obese**
- **Hypogonadotrophic hypogonadism**

Leptin Replacement

- **In these children leptin has been effective in**
  - **reducing body weight**
  - **stimulating reproductive hormone release & puberty**

Farooqi IS et al. N Engl J Med. 1999

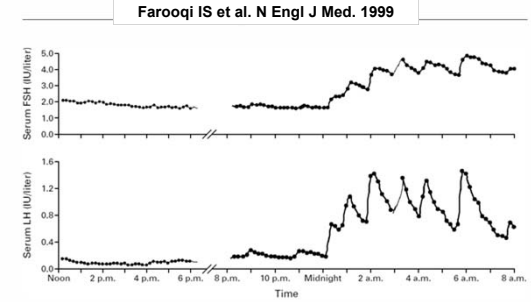
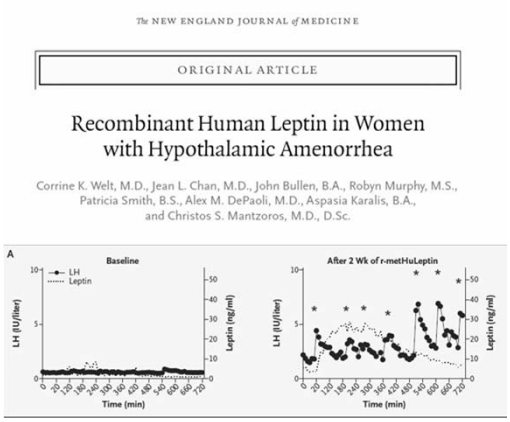


Figure 2. Serum Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) Concentrations in a Patient with Congenital Leptin Deficiency after 12 Months of Leptin Treatment.
Serum FSH and LH were measured at 10-minute intervals for 6 hours during the day and for 12 hours overnight.

Hypothalamic amenorrhoea (HA)

- **30% of amenorrhoea in women of reproductive age**
- **Inadequate GnRH secretion. Mostly due to**
  - **weight loss**
  - **exercise**
- **Low leptin levels (70% reduction)**



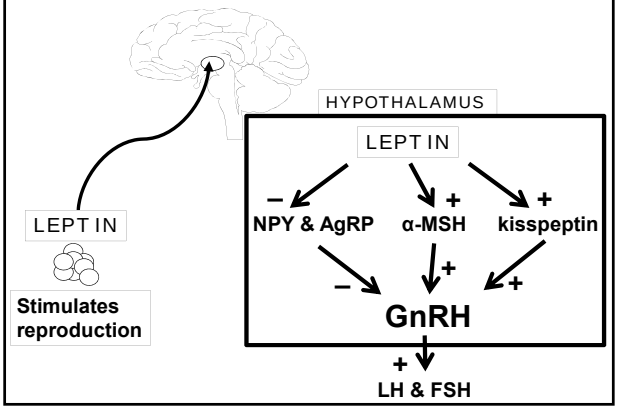
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

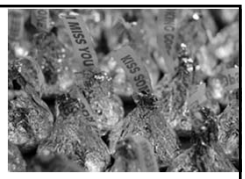
Recombinant Human Leptin in Women with Hypothalamic Amenorrhea

Corrine K. Welt, M.D., Jean L. Chan, M.D., John Bullen, B.A., Robyn Murphy, M.S., Patricia Smith, B.S., Alex M. DePaoli, M.D., Aspasia Karalis, B.A., and Christos S. Mantzoros, M.D., D.Sc.

HOW DOES LEPTIN STIMULATE REPRODUCTION ?



Kisspeptin



- **The kisspeptins are peptide products of the KiSS-1 gene.**
- **Highly expressed in the hypothalamus and the placenta**
- **Bind to G-protein coupled receptor 54**

Kisspeptin signalling is essential for puberty

Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54

Nicolas de Roux*†, Emmanuelle Genin‡, Jean-Claude Carel¶, Fumihiko Matsuda‖, Jean-Louis Chaussain¶, and Edwin Milgrom*

10972–10974 | PNAS | September 16, 2003 | vol. 100 | no. 19

The NEW ENGLAND JOURNAL of MEDICINE

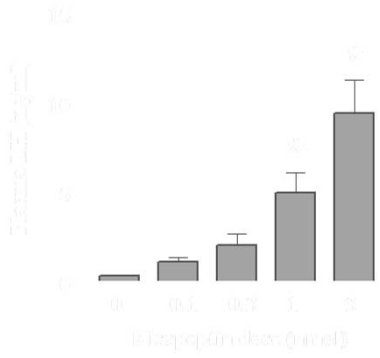
ORIGINAL ARTICLE

The GPR54 Gene as a Regulator of Puberty

Stephanie B. Seminara, M.D., Sophie Messager, Ph.D., Emmanouella E. Chatzidaki, B.Sc., Rosemary R. Thresher, Ph.D., James S. Acierno, Jr., B.S., Jenna K. Shagoury, B.S., Yousef Bo-Abbas, M.D., Wendy Kuohung, M.D., Kristine M. Schwinof, M.A., Alan G. Hendrick, Ph.D., Dirk Zahn, Ph.D., John Dixon, B.A., Ursula B. Kaiser, M.D., Susan A. Slaugenhaupt, Ph.D., James F. Gusella, Ph.D., Stephen O'Rahilly, M.D., Mark B.L. Carlton, Ph.D., William F. Crowley, Jr., M.D., Samuel A.J.R. Aparicio, B.M., B.Ch., Ph.D., and William H. Colledge, Ph.D.

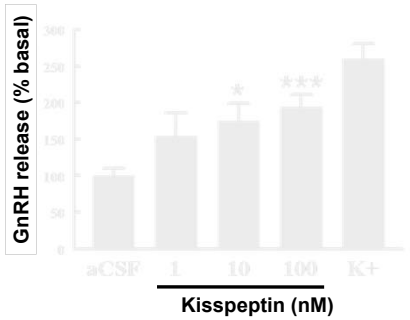
Does kisspeptin stimulate reproductive hormone release ?

ICV kisspeptin stimulates LH release in rats



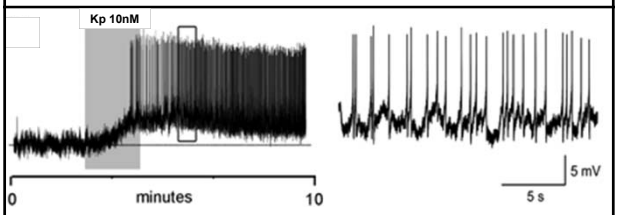
Thompson et al J Neuroendocrinol 2004

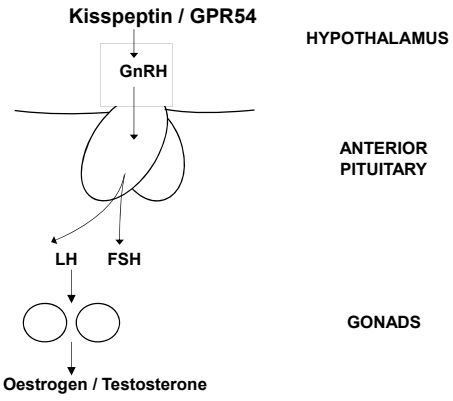
Kisspeptin releases GnRH from hypothalamic explants



Thompson et al J Neuroendocrinol 2004

Kisspeptin directly depolarises GnRH neurons





HYPOTHALAMUS

ANTERIOR PITUITARY

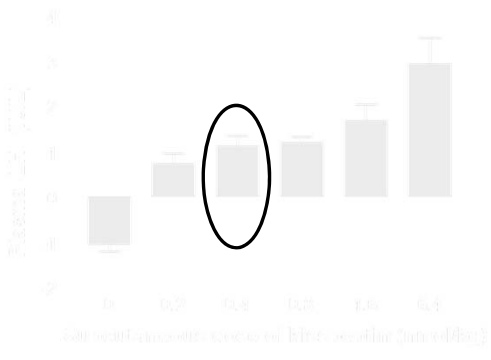
GONADS

Does kisspeptin stimulate reproductive hormone release in humans ?

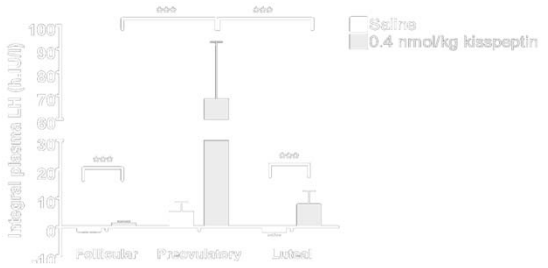
Kisspeptin increases luteinising hormone release

Dhillo *et al.* J Clin Endocrinol Metab 2005

sc kisspeptin increases plasma LH in normal women



Kisspeptin increases LH release in women



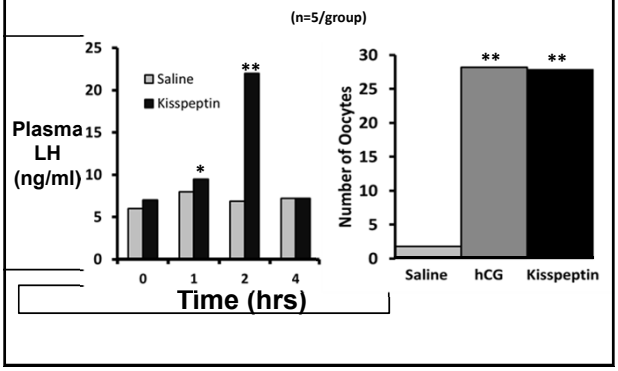
Dhillo *et al.* J Clin Endocrinol Metab 2007

Is kisspeptin useful in IVF treatment ?

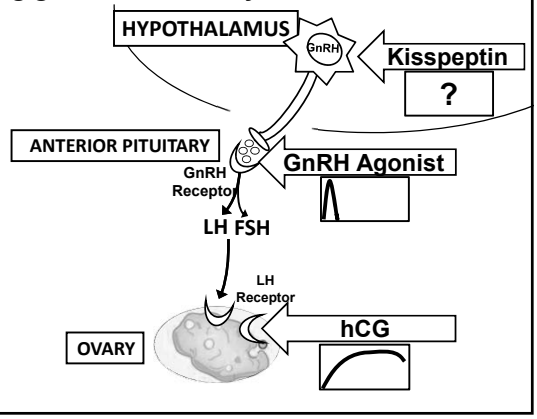
Ovarian Hyper-Stimulation Syndrome (OHSS)

- **Associated with hCG use**
  - **hCG used in IVF protocols to trigger oocyte maturation**
  - **OHSS occurs due to prolonged LH-like action of hCG**

Kisspeptin induces ovulation in rats



Triggers of Oocyte Maturation

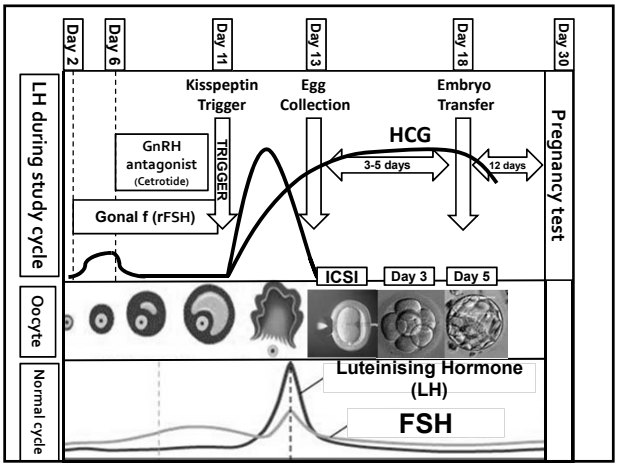


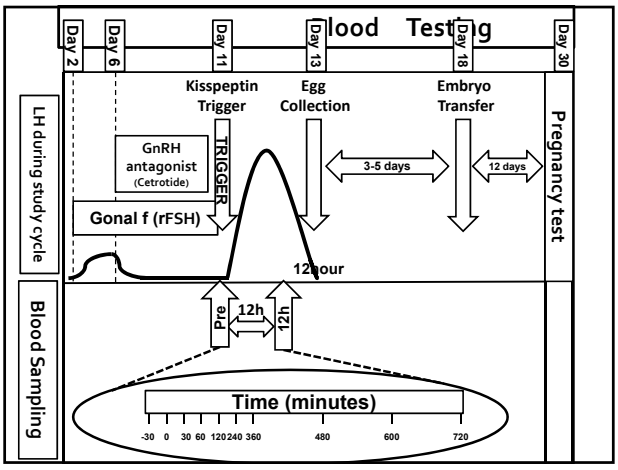
Hypothesis

Kisspeptin is a novel physiological trigger for inducing oocyte maturation in IVF therapy

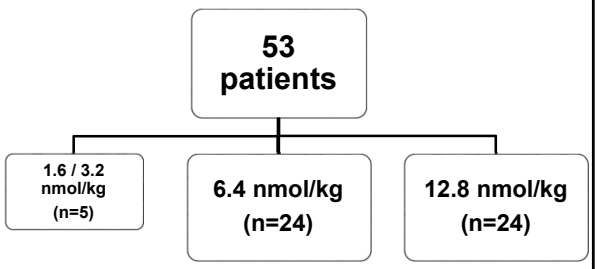
Study Population

- **Age 18-34 years**
- **Regular menstrual cycles 24-35 days**
- **BMI 18-29 kg/m^2**
- **Follicular phase FSH ≤ 12 iU/l**
- **Serum AMH 10-40 pmol/L**
- **No more than one previous IVF cycle**
- **Both ovaries intact**



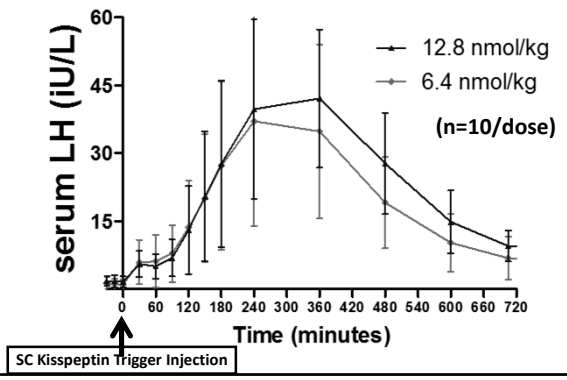


Kisspeptin Dosage

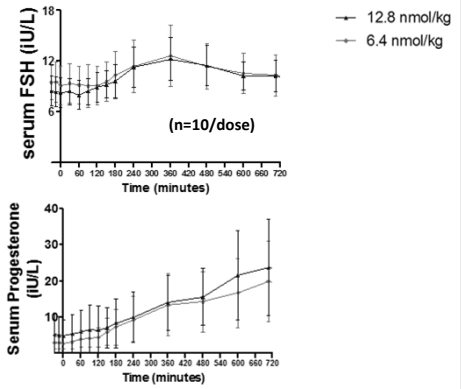


Results

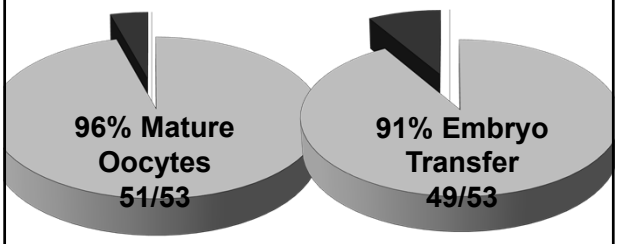
Serum LH during 12hrs following Kisspeptin Trigger



Hormones during 12hrs following Kisspeptin Trigger



Kisspeptin triggers Oocyte Maturation in IVF therapy

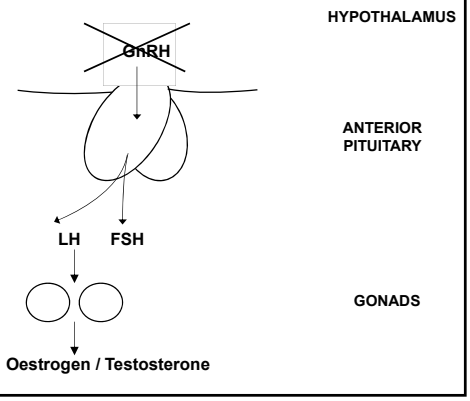


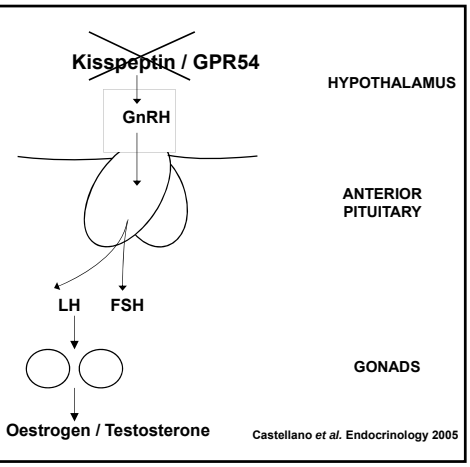
Results

- **Biochemical pregnancy rate 40% (21/53)**
- **Clinical pregnancy rates 23% (12/53)**
- **10 live healthy births to date**

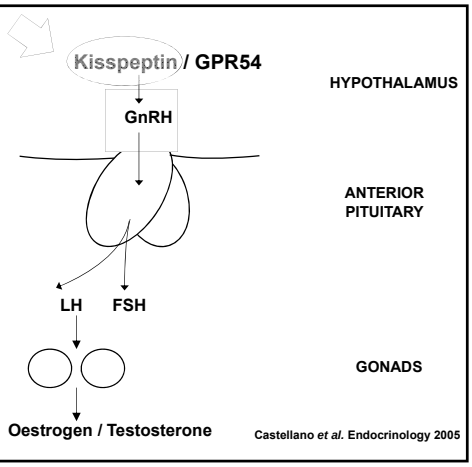
What are effects of kisspeptin women with hypothalamic amenorrhea ?

Hypothalamic amenorrhoea



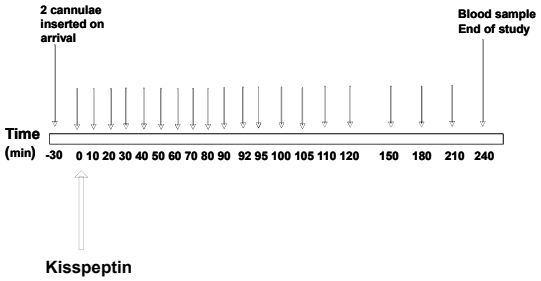


Castellano *et al.* Endocrinology 2005



Castellano *et al.* Endocrinology 2005

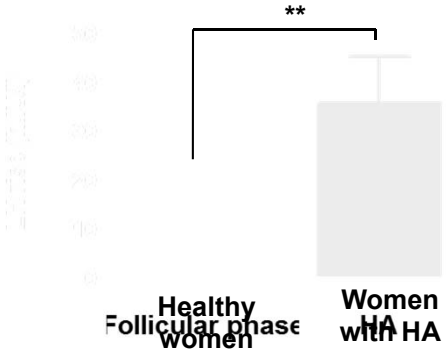
Effects of kisspeptin injection in women with hypothalamic amenorrhea



Kisspeptin increases luteinising hormone release in women with HA

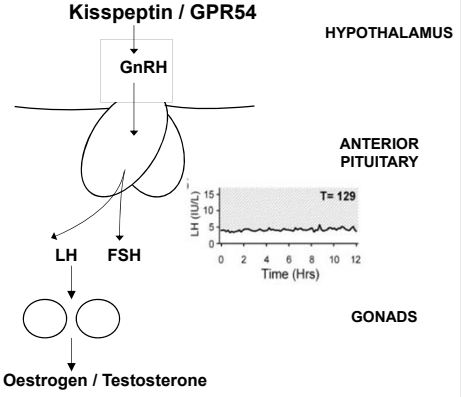
Jayasena *et al.* J Clin Endocrinol Metab 2009

Women with HA are more responsive to kisspeptin than healthy women

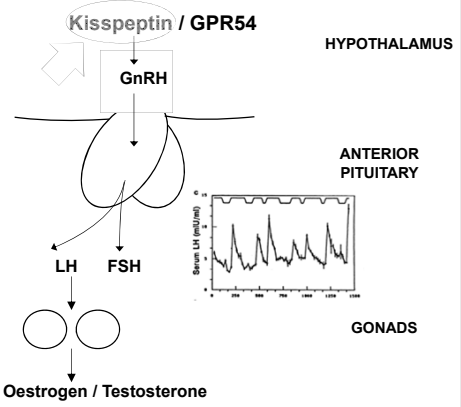


Can kisspeptin-54 restore LH pulsatility in women with hypothalamic amenorrhoea

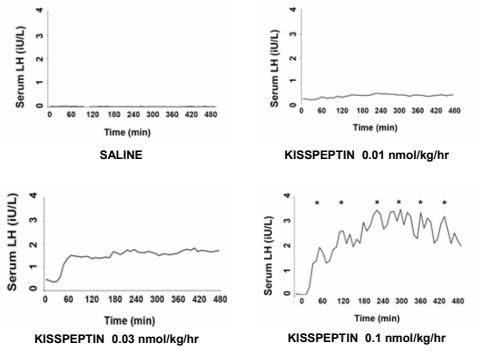
Hypothalamic amenorrhoea



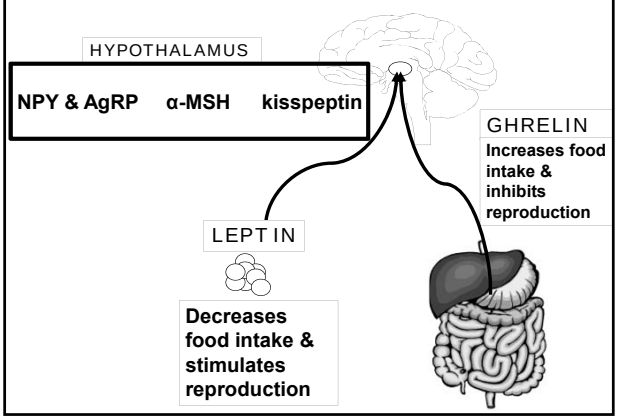
Hypothalamic amenorrhoea



Kisspeptin restores LH pulsatility in women with HA



SUMMARY




human
reproduction
update
The relationship between gut and adipose hormones, and reproduction
Alexander N. Comninos, Channa N. Jayasena, and Waljit S. Dhillo*
Human Reproduction Update. 2014 Mar-Apr;20(2):153-74.0

The endocrinology of obesity: impact on fertility, pregnancy, risk of miscarriage and child health - **Lesley Regan (United Kingdom)**

Contribution not submitted by the speaker

Erasmus MC
University Medical Center Rotterdam

Sophia Children's Hospital

Strategies and benefits of periconception lifestyle interventions

Régine P.M. Steegers-Theunissen, MD, PhD

Professor in Periconception Epidemiology

Dutch Association of Parent and Patient Organizations
Honorary Visiting Professor of the University of Southampton, England
Department of Obstetrics and Gynaecology, and Clinical Genetics
Erasmus MC, University Medical Center, Rotterdam, The Netherlands

14th Pre-congress course 'Early Pregnancy & Endocrinology'
Eshre Annual Meeting, Munich, June 29th, 2014

Erasmus MC

Disclosure of all commercial and/or financial relationships

with manufacturers of pharmaceutical, laboratory supplies

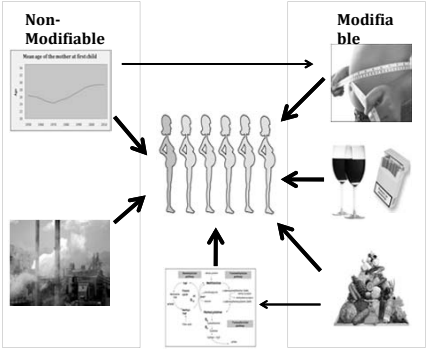
and/or medical devices

Erasmus MC

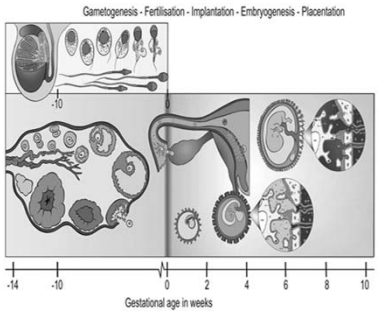
Learning objectives

1) **Definition of the periconception period**
2) **Preconception recommendations**
3) **Preconception interventions**
4) **Challenges and opportunities of mHealth**

Environmental conditions



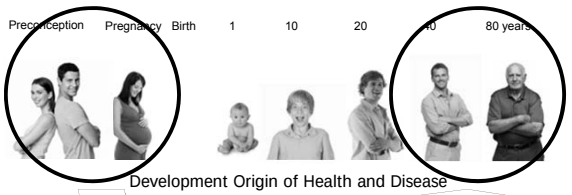
The periconception window



Steegers-Theunissen et al, Hum Reprod Update 2013, 19(6):640-55

human reproduction update

Erasmus MC



Development Origin of Health and Disease

Reproductive population and period are the 'target population' and 'window of opportunity' in the prevention of chronic age-related diseases

Erasmus MC

Erasmus MC

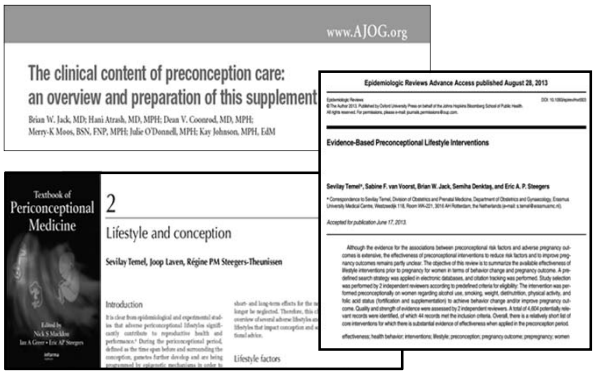
How can we create new life in healthy parental conditions with beneficial short term and long term health consequences?

Preconception care

- General individual preconception care
- Specialist individual preconception care
- Outpatient clinic tailored on nutrition and lifestyle
- eHealth for parents-to-be

~~Ziekte perinataal en~~
op volwassen leeftijd

Preconception interventions



Preconception recommendations

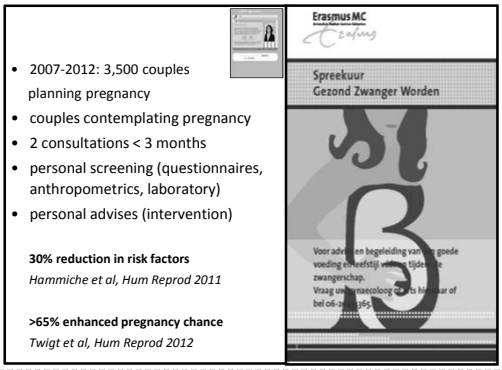
- Healthy diet: high fruits, vegetables, fish
  low satured fats, animal proteins, carbohydrates
- Quit smoking, social alcohol and drug use
- Weight loss: BMI <25
- Folic acid supplement of 0.4 mg/d from preconception to 10 wks
- Vitamin D supplement of 10 ug/d
- Mild to moderate exercise

Preconception nutrition and lifestyle counseling in outpatient clinic

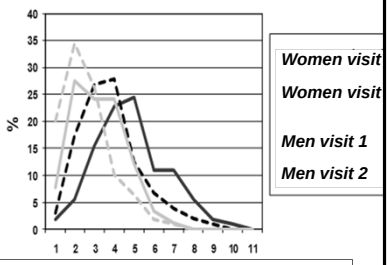
- 2007-2012: 3,500 couples planning pregnancy
- couples contemplating pregnancy
- 2 consultations < 3 months
- personal screening (questionnaires, anthropometrics, laboratory)
- personal advises (intervention)

30% reduction in risk factors
Hammiche et al, Hum Reprod 2011

>65% enhanced pregnancy chance
Twigt et al, Hum Reprod 2012



Rotterdam Reproduction Risk score Modifiable risk factors



R-3 score:	**Women:**	**3.9 vs.2.8; p<0.01***
R-3 score:	**Men:**	**2.3 vs. 1.6; p<0.01***

Hammiche et al., Human Reproduction 2011

Preconception Dietary Risk score

4 slices of whole wheat bread

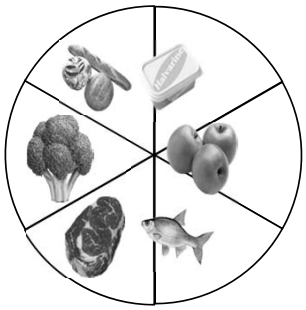
Intake of mono- or polysaturated fatty acids

200g vegetables/day

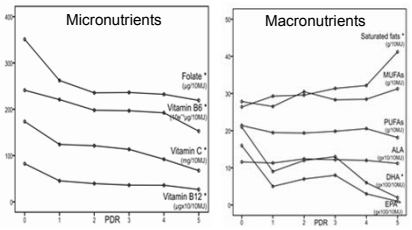
2 pieces of fruit/day

3 servings of meat/week

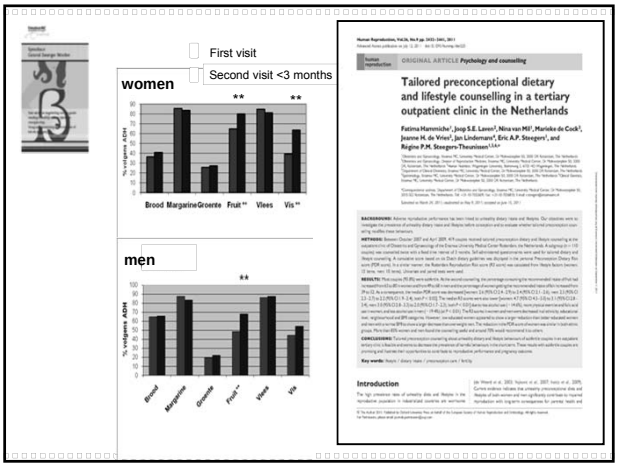
1 serving of fish/week



Preconception Dietary Risk score Validation



Huijgen et al, e-SPEN Journal, 2014



Tailored preconceptional dietary and lifestyle counselling in a tertiary outpatient clinic in the Netherlands

The chance of ongoing pregnancy IVF/ICSI population

Higher Preconception risk score the higher the adequacy of the diet

		Odds Ratio	95%CI	p
Women				
	Age[2]	0.97	0.96-0.99	<0.01
	BMI	1.1	0.99-1.2	0.05
	PDR	**1.49**	**1.03-2.1**	**0.03**
	Smoking	0.45	0.14-1.4	0.18
Men				
	Smoking	0.62	0.25-1.5	0.30
	BMI	0.96	0.87-1.05	0.35
	PDR	**2.0**	**0.79-5.2**	**0.14**

A beneficial increase of the PDR with 1 point is associated with a 49% increased chance of ongoing pregnancy after IVF/ICSI treatment.

Twigt et al., Human Reproduction 2012

Device independent mHealth tool coaching on nutrition and lifestyle

Erasmus MC

https://www.slimmerzwanger.nl/nl/demo-en.php

Parents-to-be and health care givers

Internet excellent medium to reach the target group anonymously (cheap)

mHealth tool for tailored coaching on nutrition and lifestyle

Erasmus MC

Screening at baseline, 6,12,18,24 weeks:

Pregnancy status, LMP, BMI

- Vegetable intake
- Fruit intake
- Folic acid use
- Smoking
- Alcohol use

Coaching 26 weeks SMS, email,website:

- facts, tips,
- rewards: vouchers, recipes, free folic acid

Collaborations: patient organizations, health care professionals, health care insurance, drugstore, publisher

Compliance and Usability

Erasmus MC

Survey Achmea-SAG 2012

August 2013

Evaluation preconception and antenatal outpatient clinics (juni-sept 2012)

86% participation

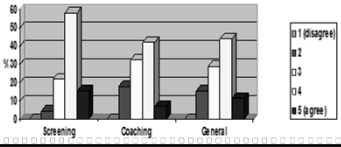
6% no smartphone

8% other reasons

Survey

76% compliance 26 weeks coaching

49-74% positive usability



August 2013

Survey after 4 months of use

Erasmus MC

Overall judgement n=409

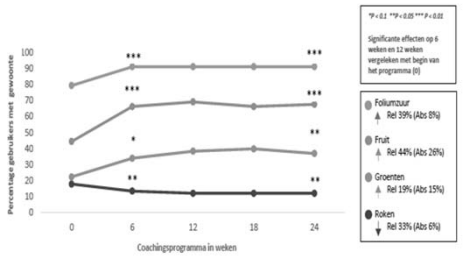
	Disagree (%)		Agree (%)	
	0	**1**	**2**	**3**
▪ I have more attention for my nutrition	0	14	25	61
▪ I have more attention for my lifestyle	0	15	23	62
▪ Slimmer Zwanger supports me very much	0	27	39	34
▪ I will not take a subscription when I have to pay	0	6	18	77
▪ I like that the program is also for my partner	0	3	51	46

August 2013

First efficacy

Erasmus MC

Survey Achmea-SAG 2012

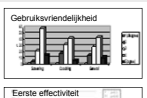


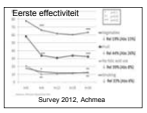
Smarter pregnant version 2.0 *CE-1*

Personal lifestyle coaching program of 26 weeks
for couples and health care professionals

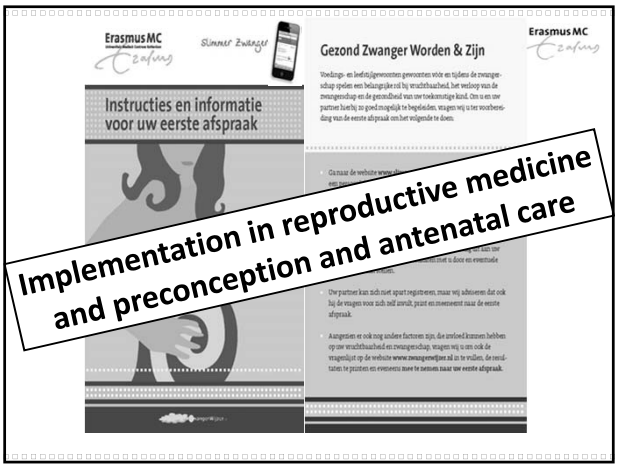
http://www.slimmerzwanger.nl/

https://www.slimmerzwanger.nl/nl/demo-en.php





E-health program > september 2013 extended with coaching on:
- medication use: safety and high compliance
- (complex) treatment, e.g. IVF, reumatic artitis
- compliance of hospital appointments
- vitamine D supplement use
- physical exercise: step- kilometercounter
- rewardings: 3 recipes/week
  vouchers folic acid, pregnancy test



Erasmus MC

References

Hammiche F, Laven JS, Twigt JM, Boellaard WP, Steegers EA, Steegers-Theunissen RPM. Body mass index and central adiposity are associated with sperm quality in men of subfertile couples. Human Reprod 2012; 27:2365-72.

Hammiche F, Laven JS, van Mil N, de Cock M, de Vries JH, Lindemans J, Steegers EAP, Steegers-Theunissen RPM. Tailored preconceptional dietary and lifestyle counselling in a tertiary outpatient clinic in the Netherlands. Human Reprod. 2011; 26:2432-41.

Huijgen NA, van de Kamp ME, Twigt JM, de Vries JHM, Eilers PHC, Steegers EA, Laven JS, Steegers-Theunissen RP . The Preconception Dietary Risk score; a simple tool to assess an inadequate habitual diet for clinical practice. e-SPEN Journal 2014 Feb; 9(1):e13-e19
.

Jack BW, Atrash H, Coonrod DV, Moos MK, O'Donnell J, Johnson K. The clinical content of preconception care: an overview and preparation of this supplement. Am J Obstet Gynecol. 2008 Dec;199(6 Suppl 2):S266-79

Steegers-Theunissen RPM, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. Human Reprod Update 2013; 19:640-55.

Temel S, Laven JS, Steegers-Theunissen RPM. Lyfestyle and conception. Chapter 2 in Textbook of Periconceptional Medicine. Macklon NS, Greer IA, Steegers EA (Eds), Informa Uk Ltd, 2009.

Temel S, van Voorst SF, Jack BW, Denktaş S, Steegers EA. Evidence-based preconceptional lifestyle interventions. Epidemiol Rev. 2014;36(1):19-30.

Twigt JM, Bolhuis ME, Steegers EA, Hammiche F, van Inzen WG, Laven JS, Steegers-Theunissen RPM. The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Hum Reprod 2012; 27:2526-2531.

26

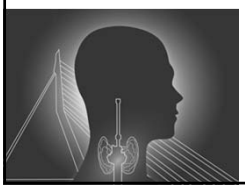
Should pre-conceptional subclinical hypothyroidism be treated?

R.P. Peeters, MD PhD

30th Annual Symposium – ESHRE 2014

Pre-congress course

June 29th, 2014



Erasmus MC
University Medical Center Rotterdam

Disclosure

- Lecture and consultancy fees from Genzyme

Erasmus MC

Learning objectives:

- To understand the changes in thyroid physiology during pregnancy
- To know the adverse outcomes associated with sublinical hypothyroidism
- To make a balanced decision on possible treatment of SCH with the current available evidence

Erasmus MC

Should pre-conceptional subclinical hypothyroidism be treated?

YES !

But only if a non-pregnancy upper limit of TSH is used…

Erasmus MC

Hypothetical case:

- You are on board of a plane with a technical problem on board
- All passengers have to jump out of the plane before it hits the ground
- There are plenty of parachutes on board

Question:
Who would use a parachute when jumping of the plane?

Is this evidence based?

Erasmus MC

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell BMJ, 2003

Results We were unable to identify any randomised controlled trials of parachute intervention.

Hypothetical case:

- You are on board of a plane with a technical problem on board
- All passengers have to jump out of the plane before it hits the ground
- There are plenty of parachutes on board

Question:
Who would now use a parachute, despite the complete lack of evidence that it works?

Erasmus MC

Why use a parachute, despite the lack of evidence?

- There is a good theoretical basis why a parachute should work
- Not using a parachute results in a poor clinical outcome
- Using a parachute does not result in an increased health risk

Why use levothyroxine despite the lack of evidence?

- There is a good theoretical basis why levothyroxine should work
- Not using levothyroxine results in a poor clinical outcome
- Using levothyroxine does not result in an increased health risk

Why use levothyroxine preconceptionally, despite the lack of evidence in SCH?

- There is a good theoretical basis why levothyroxine should work
- Not using levothyroxine results in a poor clinical outcome
  - Fertility
  - Pregnancy Loss
  - Child outcome
- Using levothyroxine does not result in an increased health risk

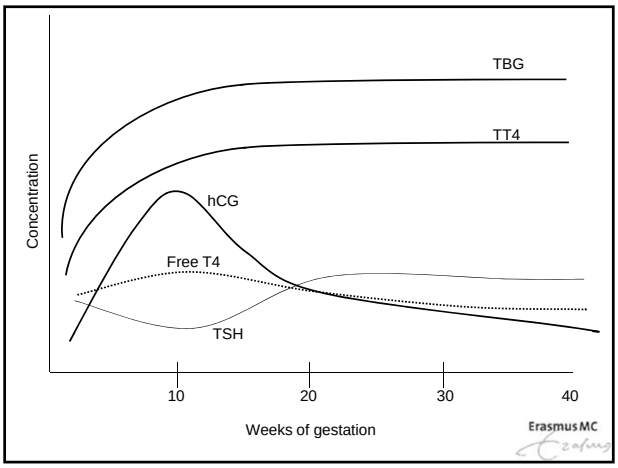
Why use levothyroxine preconceptionally, despite the lack of evidence in SCH?

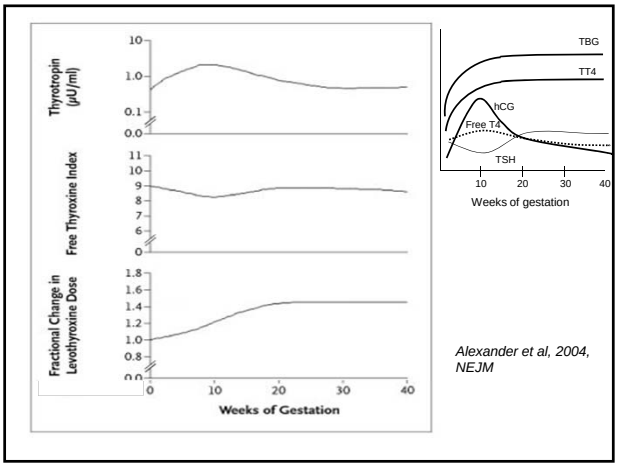
- There is a good theoretical basis why levothyroxine should work
- Not using levothyroxine results in a poor clinical outcome
  - Fertility
  - Pregnancy Loss
  - Child outcome
- Using levothyroxine does not result in an increased health risk

During pregnancy

- Increased requirement of Thyroid Hormone
  - Increase in serum TBG levels
  - Increase in GFR and urinary iodine excretion
  - Increase in placental transport and metabolism of TH
  - Fetal need for TH
- Stimulation of the maternal thyroid by hCG

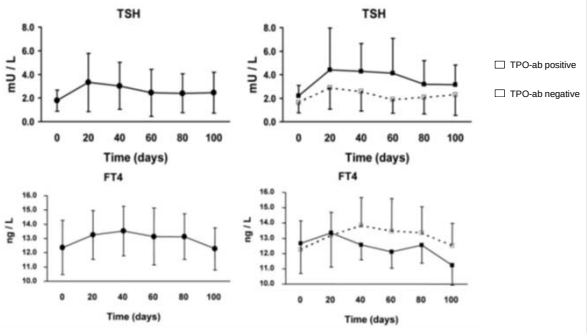
Erasmus MC





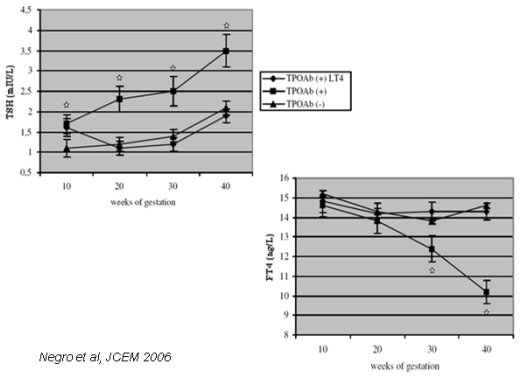
Alexander et al, 2004, NEJM

Course of TSH and FT4 after overian hyperstimulation



Poppe et al, JCEM 2004

TSH and FT4 in relation to gestational age



Negro et al, JCEM 2006

Why use levothyroxine preconceptionally, despite the lack of evidence in SCH?

- There is a good theoretical basis why levothyroxine should work
- Not using levothyroxine results in a poor clinical outcome
  - Fertility
  - Pregnancy Loss
  - Child outcome
- Using a parachute does not result in an increased health risk levothyroxine

What's the definition of SCH?

- An increased TSH in combination with a normal FT4
- This diagnosis should not be made on a single measurement
- The majority of cases with SCH are due to autoimmune thyroid disease

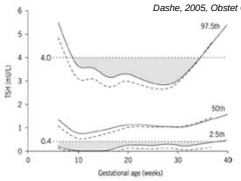
-> What's a normal TSH ?

TSH reference range during pregnancy

ATA & ENDO Soc guidelines advocate the use of pregnancy-specific population-based RRs

If not available:
TSH < 2.5mU/l 1st trimester
TSH < 3.0 mU/l 2nd trimester

Dashe, 2005, Obstet Gynecol



Trimester specific reference ranges

	First	Second	Third
Haddow et al (13)	0.94 (0.06-2.73)	1.29 (0.3-3.70)	
Stricker et al (14)	1.04 (0.05-2.83)	1.02 (0.27-2.79)	1.14 (0.3-2.90)
Panesar et al (15)	0.80 (0.03-2.30)	1.10 (0.03-3.10)	1.30 (0.10-3.50)
Soldin et al (16)	0.98 (0.24-2.99)	1.09 (0.46-2.95)	1.20 (0.40-2.79)
Bocos-Terraz et al (17)	0.92 (0.03-2.65)	1.12 (0.12-2.64)	1.29 (0.23-3.56)
Marwaha et al (18)	2.10 (0.60-5.00)	2.40 (0.43-5.78)	2.10 (0.71-5.70)

Country	(N)
USA	(1126)
Switzerland	(2272)
China	(343)
USA	(216)
Spain	(1198)
India	(331) +
Total	5486

TSH reference range during pregnancy, studies since 2011

Author (Country)	N	Gestation (week)	Median	Lower-upper
Bestwick et al. (UK), *Clin Chim Acta 2013*	16,334	<16	1.11	0.06 - 3.50
Bestwick et al. (Italy) *Clin Chim Acta 2013*	5505	<16	1.07	0.04 - 3.19
Li et al. (China) *JCEM 2014*	640	7-12	1.47	0.10 - 4.34
Männisto et al. (Finland)	4333	T1	1.11	0.08 – 3.54
Thyroid 2011	747	T2	1.37	0.11 – 4.24
Medici et al. (The Netherlands) *JCEM 2012*	5186	8-18		0.03 - 4.04
La'ulu et al. (USA) *Clin Chem 2011*	2172	10-13	0.94	0.02 - 2.69

Total 34,917

What's a normal TSH, and how to define SCH?

- The upper limit of normal during pregnancy varies between populations.
- Before pregnancy, there is no reason to use pregnancy cut-offs for TSH to diagnose SCH

SCH prior to conception is associated with infertility

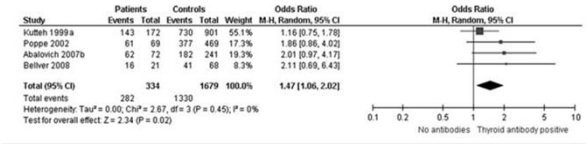
2 < TSH < 4.22 TSH > 4.22

	SH grade 1		SH grade 2		TAI	
	n/*N*	%	*n*/*N*	%	*n*/*N*	%
Infertile patients ($n = 244$)	9/71	12.7[a]	25/244	10.2[b]	62/244	26.6
Control group ($n = 155$)	3/86	3.5	3/155	1.9	10/69	14.5

P<0.005

Abalovich et al, Gyn Endo, 2007

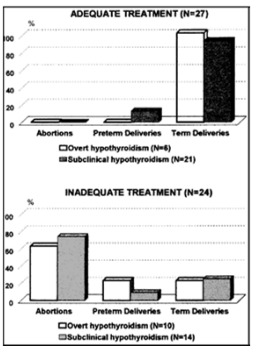
Thyroid autoimmunity is associated with infertility



Boogaard et al, Human Reprod Update, 2011

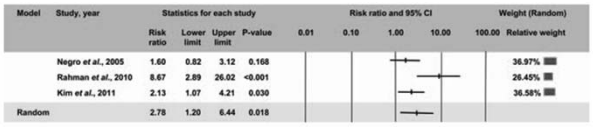
SCH prior to conception is associated with pregnancy loss

- 150 pregnancies in primary hypothyroidism
- 99 conceived under euthyroidism
  -> 4/99 = 4% abortion rate
- 16 conceived under overt hypo, 35 SCHypo
  -> 16/51= 31,4% abortion rate



Abalovich, Thyroid 2002

L-T4 therapy and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies



First trimester low FT4 is associated with child development

Autistic symptoms

Maternal Thyroid Parameters	Pervasive Developmental Problems at Age 6 Years			
	Borderline Problems n = 263		Clinical Problems n = 123	
	OR (95% CI)	*p*	OR (95% CI)	*p*
TSH per SD	0.91 (0.77–1.07)	0.27	0.92 (0.72–1.17)	0.49
fT_4 per SD	0.93 (0.80–1.09)	0.37	0.95 (0.77–1.17)	0.62
Mild hypothyroxinemia	1.31 (0.84–2.04)	0.23	1.41 (0.78–2.57)	0.26
Only mild hypothyroxinemia	0.77 (0.38–1.55)	0.46	0.51 (0.16–1.64)	0.26
Severe hypothyroxinemia	2.02 (1.16–3.51)	0.01	2.60 (1.30–5.18)	0.01
TPO-Abs	1.47 (0.85–2.55)	0.17	0.78 (0.28–2.16)	0.63

Roman et al., Ann Neurol 2013

Why use levothyroxine preconceptionally, despite the lack of evidence in SCH?

- There is a good theoretical basis why levothyroxine should work
- Not using levothyroxine results in a poor clinical outcome
  - Fertility
  - Pregnancy Loss
  - Child outcome
- Using levothyroxine does not result in an increased health risk

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

- **Pregnancy – Category A**
- Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. LEVOTHYROXINE should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

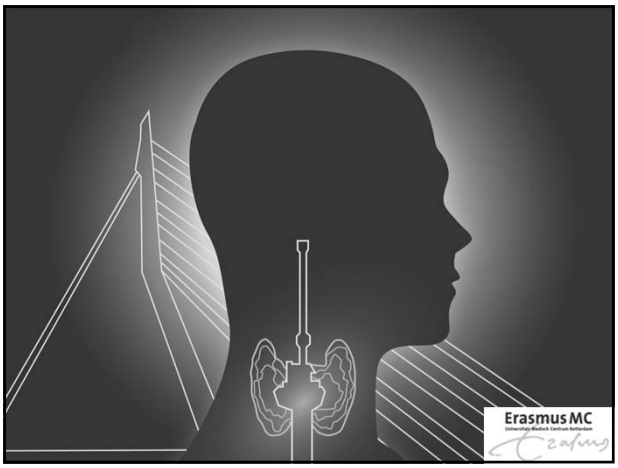
Why use levothyroxine preconceptionally, despite the lack of evidence in SCH?

- There is a good theoretical basis why levothyroxine should work
- Not using levothyroxine results in a poor clinical outcome
  - Fertility
  - Pregnancy Loss
  - Child outcome
- Using levothyroxine does not result in an increased health risk

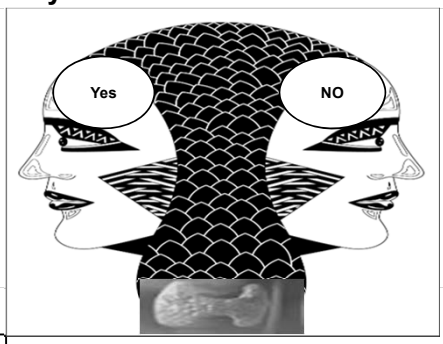
YES !

But only if a non-pregnancy upper limit of TSH is used…

Erasmus MC


Erasmus MC

Should pre-conceptional subclinical hypothyroidism be treated before ART?



Kris Poppe MD, PhD - Free University of Brussels

Kris Poppe

Should pre-conceptional subclinical hypothyroidism be treated before ART?

Disclosure of Conflict of Interest (List)

Receipt of honoraria from Merck- Serono in 2011 (ETA meeting)

Agenda

- ***Why NOT to treat SCH in relation to ART***
  - (female) infertility
  - controlled ovarian hyperstimulation (COH)
  - observational studies
  - interventional studies
- ***Conclusions - YING (any yang?)***
  - ***Learning objectives***

- Why NOT to treat SCH in relation to ART

Thyroid AI (AITD or TAI) & Female infertility

Table 1 Studies on the risk of infertility associated with thyroid autoimmune thyroid disorder.

Study and country	Thyroid antibodies measured	Cause of infertility	Control	Number positive for thyroid antibody (n/total)		Relative risk (95% CI)	*P* value
				Patients	Controls		
Wilson *et al.* (1975),[25] UK	Microsomal and thyroglobulin	OD	Age-matched, postpartum	8/77	11/77	0.7 (0.3–1.9)	NS
Roussev *et al.* (1996),[26] US	Microsomal and thyroglobulin	Idiopathic, OD, endometriosis	Healthy, nonpregnant	5/63	0/15	1.2 (0.1–11)	NS
Geva *et al.* (1997),[27] Israel	Microsomal and thyroglobulin	Idiopathic, tubal disorders	Age-matched, healthy, nulligravidae	15/80	2/40	3.8 (0.8–17.3)	NS
Kutteh *et al.* (1999),[28] US	Peroxidase and thyroglobulin	Idiopathic, OD, tubal disorders, endometriosis	Reproductive age, parous	132/688	29/200	1.3 (0.9–2.1)	NS
Kaider *et al.* (1999),[29] US	Peroxidase and thyroglobulin	Idiopathic, OD, endometriosis	Fertile	51/167	16/109	2.1 (1.1–3.9)	0.02
Reimand *et al.* (2001),[30] Estonia	Microsomal	Idiopathic, OD, endometriosis	Unselected population	2/108	15/392	0.5 (0.1–2.2)	NS
Poppe *et al.* (2002),[31] Belgium	Peroxidase	All causes	Age-matched, fertile	61/438	8/100	1.7 (0.9–3.5)	NS
Janssen *et al.* (2004),[32] Germany	Peroxidase and thyroglobulin	OD (PCOS)	Age-matched, no PCOS	47/175	14/168	3.2 (1.9–5.6)	<0.0001
Abalovich *et al.* (2007),[33] Argentina	Peroxidase	All causes	Age-matched, fertile	62/244	10/69	1.8 (1.0–3.2)	NS
Petta *et al.* (2007),[34] Brazil	Peroxidase and thyroglobulin	Endometriosis	Fertile, no endometriosis	13/148	25/158	0.5 (0.3–1.0)	NS

Abbreviations: NS, not significant; OD, ovulatory dysfunction; PCOS, polycystic ovary syndrome.

Poppe K et al. Nat Clin Pract Endocrinol Metab. 2008

Arch Gynecol Obstet
DOI 10.1007/s00404-011-2040-5

REPRODUCTIVE MEDICINE

Prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome

Maryam Kachuei · Fatemeh Jafari · Ali Kachuei · Ammar H. Keshteli

	PCOS	Controls	p
age	23.9 ± 5.2	24.3 ± 3.17	n.s.
TPO-Ab (IU/ml)	216 ± 428	131 ± 364	0.04
TPO-Ab % > 75 IU/ml	30.6	27.8	n.s.
TSH (IU/ml)	2.7 ± 3.8	2.2 ± 1.5	n.s.
Goiter	62.3 %	35.7 %	0.0001

Subclinical hypothyroidism (SCH) & Female infertility

Definition of SCH

- **Most studies still used a serum TSH cut-off ~ 4 mIU/L during the first trimester**
  --- > non-pregnant ranges
- **Trimester, method (and population) specific reference ranges should be obtained**
  --- > some authors / guidelines propose now a serum TSH < 2.5 mIU/L also before pregnany

When individuals "at risk" for thyroid dysfunction and pregnancy which are identified, prenatal measurement prenatal measurement of serum TSH is recommended.
If it is above 2.5 mIU/liter, the test should be confirmed by repeat assay.

J Clin Endocrinol Metab 97: 2543–2565, 2012

SPECIAL FEATURE
Clinical Practice Guideline

Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

Leslie De Groot, Marcos Abalovich, Erik K. Alexander, Nobuyuki Amino, Linda Barbour, Rhoda H. Cobin, Creswell J. Eastman, John H. Lazarus, Dominique Luton, Susan J. Mandel, Jorge Mestman, Joanne Rovet, and Scott Sullivan

Table 3 Prevalence of subclinical hypothyroidism in infertile women.

Study	Study design	Prevalence of SCH in patients (% [n/total])	Prevalence of SCH in controls	Definition of SCH
Bohnet *et al.* (1981)[80]	Prospective	11% (20/185)	No controls	Basal TSH >3mIU/l or peak TSH >15mIU/l[d]
Gerhard *et al.* (1991)[35]	Prospective	43% (80/185)[a]	No controls	Peak TSH >20mIU/l[d]
Shalev *et al.* (1994)[81]	Retrospective	0.7% (3/444)	No controls	Basal TSH >4.5mIU/l
Arojoki *et al.* (2000)[82]	Retrospective	1.3% (4/299)	2–3%[b]	Basal TSH >5.5mIU/l
Grassi *et al.* (2001)[37]	Prospective	4.6% (6/129)	No controls	Basal TSH >4.5mIU/l
Poppe *et al.* (2002)[31]	Prospective	0.9% (4/438)	<1%[c]	Basal TSH >4.2mIU/l
Raber *et al.* (2003)[83]	Prospective	34.0% (96/283)	No controls	Basal TSH >4mIU/l or peak TSH >15mIU/l[d]
Abalovich *et al.* (2007)[33]	Retrospective	10.2% (25/244)	1.9%[c]	Basal TSH >5mIU/l

[a]1/185 (0.5%) patients had a basal serum TSH >6mIU/l. [b]Prevalence in the Finnish population. [c]Fertile women. [d]Peak serum TSH after thyrotropin-releasing hormone stimulation test. Abbreviation: SCH, subclinical hypothyroidism.

Poppe K et al. Nat Clin Pract Endocrinol Metab. 2008

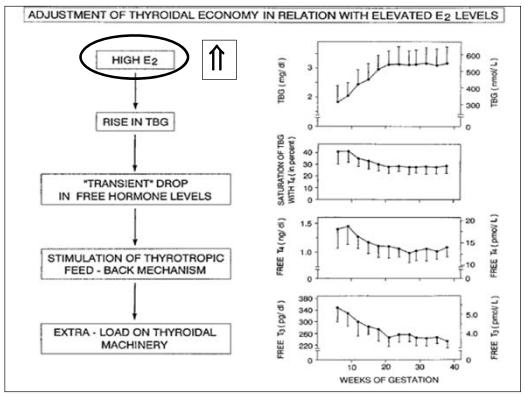
Conclusions

- Thyroid autoimmunity (TAI) / dysfunction (SCH)
- **no strong evidence that the prevalence is increased in infertile women**

- TAI is the most frequent cause of SCH in women

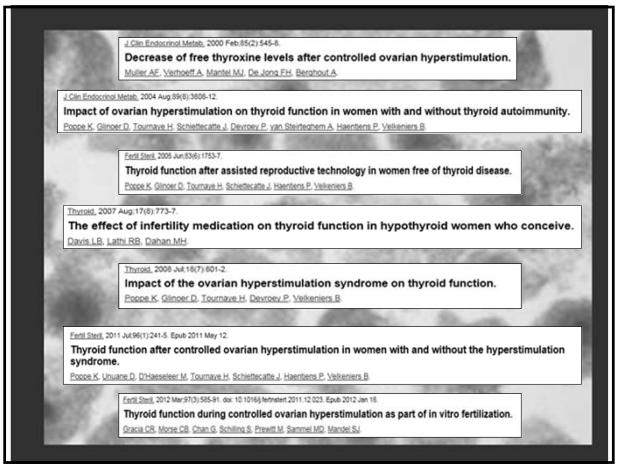
- Definition(s) of SCH ?

Thyroid & Controlled ovarian hyperstimulation (COH)



Glinoer Endo Reviews 1997

- **Depending on the type and duration of COH, the estradiol (E2) levels increase before (and eventually during the early stages of) pregnancy**
  - **the E2 levels at early those moments are comparable with those in the 2nd trimester of pregnancy**
    - **2000-4000 ng/L**



Points of interest

→ **the Δ E2 (increase)**
- **type of ovarian stimulation**
- **ovarian hyperstimulation syndrome (OHSS)**

→ **the presence of thyroid autoimmunity**
and/or
→ **patients under LT4 treatment**

Thyroid function after assisted reproductive technology in women free of thyroid disease

Kris Poppe, M.D.,[a] *Daniel Glinoer, M.D., Ph.D.,*[b] *Herman Tournaye, M.D., Ph.D.,*[c] *Johan Schiettecatte,*[c] *Patrick Haentjens, M.D., Ph.D.,*[a] *and Brigitte Velkeniers, M.D., Ph.D.*[a]

[a]Department of Endocrinology, Vrije Universiteit Brussel, Brussels; [b]Department of Endocrinology, Université Libre de Bruxelles, Brussels; and [c]Center for Reproductive Medicine, Vrije Universiteit Brussel, Brussels, Belgium

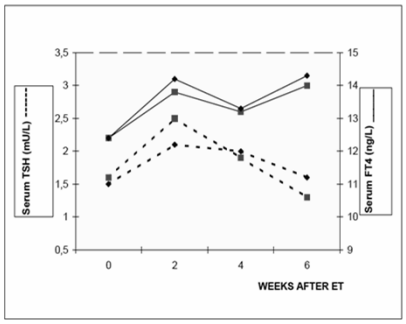
Fertility and Sterility® Vol. 83, No. 6, June 2005 1753

	All patients	ongoing	miscarriage
n (%)	77 (100)	45 (58)	32 (42)
age (yrs)	31 ± 5	31 ± 5	31 ± 5
TSH (mU/l)	1.6 ± 0.8	1.6 ± 0.8	1.5 ± 0.7
FT4 (ng/l)	12.4 ± 1.8	12.2 ± 1.8	12.4 ± 1.9
ET (n)	2.1 ± 0.6	2.1 ± 0.6	2.2 ± 0.7

ET : number of transferred embryos
all values expressed as mean ± SD

FIGURE 1

Pattern of change over time for the TSH and FT4 serum values (mean ± SD) collected at four periods: before ART (time 0) and at weeks 2, 4 and 6 after ET. The pattern of change over time is comparable for patients with ongoing pregnancies (*squares*) and miscarriage (*diamonds*).



Conclusions

- **Serum TSH and FT4 significantly increased after COH**
- **Thyroid hormone profiles are comparable between women with**
  miscarriage &
  ongoing pregnancies
- **Miscarriage is a multifactorial process**

Thyroid function during ovarian stimulation: a systematic review

Gesthimani Mintziori, M.Sc., Dimitrios G. Goulis, Ph.D., Konstantinos A. Toulis, M.Sc., Christos A. Venetis, M.Sc., Efstratios M. Kolibianakis, Ph.D., and Basil C. Tarlatzis, Ph.D.

Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

Conclusion(s): The current evidence is inconclusive regarding OS effect on thyroid function or TAI. Serum TSH concentrations may be increased during or within 1 month after OS, exceeding the threshold of 2.5 mU/L suggested for the first trimester of pregnancy, but further prospective studies are needed to provide conclusive evidence for or against universal evaluation of thyroid function and TAI in women undergoing OS. (Fertil Steril® 2011;96:780-5. ©2011 by American Society for Reproductive Medicine.)

Observational studies
SCH - ART

*** in-vitro**
*** during pregnancy**
*** neuro-intellectual outcome**

Thyroid Function in Infertile Patients Undergoing Assisted Reproduction

Am J of Reprod Immunology (2013)

Angela Fumarola[1], Giorgio Grani[1], Daniela Romanzi[2], Marianna Del Sordo[1], Marta Bianchini[1], Alessia Aragona[1], Daniela Tranquilli[2], Cesare Aragona[2]

Table I Number of oocytes retrieved, number and scoring of embryos transferred after fertilization, and number of clinical pregnancies, compared between groups with TSH ≤2.5 or >2.5 mIU/L

	TSH < 2.5 mIU/L (n = 206)	TSH > 2.5 mIU/L (n = 57)	P	All cycles (n = 263)
Mean age (range), years	37.72 (26–48)	38.65 (24–48)	NS	37.92 (24–48)
TSH (range), mIU/L	1.34 (0.05–2.49)	3.33 (2.50–8.52)	–	1.75 (0.05–8.52)
fT3 (range), pg/mL	3.13 (0.89–6.70)	2.85 (1.40–5.45)	<0.01	3.07 (0.89–6.70)
fT4 (range), ng/dL	1.23 (0.50–2.91)	1.08 (0.76–1.58)	<0.001	1.20 (0.50–2.91)
Poor ovarian response[a]	49 (23.8%)	12 (21.1%)	NS	61 (23.2%)
	(n = 157)	(n = 45)		(n = 202)
Clinical pregnancies	35 (22.3%)	4 (8.9%)	0.045	39 (19.3%)
Retrieved oocytes				
0–4	98 (62.4%)	24 (53.3%)	NS	122 (60.4%)
5–9	51 (32.5%)	17 (37.8%)		68 (33.7%)
≥ 10	8 (5.1%)	4 (8.9%)		12 (5.9%)
Transferred embryos				
0	17 (10.8%)	2 (4.4%)	NS	19 (9.4%)
1	40 (25.5%)	15 (33.3%)	NS	55 (27.2%)
2	38 (24.2%)	11 (24.4%)	NS	49 (24.3%)
3	62 (39.5%)	17 (37.9%)	NS	79 (39.1%)
Quality score of embryos[b]				
I	0.28 (0.21–0.35)	0.42 (0.26–0.57)	NS	0.31 (0.25–0.37)
II	0.39 (0.31–0.46)	0.38 (0.23–0.52)	NS	0.38 (0.32–0.45)
III	0.21 (0.15–0.27)	0.13 (0.05–0.20)	NS	0.19 (0.14–0.24)
IV	0.05 (0.02–0.09)	0.05 (−0.02–0.12)	NS	0.05 (0.03–0.08)

P values < 0.05 were considered statistically significant (chi square test).
[a]Excluded from further evaluations.
[b]Rate of embrios of showed quality over the total number of embryos transferred in each cycle, mean. In brackets the 95% confidence interval; Mann–Whitney U test.

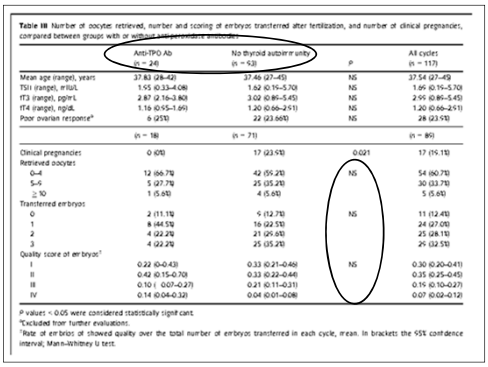


Table III Number of oocytes retrieved, number and scoring of embryos transferred after fertilization, and number of clinical pregnancies, compared between groups with or without

	Anti-TPO Ab (n = 24)	No thyroid autoimmunity (n = 93)	P	All cycles (n = 117)
Mean age (range), years	37.83 (28–42)	37.46 (27–45)	NS	37.54 (27–49)
TSH (range), mIU/L	1.55 (0.33–4.08)	1.62 (0.19–5.70)	NS	1.69 (0.19–5.70)
fT3 (range), pg/mL	2.87 (2.16–3.80)	3.02 (0.86–5.45)	NS	2.99 (0.86–5.45)
fT4 (range), ng/dL	1.16 (0.95–1.69)	1.20 (0.66–2.51)	NS	1.20 (0.66–2.51)
Poor ovarian response[a]	6 (25%)	22 (23.66%)	NS	28 (23.9%)
	(n = 18)	(n = 71)		(n = 89)
Clinical pregnancies	0 (0%)	17 (23.9%)	0.021	17 (19.1%)
Retrieved oocytes				
0–4	12 (66.7%)	42 (59.2%)	NS	54 (60.7%)
5–9	5 (27.7%)	25 (35.2%)		30 (33.7%)
≥ 10	1 (5.6%)	4 (5.6%)		5 (5.6%)
Transferred embryos				
0	2 (11.1%)	9 (12.7%)	NS	11 (12.4%)
1	8 (44.5%)	16 (22.5%)		24 (27.0%)
2	4 (22.2%)	21 (29.6%)		25 (28.1%)
3	4 (22.2%)	25 (35.2%)		29 (32.5%)
Quality score of embryos[b]				
I	0.22 (0–0.43)	0.33 (0.21–0.48)	NS	0.30 (0.20–0.41)
II	0.42 (0.15–0.70)	0.33 (0.22–0.44)		0.35 (0.25–0.45)
III	0.10 (−0.07–0.27)	0.21 (0.11–0.31)		0.19 (0.10–0.27)
IV	0.14 (0.04–0.32)	0.04 (0.01–0.08)		0.07 (0.02–0.12)

P values: < 0.05 were considered statistically significant.
[a]Excluded from further evaluations.
[b]Rate of embryos of showed quality over the total number of embryos transferred in each cycle, mean. In brackets the 95% confidence interval; Mann-Whitney U test.

Hypothyroidism during Pregnancy

Country (period of study)	Observed cases with Hypothyroidism	Severity of Hypothyroidism	TSH (mIU/L)	Time of Screening and/or Diagnosis	First Author (reference)
US (1975-					ontoro 243)
US (1981-					eung 244)
Jap (1986-					imijo 253)
US (after					Jhin 245)
Belg (1990-					inoer 246)
US (1990-					illan 247)
US (2000-					axey 250)
UI (2002-					nidya 251)
US (1999-					Goldman 252)
Finl (1985-					nnisto 207)
Ind (not rep					ahu 255)
Nether (2003-2004)	(IR: 0.44%)				nhadi (208)

The incidence rates varied from 0.4% to 11.1% and SCH represented 2/3 of all cases

All together, they yielded a 2.4% overall incidence of gestational hypothyroidism (1.425 cases identified among 60.366 pregnancies)

Krassas et al. Endocrine Reviews 2010

Health problems related to SCH and hypothyroidism

1.Obstetrical complications
- **Miscarriage**
- **Hypertension**
- **Preeclampsia**
- **Gestational DM**
- **Placental abruption**
- **Preterm Delivery**
- **Cesarean delivery**

2.Neonatal complications
- **Perinatal Death**
- **NICU Admission**
- **Apgar Score < 3 CHF**
- **Respiratory Distress**
- **Low Birth Weight**
- **High Birth Weight**

3.Neuropsychological outcome of the offspring

human reproduction update

Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review

Emmy van den Boogaard [1], Rosa Vissenberg [2], Jolande A. Land [3], Madelon van Wely [1], Joris A.M. van der Post [4], Mariette Goddijn [1], and Peter H. Bisschop [5,*]

Preterm delivery in SCH

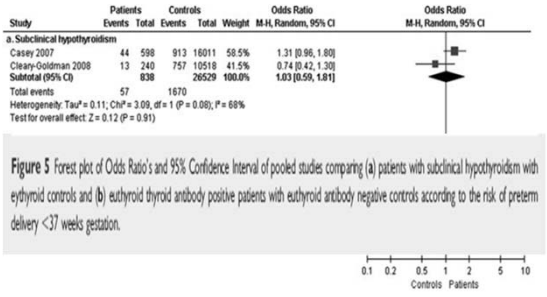


Figure 5 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing (**a**) patients with subclinical hypothyroidism with eythyroid controls and (**b**) euthyroid thyroid antibody positive patients with euthyroid antibody negative controls according to the risk of preterm delivery <37 weeks gestation.

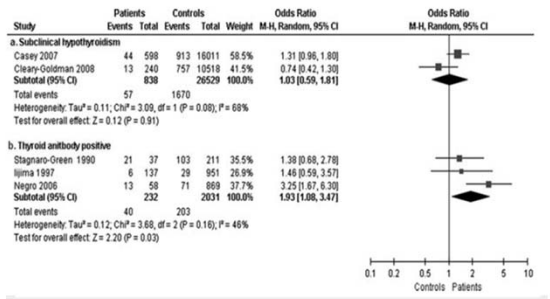
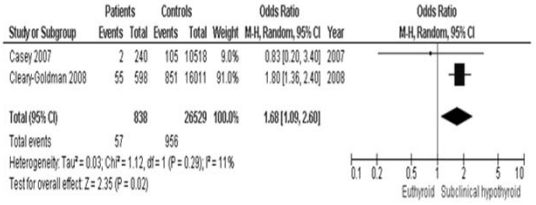


Figure 5 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing (**a**) patients with subclinical hypothyroidism with eythyroid controls and (**b**) euthyroid thyroid antibody positive patients with euthyroid antibody negative controls according to the risk of preterm delivery <37 weeks gestation.

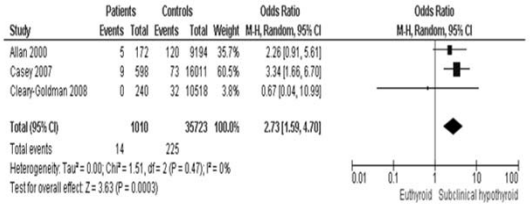
Placental abruption in SCH

Figure 5 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyroidism with euthyroid controls according to the risk of placental abruption



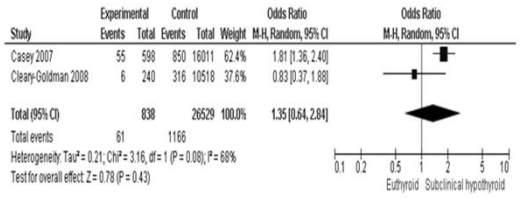
Perinatal mortality in SCH

Figure 7 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyroidism with euthyroid controls according to the risk of perinatal mortality



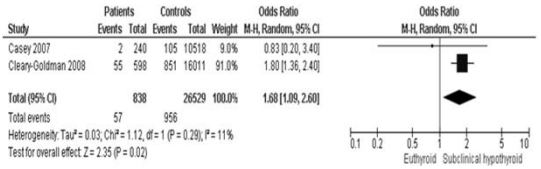
Gestational DM in SCH

Figure 2 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyroidism with euthyroid controls according to the risk of Gestational Diabetes Mellitus



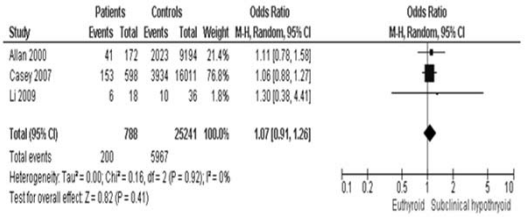
Preeclampsia in SCH

Figure 4 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyriodism with euthryoid controls according to the risk of preeclampsia



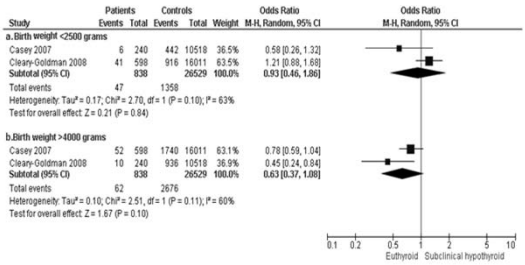
Risk of Caesarean section in SCH

Figure 6 Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyroidism with euthyroid controls according to the risk of Caesarean Section



Birth weight in SCH

Figure 8 a and b: Forest plot of Odds Ratio's and 95% Confidence Interval of pooled studies comparing patients with subclinical hypothyroidism with euthyroid controls according to the risk of a) birth weight <2500 grams and b) birth weight >4000 grams



What is a normal thyroid-stimulating hormone (TSH) level? Effects of stricter TSH thresholds on pregnancy outcomes after in vitro fertilization

TABLE 1

No difference in clinical outcomes by different proposed TSH thresholds.

Parameter	TSH ≥2.5 mIU/L (n = 248)	TSH <2.5 mIU/L (n = 807)	*P* value	TSH ≥4.5 mIU/L (n = 56)	TSH <4.5 mIU/L (n = 999)	*P* value
TSH (mIU/L), median (IQR)[a]	3.2 (2.8–3.8)	1.5 (1.2–1.9)		5.1 (4.4–6.7)	1.7 (1.3–2.3)	
Age (y), mean ± SD	37.1 ± 4.7	36.7 ± 4.8	NS	36.1 ± 4.8	36.8 ± 4.8	NS
PRL (ng/mL), mean ± SD	12.6 ± 7.2	11.1 ± 6.4	.003	11.4 ± 8.0	11.4 ± 6.6	NS
Clinical pregnancy, %	51.6	46.7	NS	53.7	47.6	NS
Delivery, %	39.1	33.5	NS	42.9	34.3	NS
Miscarriage, %	12.5	13.3	NS	8.9	13.3	NS

Note: IQR = interquartile range; NS = nonsignificant.
[a] Because data did not fit a normal distribution, values are described as medians and IQR.

Reh. Correspondence. Fertil Steril 2010.

Reh A, et al. Fertility and Sterility December 2010

Gynecol Obstet Invest. 2013 Dec 14. [Epub ahead of print]

Association of TSH Concentrations and Thyroid Autoimmunity with IVF Outcome in Women with TSH Concentrations within Normal Adult Range.

Mintziori G[1], Goulis DG, Gialamas E, Dosopoulos K, Zouzoulas D, Gitas G, Venetis CA, Toulis KA, Kolibianakis EM, Tarlatzis BC.

- Background/Aims:
  - to evaluate the association of serum TSH and presence of TAI with the live birth rate in euthyroid women undergoing in vitro fertilization (IVF).
- Methods:
  1. Retrospective design 158 euthyroid women (TSH 0.5-4.5 mIU/L) who underwent IVF from January 2006 to December 2010.
  2. Thyroid parameters were measured on day 3 of the previous non treatment cycle.
  3. Women were sub grouped and analyzed according to their TSH (low: 0.5-2.5 vs. high: 2.6-4.5 mIU/L) and TAI (+ vs. -).
- Conclusion
  - **No difference in the live birth rate** was found between the TSH (low: 34.2% vs. high: 36.8%, p = 0.763) or TAI (present: 26.7% vs. absent: 34.3%, p = 0.568) subgroups.

Clinical Endocrinology (2014) **80**, 122–127 doi: 10.1111/cen.12220

ORIGINAL ARTICLE

Live birth rates following *in vitro* fertilization in women with thyroid autoimmunity and/or subclinical hypothyroidism

Joyce Chai, Wing-Yee T. Yeung, Chi-Yan V. Lee, Hang-Wun R. Li, Pak-Chung Ho and Hung-Yu E. Ng

Table 3. Outcomes of *in vitro* fertilization

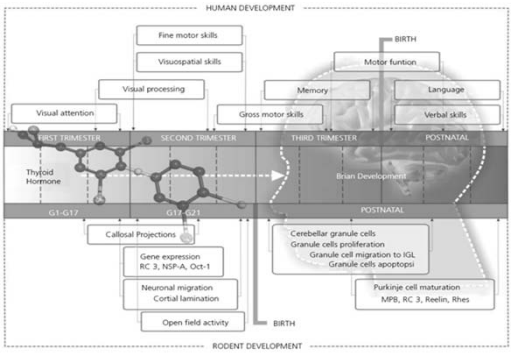
	TAI positive		TAI negative		
	Euthyroid	Subclinical	Euthyroid	Subclinical	*P*-value
Clinical pregnancy rate per cycle initiated, % (n)	44·9 (40/89)	42·4 (14/33)	45·8 (192/419)	41·9 (36/86)	NS
Miscarriage rate, % (n)	20·0 (8/40)	14·3 (2/14)	19·3 (37/192)	8·3 (3/36)	NS
Live birth rate per fresh cycle, % (n)	32·6 (29/89)	33·3 (11/33)	36·0 (151/419)	36·0 (31/86)	NS

Table 4. Clinical outcomes by different TSH thresholds

	TSH < 2·5 mIU/l (*n* = 508)	TSH ≥ 2·5 mIU/l (*n* = 119)	*P*-value	TSH < 3·5 mIU/l (*n* = 586)	TSH ≥ 3·5 mIU/l (*n* = 41)	*P*-value	TSH < 4·5 mIU/l (*n* = 602)	TSH ≥ 4·5 mIU/l (*n* = 25)	*P*-value
Clinical pregnancy rate per cycle initiated, %	45·7	42·0	NS	45·1	43·9	NS	45·2	40·0	NS
Miscarriage rate, %	19·4	10·0	NS	18·2	11·1	NS	17·6	20·0	NS
Live birth rate per fresh cycle, %	35·4	35·3	NS	35·2	39·0	NS	35·5	32·0	NS

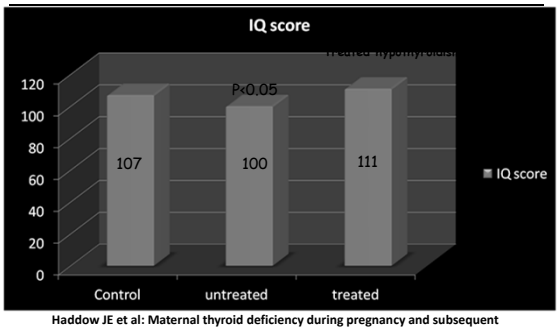
Fetal (brain) development

Thyroid disorders: deleterious effects will depend upon how soon, how long and how severe they appear during gestation during fetal life



Rovet J 2004 J Neuroendocrinology

IQ scores of children born to mother with untreated hypothyroidism during pregnancy were significantly lower than those of the control children



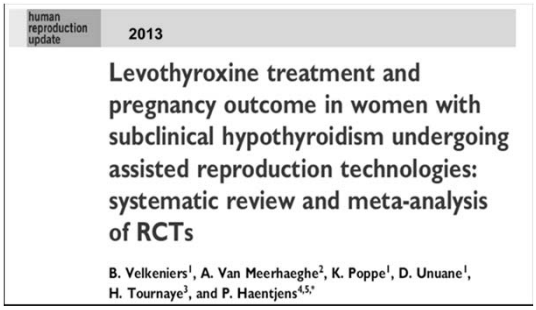
Haddow JE et al: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549, 1999

Conclusions - SCH

- **Of the 7 different outcomes that were investigated in the meta-analysis:**
  - **4 did NOT show a positive association**
  - **3 did**
- **The few data published on the pregnancy outcome in relation to SCH are negative**
  - **but maybe this is more the case for the presence of TAI ?**
- **More associated with neuro-intellectual outcome ?**

Intervention trials in (infertile) women with SCH

Pregnancy Outcome
Cognitive developement


human reproduction update 2013

Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs

B. Velkeniers[1], A. Van Meerhaeghe[2], K. Poppe[1], D. Unuane[1], H. Tournaye[3], and P. Haentjens[4,5,*]

Table I•a Characteristics of the 3 randomized clinical trials included in the primary analyses

RCT	Country	Population	Causes of infertility, according to treated and control groups of trial	Intervention
Negro et al. (2005)	Italy	86 TPO-Abs-positive infertile women undergoing IVF/ICSI	Ovarian dysfunction, n (%), treated 11 (31), placebo 13 (36) Tubal factors, n (%), treated 10 (28), placebo 9 (25) Endometriosis, n (%), treated 7 (19), placebo 9 (25) Idiopathic, n (%), treated 8 (22), placebo 5 (14)	Levothyroxine 1 μg/kg/day
Abdel Rahman et al. (2010)	Egypt	70 infertile women with subclinical hypothyroidism undergoing IVF/ICSI	Ovarian dysfunction, n (%), treated 13 (37), placebo 12 (34) Tubal factors, n (%), treated 9 (26), placebo 11 (31) Endometriosis, n (%), treated 7 (20), placebo 5 (14) Idiopathic, n (%), treated 6 (17), placebo 7 (20)	Levothyroxine 50 to 100 μg/day to normalize TSH before ART
Kim et al. (2011)	South Korea	64 infertile women with subclinical hypothyroidism undergoing IVF/ICSI	Tubal factor, n (%), treated 10 (31), not treated 9 (28) Endometriosis III or IV, n (%), treated 6 (19), not treated 7 (22) Male factor, n (%), treated 13 (41), not treated 13 (41) Unexplained, n (%), treated 3 (9), not treated 3 (9)	Levothyroxine 50 μg/day before pregnancy; Titration during pregnancy to maintain TSH < 2.5 mIU/L

Table I-b Trial characteristics (cont'd)

RCT	Reference values for thyroid status	Definition of thyroid status and thyroid hormone values
Negro et al. (2005)	TSH 0.27–4.2 mIU/L fT4 9.3–18.0 ng/L or 12–33.5 pmol/L TPO-Ab 0–100 kIU/L	values within normal limits and controlled before ART procedure, after treatment mean (SD) for TSH: 1.6 (0.8) mean (SD) for fT4: 12.0 (2.0) mean (SD) baseline TSH: 1.9 (0.7) before treatment, 1.1 (0.3) after treatment; not treated 1.7 (0.7) mean (SD) baseline fT4: 11.2 (1.8) before treatment, 14.1 (2.5) after treatment; not treated 11.7 (2.1)
Abdel Rahman et al. (2010)	TSH 0.27–4.2 mIU/L fT4 9.0–25.9 ng/L or 0.9-2.59 ng/dL	TSH >= 4mUI/L, fT4 within normal range and controlled before start ART mean (SD) baseline TSH before treatment: placebo 4.8 (0.7), treated 4.7 (0.5) mean (SD) baseline fT4 before treatment: placebo 1.04 (0.49), treated 1.0 (0.4) mean (SD) after treatment: TSH placebo 4.9 (0.3), treated 1.1 (0.7); fT4placebo 1.01 (0.5), treated 0.95 (0.4)
Kim et al. (2011)	TSH 0.27–4.0 mIU/L fT4 0.9–2.59 ng/dL	TSH > 4.5 mUI/L, fT4 within normal range and controlled on the day of beta-HCG measurement mean (SD) baseline TSH before treatment : placebo 6.7 (1.8), treated 6.6 (1.7) mean (SD) baseline fT4 before treatment: placebo 1.2 (0.2); treated 1.2 (0.2) mean (SD) after treatment on day of beta-HCG measurement: TSH placebo 6.9 (2.0), treated 2.3 (0.4); fT4 placebo1.0 (0.2), treated 1.4 (0.3)

Table II Summary of outcomes and effect sizes for the primary and secondary analyses.

Outcome	Number of studies	Number of participants	Statistical method	Effect size, calculated	I^2
Primary end-point (primary analyses)					
Delivery	3	220	RR (Random, 95% CI)	**2.76 [1.20, 6.44]**	70%
Delivery	3	220	ARD (Random, 95% CI)	**36.3% [3.5%, 69.0%]**	88%
Delivery	3	220	NNT (Random, 95% CI)	**3 [1, 28]**	NA
Secondary end-points (secondary analyses)					
Oocytes retrieved	2	134	SMD (Random, 95% CI)	0.08 [−0.26, 0.42]	0%
Mature oocytes	2	134	SMD (Random, 95% CI)	0.64 [−0.20, 1.46]	78%
Fertilized oocytes	2	134	SMD (Random, 95% CI)	**0.55 [0.03, 1.08]]**	47%
Embryos transferred	1	64	SMD (Random, 95% CI)	0.00 [−0.22, 0.22]	NA
Embryos cryopreserved	1	64	SMD (Random, 95% CI)	−0.70 [−0.53, 1.93]	NA
Embryo implantation	1	64	RR (Random, 95% CI)	**1.81 [1.01, 3.25]**	NA
Embryo implantation	1	64	ARD (Random, 95% CI)	**12.0% [0.5,% 23.5%]**	NA
Embryo implantation	1	64	NNT (Random, 95% CI)	**9 [5, 200]**	NA
Clinical pregnancy	3	220	RR (Random, 95% CI)	1.75 [0.90, 3.38]	82%
Clinical pregnancy	3	220	ARD (Random, 95% CI)	32.0% [−12.1, 76.0]	93%
Clinical pregnancy	3	220	NNT (Random, 95% CI)	NA	NA
Miscarriage	3	119	RR (Random, 95% CI)	**0.45 [0.24, 0.82]**	26%
Miscarriage	3	119	ARD (Random, 95% CI)	**−31.3% [−48.2%, −14.5%]**	0%
Miscarriage	3	119	NNT (Random, 95% CI)	**3 [2, 7]**	NA

NA, not applicable; NA for effect size column means, NNT not calculated as difference not statistically significant; NA for I^2 column means, one trial only.
For RRs values of >1 are in favour of LT4 treatment; for SMDs and ARDs, values >0 are in favour of LT4 treatment.
95% CIs excluding the value of no effect (1 for RRs; 0 for differences) are printed bold.

Conclusions

- **LT4 treatment had no effect on clinical pregnancy (RR 1.75; 0.90–3.38)**
  - LT4 treatment resulted in a significantly higher delivery rate, with a pooled relative risk (RR) of 2.76 (95% confidence limits 1.20–6.44)
  - LT4 treatment significantly lowered miscarriage rate with a pooled RR of 0.45 (0.24–0.82)
- **! Patients with TAI**

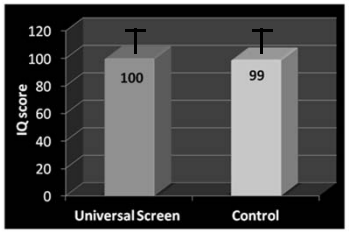
Antenatal Thyroid Screening and Childhood Cognitive Function

- **Screening group: serum TSH > 97.5th percentile and/or free T4 levels < 2.5th percentile in screening group**
- **Intervention: 150 µg LT4/day**
- **Primary outcome: IQ at 3 years of age in children of women**

Lazarus JH et al, NEJM 2012

Cognitive Development: CATS 2012

Primary endpoint: IQ score



The proportions of children with an IQ of less than 85 were 12.1% in the screening group and 14.1% in the control group (difference, 2.1 percentage points; 95% CI, −2.6 to 6.7; P = 0.39)

Courtesy of John Lazarus ITC 2010 Lazarus JH et al, NEJM 2012

Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy (Review)

Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E

THE COCHRANE COLLABORATION®

published in The Cochrane Library 2013, Issue 5

Authors' conclusions

This review found no difference between levothyroxine therapy and a control for treating pregnant euthyroid women with thyroid peroxidase antibodies for the outcome of pre-eclampsia, however a reduction in preterm birth and a trend towards reduced miscarriage with levothyroxine was shown. This review also showed no difference for pre-eclampsia or preterm birth when selenium was compared with placebo, however a promising reduction in postpartum thyroiditis was shown. Childhood neurodevelopmental delay was not assessed by any trial included in the review.

Given that this review is based on four trials of moderate risk of bias, with only two trials contributing data (n = 284), there is insufficient evidence to recommend the use of one intervention for clinical or subclinical hypothyroidism pre-pregnancy or during pregnancy over another, for improving maternal, fetal, neonatal and childhood outcomes.

I know …

THYROID
Volume 21, Number 10, 2011
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2011.0087

Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum

Alex Stagnaro-Green (Chair),[1] Marcos Abalovich,[2] Erik Alexander,[3] Fereidoun Azizi,[4] Jorge Mestman,[5] Roberto Negro,[6] Angelita Nixon,[7] Elizabeth N. Pearce,[8] Offie P. Soldin,[9] Scott Sullivan,[10] and Wilmar Wiersinga[11]

SPECIAL FEATURE
Clinical Practice Guideline

Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

Leslie De Groot, Marcos Abalovich, Erik K. Alexander, Nobuyuki Amino, Linda Barbour, Rhoda H. Cobin, Creswell J. Eastman, John H. Lazarus, Dominique Luton, Susan J. Mandel, Jorge Mestman, Joanne Rovet, and Scott Sullivan

— SCH

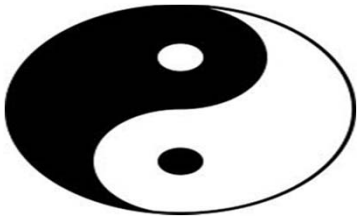
for SCH

for SCH

- **RECOMMENDATION 9**
  Women who are positive for TPOAb and have SCH should be treated with LT_4. **Level B-USPSTF**

  Dissent from one committee member: There is no consistent prospective evidence demonstrating that women who are TPOAb+, but who have SCH only, achieve maternal or perinatal benefit from LT_4 treatment. Correspondingly, there is no indication to treat women who are TPOAb+ and have SCH with LT_4.

Conclusions

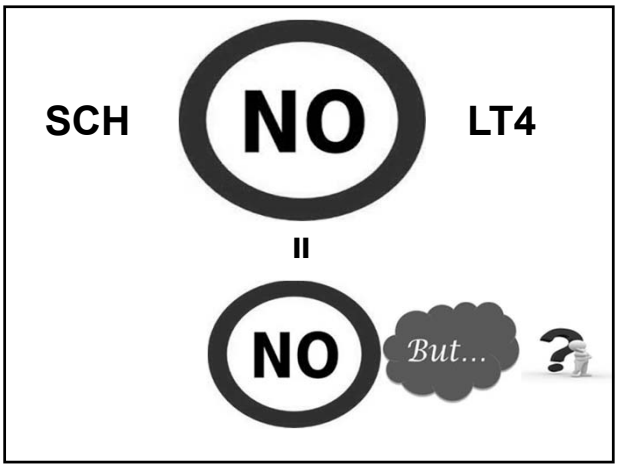


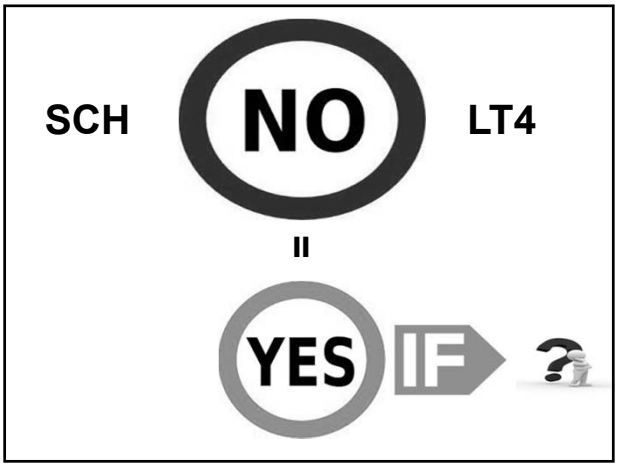
YING *(any yang)* ?

LT4 - SCH

SCH NO LT4

II





In my opinion, "yes if" will depend on

1. Trials in progress
- Thyroid Therapy for Mild Thyroid Deficiency in Pregnancy; *(NCT00388297)*
- TABLET study
- T4 live

2. Role of TAI ?!

3. Definition of SCH

3. The lecture of R. Peeters

Learning Objectives

1. There is a continuous interaction between thyroid hormones and gonadal function
2. SCH should be defined properly (there is NO impact of hCG before pregnancy…)
3. The presence of TAI is the most important cause of SCH and can be an independent predictor of pregnancy outcome
4. The lack of RCT's objects us to answer the Q whether LT4 should be given in case of SCH

Endocrinology
- B. Velkeniers; D. Unuane
- D. Glinoer (ULB)

Centre for Reproductive Medicine
- H. Tournaye; J. Schiettecatte, P. Haentjens

ESHRE Annual Meeting 2014
Pre Congress Course 11
Munich

Immunological and endocrine aspects of implantation

Thomas Strowitzki, Prof. Dr.
Dept. Gyn. Endocrinology and Reproductive Medicine,
University of Heidelberg
Medical Director

Disclosure

Lecturer for Bayer Health Care: Endometriosis

Research grant Merck Serono:
Endometrial stromal cell cultures

Learning Objectives

- Physiology of endometrial development and decidualization and its endocrine and molecular regulation resulting in endometrial receptivity
- Immunological aspects during the implantation process
- Physiology of implantation of the human embryo and its signaling network
- Translation of lessons that we have learned from basic science into clinical care

Important steps during implantation

- Endometrial development
- Decidualization
- Embryo competence
- Immune tolerance
- Cross talk between maternal and embryonic site
- Stromal cell migration and endometrial embryo selection (Weimar et al. 2013)

Impact of implantation failures

- Low conception rates
- High rate of early pregnancy loss
- Adverse effects during the course of pregnancy
- Preterm birth

But

No single biomarker identified up to now!

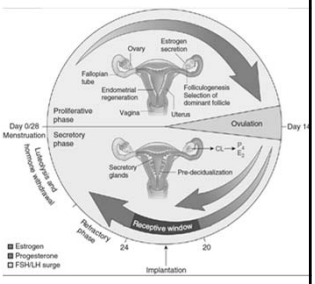
Endometrial Receptivity – Cellular Compartments

- Endometrial epithelium and glands
- Stromal cells
- Immuncompetent cells in the stroma (uterine NK cells, dendritic cells, T-cells)
- Endometrial endothelial cells

Cross talk between cellular compartments –
Signals transmitted from epithelium to stroma to induce decidualization

Uterine responses to ovarian hormones

- Proliferative phase
- Secretory phase: Progesterone – absolute requirement for implantation in all species
- Window of implantation (7-10 days after ovulation)



Cha et al. Nature Medicine (2012) 18: 1754-1767

Markers of decidualization

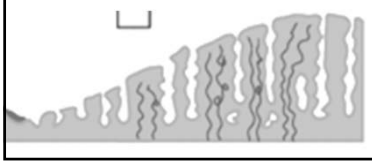
- Prolactin
- IGFBP-1
- Pinopodes

Progesterone – importance for implantation

- Genomic (by nuclear receptor PR-A and PR-B) and non-genomic actions (Halasz and Szekeres-Bartho 2013)
- Secretory transformation and decidualization
- Control of trophoblast invasion
- Suppression of epithelial E2 sensitivity
- Regulation of factors involved in implantation (Large and DeMayo, 2012)
- Anti-inflammatory response essential for postimplantation embryo support (Quenby and Brosens, 2013)

Some factors of decidualization

Indian Hedgehog IHH
Wnt and BMP2
GLUT
IGF/IGFBP-1
prostaglandins



cell morphology
Progesterone
SRC-1
prolactin
IL-6
Msx1
Kruppel like factor 5
MPIF-1
MIF
ERK-1
TIMP-3 secretion
HOXA10
COX2
SP1
amphiregulin
C/EBPß
FOXO1 expression
STAT-3

IHH Indian hedgehog

- Progesterone induced morphogen
- Located in the epithelium
- Downstream effectors expressed in the stromal compartment (for ex. COUP-TFII, Nr2f2)
- Transmitter of P4 action between cellular compartments

Bmp 2 (Bone morphogenetic Protein 2)

- Bmp 2 expressed in stroma near the implantation site
- Wnt4 downstream of Bmp2
- Failure of implantation in Bmp2 d/d mice
- Inhibition by dickkopf 1 reduces decidualization
- Bmp 2 attenuating siRNAs in human endometrial stromal cells prevent decidualization (Sonderegger et al. 2010)

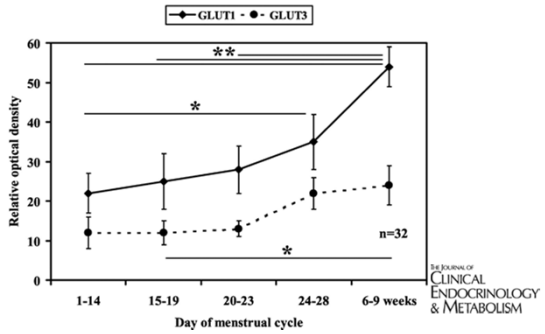
Wingless (Wnt4)

- Glycoprotein
- Functions in cell-cell communication, cell growth and differentiation
- Attenuation by siRNA in human stromal cells in vitro inhibits decidualization (Li et al. 2007)
- Mediating progesterone actions by reduced expression of Fkbp4, a co-chaperone of progesterone

Glucose transporters in human endometrium

- 7 GLUT known in the uterus (Frolova and Morley, 2011)
- GLUT 1 expressed in huiman decidua (Strowitzki et al. 2001)
- GLUT 1 upregulated in the luteal Phase (von Wolff et al. 2003)

Glucose transporters in human endometrium



Von Wolff et al. JCEM (2003) 88, 3885-3892

The uterine IGF system

- IGFBP-1 a decidual marker
- IGF-I localized in stromal cells
- IGF-I involved in decidualization
- IGF-I improves embryonic development in vitro (Yoshida et al. 1999)

The IGF system is active on both sides

Implantation – immuncompetent cells

- T cells, effector and regulated
- Dendritic cells
- Uterine NK cells
- Macrophages

Erlebacher A. Annu Rev Immunol 2013

Uterine NK cells

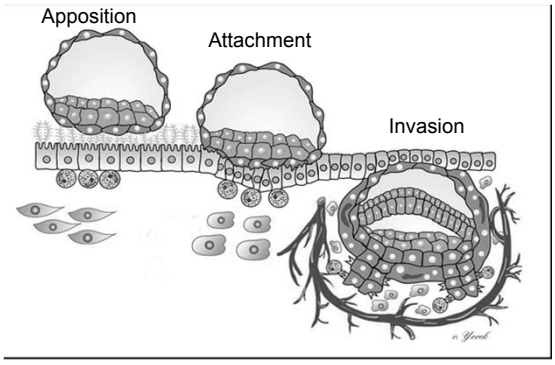
- Different from peripheral NK cells
- Interaction with trophoblast HLA-C via KIR
- Promote vascular changes at the fetomaternal interface
- Promote generation of Treg cells

Galectins

Galectin1:
- Expressed in decidua and trophoblast (Tirado-Gonzalez et al. 2013)
- Cycle dependent expression in stromal cells
- Upregulated by progesterone in stromal and decidual cells
- Modulates HLA-G expression on trophoblast
- Mediates the tolerogenic state of decidual and dendritic cells
- Pivotal regulator of fetomaternal tolerance (Fitzgerald et al. 2010)

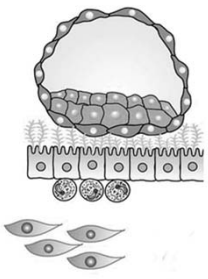
Galectin-7:
- Expressed in the luminal epithelium
- Upregulated in women with implantation failure

Die Einnistung



Die Apposition

Apposition

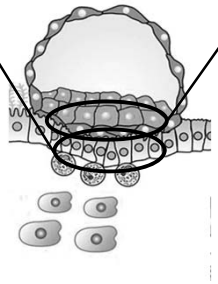


Embryo-maternal dialogue during the implantation role of hCG

- Supports the corpus luteum
- Direct influence on stromal and epithelial cells via IL-1 (Bourdiec et al. 2013)
- Facilitates implantation by decreasing TIMP-1 (Tapia-Pizarro et al. 2013)
- Stimulates osteopontin production in vitro (Racicot et al. 2013)
- Promotes LIF, VEGF, IGBBP-1, M-CSF and more

Attachment

HB-EGF
Osteopontin
LIF
GM-CSF
Activin A
Il-18
CD44



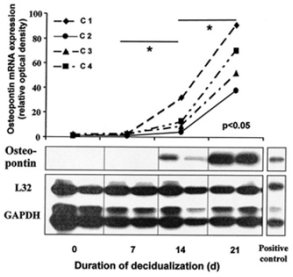
ErB4,
Integrins
Selectins
Cadherine
multiple IL-
Receptors

Galectin-9
Syndecan-1 and -4

Some factors also involved in embryo attachment

- Osteopontin (von Wolff et al. 2001, 2004)
- Integrins, in particular integrin $\alpha_v ß_3$ (Lessey et al. 1992)
- HB-EGF
- Syndecans (Germeyer et al. 2007)
- Galectin-9 (Popovici et al. 2005)

Embryo attachment - Osteopontin is up-regulated in human decidual stromal cells

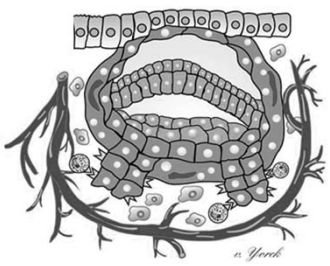


Von Wolff M et al. Fertil Steril (2004) 81: 741-748

Heparin Binding Epidermal Growth Factor HB-EGF

- Transmembrane and soluble form
- Located in the luminal epithelium
- Also produced by the blastocyst
- Regulation of implantation
- Promotes decidualization
- Regulated by progesterone and estrogens

Invasion



LIF – Leukemia Inhibiting Factor

- Of upmost importance in mouse implantation (Stewart et al. 1992)
- LIF antagonists (PEGLA) reduce human embryo attachment to decidual cells in vitro (Lalitkumar et al. 2013)
- Regulates invasiveness of trophoblast cells in vitro (Suman et al. 2013)
- Reduced in glandular epithelium in women with RIF
- But: Treatment with rec LIF doesn‘t increase pregnancy rates in IVF cycles (Brinsden et al. 2009)

Prostaglandins

- PGE2 and PGF2a abundant at the implantation site
- Important for increased vascular permeability (Vilella et al. 2013)
- COX 2 expression regulated by steroid hormones (St. Louis et al. 2010)
- Low COX 2 levels in patients with repeated implantation failure (Achache et al. 2010)

Translation from basic science into clinical practice

- Endometrial scratching
- Intralipid infusions (Fatemi und Popovic-Todorovic 2013)
- Quinolone (Yoshii et al. 2013)
- Seminal plasma (von Wolff et al. 2013)

Further possible options
- ASS
- Heparins
- Immunoglobulins
- Corticosteroids

Summary Implantation

- Very limited time of endometrial receptivity – WOI
- Dynamic process between decidua and embryo
- Decidualization of upmost importance and regulated by many endocrine and immune factors
- Control of selection of the embryo by decidua
- 3 steps of implantation
- Paucity of translation into clinical practice

Bibliography I

Achache H, Tsafrir A, Prus D, Reich R, Revel A. Defective endometrial prostaglandin synthesis identified in patients with repeated implantation failure undergoing in vitro fertilization. Fertil Steril. 2010;94:1271-1278

Arck PC, Hecher K. Fetomaternal immune cross-talk and ist consequences for maternal and offspring's health. Nature medicine. 2013;19: 548-556

Bourdiec A, Calvo E, Rao CV, Akoum A. Transcriptome analysis reveals new insights into the modulation of endometrial stromal cell receptive phenotype by embryo-derived signals interleukin-1 and human chorionic gonadotropin: possible involvement in early embryo implantation. PLoS One. 2013;8:e64829

Brinsden PR, Alam V, de Moustier B, Engrand P. Recombinant human leukemia inhibitory factor does not improve implantation and pregnancy outcomes after assisted reproductive techniques in women with recurrent unexplained implantation failure. Fertil Steril. 2009;91(4 Suppl):1445-1447

Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. Nature medicine. 2012 ;18: 1754-1767

Erlebacher A. Immunology of the maternal-fetal interface. Annu Rev Immunol. 2013;31:387-411.

Fatemi HM, Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. Reprod Biomed Online. 2013;27:530-538

Fitzgerald JS, Germeyer A, Huppertz B, Jeschke U, Knöfler M, Moser G, Scholz C, Sonderegger S, Toth B, Markert UR. Governing the invasive trophoblast: current aspects on intra- and extracellular regulation. Am J Reprod Immunol. 2010;63: 492-505

Frolova AI, Morley KH. Glucose transporters in the uterus: an analysis of tissue distribution and proposed physiological roles. Reproduction. 2011;142: 211-220

Genbacev OD, Prakobphol A, Foulk RA, Krtolica AR, Ilic D, Singer MS, Yang ZQ, Kiessling LL, Rosen SD, Fisher SJ. Trophoblast L-selectin-mediated adhesion at the maternal-fetal interface. Science. 2003;299:405-408

Germeyer A, Klinkert MS, Huppertz AG, Clausmeyer S, Popovici RM, Strowitzki T, von Wolff M. Expression of syndecans, cell-cell interaction regulating heparan sulfate proteoglycans, within the human endometrium and their regulation throughout the menstrual cycle. Fertil Steril. 2007;87:657-663

Bibliography II

Halasz M, Szekeres-Bartho J. The role of progesterone in implantation and trophoblast invasion. J Reprod Immunol. 2013;97:43-45

Lalitkumar S, Boggavarapu NR, Menezes J, Dimitriadis E, Zhang JG, Nicola NA, Gemzell-Danielsson K, Lalitkumar LP. Polyethylene glycated leukemia inhibitory factor antagonist inhibits human blastocyst implantation and triggers apoptosis by down-regulating embryonic AKT. Fertil Steril. 2013;100:1160-1169

Large MJ, DeMayo FJ. The regulation of embryo implantation and endometrial decidualization by progesterone receptor signaling. Mol Cell Endocrinol. 2012;358:155-165

Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, Buck CA. Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. J Clin Invest. 1992;90:188-195

Nikas G. Endometrial receptivity: changes in cell-surface morphology. Semin Reprod Med. 2000;18:229-235

Popovici RM, Krause MS, Germeyer A, Strowitzki T, von Wolff M. Galectin-9: a new endometrial epithelial marker for the mid- and late-secretory and decidual phases in humans. J Clin Endocrinol Metab. 2005;90:6170-6176

Quenby S, Brosens JJ. Human implantation: a tale of mutual maternal and fetal attraction. Biol Reprod. 2013;88:81

Racicot KE, Wünsche V, Auerbach B, Aldo P, Silasi M, Mor G. Human Chorionic Gonadotropin Enhances Trophoblast-Epithelial Interaction in an In Vitro Model of Human Implantation. Reprod Sci. 2014 Feb 11. [Epub ahead of print]

Sonderegger S, Pollheimer J, Knöfler M. Wnt signalling in implantation, decidualisation and placental differentiation--review. Placenta. 2010;31:839-847

Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I, Köntgen F, Abbondanzo SJ. Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. Nature. 1992;359(6390):76-79

St-Louis I, Singh M, Brasseur K, Leblanc V, Parent S, Asselin E. Expression of COX-1 and COX-2 in the endometrium of cyclic, pregnant and in a model of pseudopregnant rats and their regulation by sex steroids. Reprod Biol Endocrinol. 2010;8:103

Strowitzki T, Capp E, von Wolff M, Müller-Höcker J. Expression of glucose transporter 1 in human endometrial and decidual tissue. Gynecol Endocrinol. 2001;15:219-224

Bibliography III

Suman P, Shembekar N, Gupta SK. Leukemia inhibitory factor increases the invasiveness of trophoblastic cells through integrated increase in the expression of adhesion molecules and pappalysin 1 with a concomitant decrease in the expression of tissue inhibitor of matrix metalloproteinases. Fertil Steril. 2013 ;99:533-542

Tapia-Pizarro A, Argandoña F, Palomino WA, Devoto L. Human chorionic gonadotropin (hCG) modulation of TIMP1 secretion by human endometrial stromal cells facilitates extravillous trophoblast invasion in vitro. Hum Reprod. 2013; 28:2215-2227

Tirado-González I, Freitag N, Barrientos G, Shaikly V, Nagaeva O, Strand M, Kjellberg L, Klapp BF, Mincheva-Nilsson L, Cohen M, Blois SM. Galectin-1 influences trophoblast immune evasion and emerges as a predictive factor for the outcome of pregnancy. Mol Hum Reprod. 2013;19:43-53

von Wolff M, Strowitzki T, Becker V, Zepf C, Tabibzadeh S, Thaler CJ. Endometrial osteopontin, a ligand of beta3-integrin, is maximally expressed around the time of the "implantation window". Fertil Steril. 2001;76:775-781

von Wolff M, Bohlmann MK, Fiedler C, Ursel S, Strowitzki T. Osteopontin is up-regulated in human decidual stromal cells. Fertil Steril. 2004;81 Suppl 1:741-748

von Wolff M, Rösner S, Germeyer A, Jauckus J, Griesinger G, Strowitzki T. Intrauterine instillation of diluted seminal plasma at oocyte pick-up does not increase the IVF pregnancy rate: a double-blind, placebo controlled, randomized study. Hum Reprod. 2013;28:3247-3252

Vilella F, Ramirez L, Berlanga O, Martínez S, Alamá P, Meseguer M, Pellicer A, Simón C. PGE2 and PGF2α concentrations in human endometrial fluid as biomarkers for embryonic implantation. J Clin Endocrinol Metab. 2013 Oct;98(10):4123-4132

Weimar CH, Macklon NS, Post Uiterweer ED, Brosens JJ, Gellersen B. The motile and invasive capacity of human endometrial stromal cells: implications for normal and impaired reproductive function. Hum Reprod Update. 2013;19:542-557

Yoshii N, Hamatani T, Inagaki N, Hosaka T, Inoue O, Yamada M, Machiya R, Yoshimura Y, Odawara Y. Successful implantation after reducing matrix metalloproteinase activity in the uterine cavity. Reprod Biol Endocrinol. 2013;11:37

Some reviews, which might be useful I

Koot and Macklon Embryo implantation: biology, evaluation, and enhancement. Curr Opin Obstet Gynecol (2013) 25: 274-279

Barrientos G, Freitag N, Tirado-Gonzalez I, Unverdorben L, Jeschke U, Thijssen VLJL, Blois SM. Involvement of galectin-l in reproduction: past, present and future. Hum Reprod update (2014) 20: 175-193

Akhtar MA, Sur S, Raine-Fenning N, Jayaprakasan K, Thornton JG, Quenby S. Heparin for assisted reproduction. Cochrane Database Syst Rev. 2013 Aug 17;8:CD009452.

Singh M, Chaudry P, Asselin E. Bridging endometrial receptivity and implantation: Network of hormones, cytokines, and growth factors. J Endocrinol (2011) 210: 5-14

Potdar N, Gelbaya T, Nardo LG. Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis. Reprod Biomed Online (2012) 25: 561-571

Strowitzki T, Germeyer A, Popovici R, von Wolff M. The human endometrium as a fertility-determining factor. Hum Reprod Update (2006)12, 617–630

Some reviews, which might be useful II

Toth B, Jeschke U, Rogenhofer N, Scholz C, Wurfel W, Thaler CJ, Makrigiannakis A, Recurrent miscarriage: current concepts in diagnosis and treatment. J Reprod Immunol (2010)

Vitiello D, Patrizio P. Implantation and early embryonic development: Implications for pregnancy. Semin Perinatol (2007) 31: 204-207

Lessey B. Assessment of endometrial receptivity. Fertil Steril (2013) 96: 522-529

Hannan NJ, Salamonsen LA. Role of chemokines in the endometrium and in embryo implantation. Curr Opin Obstet Gynecol (2007) 19: 266-272

Toth B, Würfel W, Germeyer A, Hirv K, Makrigiannakis A, Strowitzki T. Disorders of implantation – are there diagnostic and therapeutic options. J Reprod Immunol (2011) 90: 117-123

Cheong Y, Boomsma C, Heijnen C, Macklon N. Uterine secretomics: a window on the maternal-embryo interface. Fertil Steril (2013) 99: 1093-1099

The endocrinology of the pregnancy

C.B. Lambalk

VU University Medical Center
Amsterdam, The Netherlands

European Society of Human Reproduction and Embryology Munchen, Germany June 29, Pre congress course The contribution of endocrinology & early pregnancy mangement to the success of an ART Centre

1

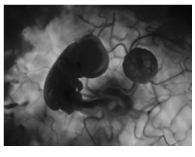
"Endocrinology of pregnancy"

- Endocrinology of Normal Pregnancy
- Endocrinology of Implantation
- Endocrinology of Early Pregnancy Loss
- Endocrinology of Ectopic Pregnancy
- Endocrinology of Preterm Labour

Introduction

'Fetal origin of development in later life'

'The womb may be more important than the home'



3

The reproductive endocrinology of the (PCOS & Twin) pregnancy

C.B. Lambalk

VU University Medical Center
Amsterdam, The Netherlands

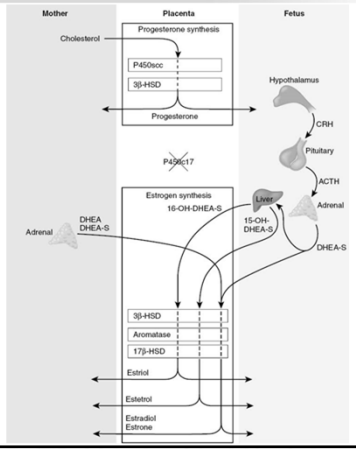
European Society of Human Reproduction and Embryology Munchen, Germany June 29, Pre congress course The contribution of endocrinology & early pregnancy mangement to the success of an ART Centre

4

Outline

- Introduction
- Background
- Polycystic ovarian syndrome and endocrinology of pregnancy
- The endocrinology of the twin pregnancy
- Conclusions

5



Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings

Celina C.C. Cohen-Bendahan[a,1], Cornelieke van de Beek[a,b,1], Sheri A. Berenbaum[c,*]

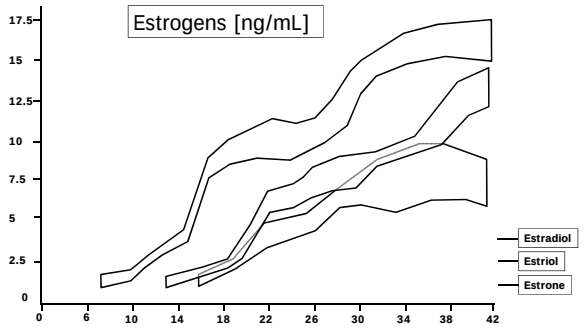
[a]Department of Child and Adolescent Psychiatry, and Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands
[b]Department of Special Education, Free University of Amsterdam, The Netherlands
[c]Departments of Psychology and Pediatrics, The Pennsylvania State University, University Park, PA, USA

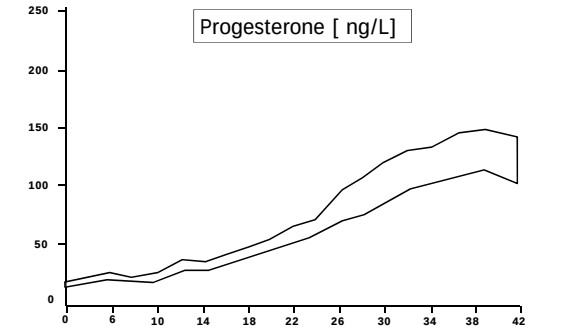
Received 5 August 2004; revised 21 October 2004; accepted 5 November 2004

Abstract

There is now good evidence that human sex-typed behavior is influenced by sex hormones that are present during prenatal development, confirming studies in other mammalian species. Most of the evidence comes from clinical populations, in which prenatal hormone exposure is atypical for a person's sex, but there is increasing evidence from the normal population for the importance of prenatal hormones. In this paper, we briefly review the evidence, focusing attention on the methods used to study behavioral effects of prenatal hormones. We discuss the promises and pitfalls of various types of studies, including those using clinical populations (concentrating on those most commonly studied, congenital adrenal hyperplasia, androgen insensitivity syndrome, ablatio penis, and cloacal exstrophy), direct measures of hormones in the general population and indirect measures of hormones in the general population (inferred from intrauterine position and biomarkers such as otoacoustic emissions, finger length ratios, and dermatoglyphic asymmetries). We conclude with suggestions for interpreting and conducting studies of the behavioral effects of prenatal hormones.

Cohen-Bendahan et al Neurosc Biobehav Rev 2005





Sex differences in prenatal hormone levels

Hormones (nmol/l)	Male			Female			*p*
	M	*SD*	*n*	*M*	*SD*	*n*	
Maternal serum							
Testosterone	6.78	3.91	56	7.15	3.81	56	ns
Estradiol	21.94	8.58	56	21.95	8.53	56	ns
Progesterone	176.36	49.90	56	173.71	54.06	56	ns
Amniotic fluid							
Testosterone	1.41	.36	61	.68	.28	61	<.001
Estradiol	.88	.26	61	1.01	.36	59	<.05
Progesterone	275.74	89.89	61	286.48	111.06	61	ns

Van de Beek et al Arch Sex Behav 2009

10

Reproductive hormone concentrations in pregnancy and neonates: a systematic review

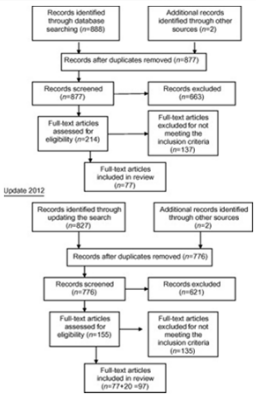
EAM Kuijper [a,*], JCF Ket [b], MR Caanen [a], CB Lambalk [a]

[a] Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, VU University Medical Center (VUmc), 1007 MB Amsterdam, The Netherlands; [b] VU Amsterdam University Library, Medical Library, Amsterdam, The Netherlands
* Corresponding author. E-mail address: e.kuijper@vumc.nl (EAM Kuijper).

Esther AM Kuijper was born 6 February 1977 in Alkmaar, The Netherlands. She studied medicine at the VU University Medical Center in Amsterdam She is a PhD student working on a thesis entitled 'Comparison of perinatal reproductive hormone status between familial dizygotic twins, non-familial dizygotic twins, monozygotic twins, singletons and their mothers'. Her current research interests are twins and endocrinology.

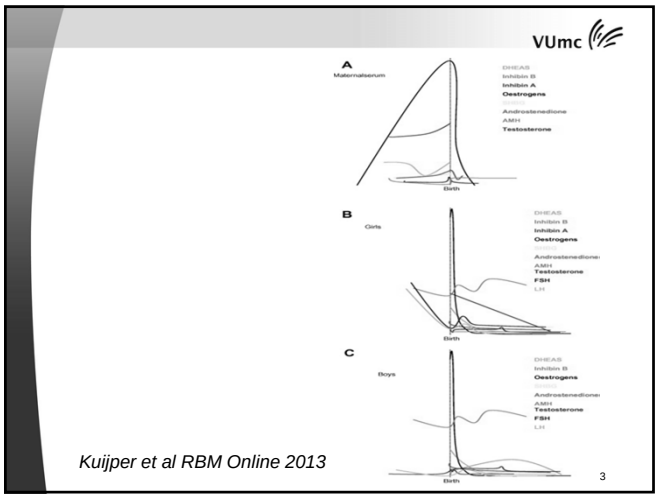
Kuijper et al RBM Online 2013

11



Kuijper et al RBM Online 2013

12



Cord blood hormones and human development

Study	Number of participants	Age of participants	Measures			Findings
			Hormones	Assay technique	Outcome measure	
Jacklin et al. (64)	84 males; 78 females	6, 9, 12, and 18 months	Androstenedione; testosterone; estrone; estradiol; progesterone	RIA	Timidity	**Males:** significant negative relationship with testosterone and progesterone, positive relationship with estradiol **Females:** no significant relationship
Jacklin et al. (65)	127 children;	Birth, 3, 6, 9, 12, 18, and 33 months	Androstenedione; testosterone; estrone; estradiol; progesterone	RIA	Muscular strength	**Males:** significant negative relationship with androstenedione, significant positive relationship with progesterone **Females:** significant negative relationship with androstenedione and progesterone
Jacklin et al. (66)	53 males; 43 females	6 years	Androstenedione; testosterone; estrone; estradiol; progesterone	RIA	Reading; Numeracy; Listening; Spatial ability	**Males:** no significant relationship **Females:** significant inverse relationship between testosterone and androstenedione and spatial ability
Hollier et al. (67)	224 males; 199 females	2 years	Testosterone	LC–MS	Vocabulary	**Males:** significant inverse relationship **Females:** no significant relationship
Whitehouse et al. (68)	372 males; 395 females	1–3 years	Testosterone	LC–MS	Language delay	**Males:** significant inverse relationship **Females:** no significant relationship
Farrant et al. (69)	235 males; 232 females	1 and 3 years	Testosterone	LC–MS	Socio-emotional engagement; Vocabulary;	**Males:** no significant relationship after control for covariates **Females:** no significant relationship
Whitehouse et al. (70)	184 males; 190 females	19–20 years	Testosterone	LC–MS	Autism Quotient	**Males:** no significant relationship **Females:** no significant relationship
Robinson et al. (71)	429 males; 430 females	2, 5, 8, and 10 years	Testosterone	LC–MS	Child Behavior Checklist	**Males:** negative relationship between testosterone and attention problems at ages 5, 8, and 10 years **Females:** negative association between testosterone and withdrawal symptoms at age 5

Hollier et al Front Endocrinol 2014

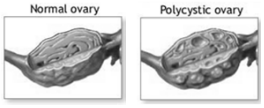
14

PCOS

Polycystic ovary syndrome (PCOS)

Criteria*:

- oligo- or anovulation
- clinical and/or biochemical signs of hyperandrogenism
- polycystic ovaries on ultrasound



**2003 Rotterdam PCOS consensus*

15

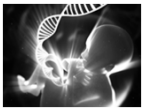
PCOS

Androgens in girls with PCOS mothers

Does prenatal exposure to androgens cause PCOS?

Origin of androgens in PCOS women:

- Maternal origin → placental passage during gestation
- Fetal origin → inherited trait which apparent during/after puberty



16

PCOS

Insights into the Development of Polycystic Ovary Syndrome (PCOS) from Studies of Prenatally Androgenized Female Rhesus Monkeys

Abbott et al, 1998. Trends Endocrinol Metab 9:62-67

Hyperandrogenism and Hyperinsulinism in Children of Women with Polycystic Ovary Syndrome: A Controlled Study

Kent et al, 2008. J Clin Endocrinol Metab 93:1662–1669

Male twins reduce fitness of female co-twins in humans

Lummaa et al, 2007. Proc Natl Acad Sci USA 104:10915-10920

17

PCOS

However,

Males Do Not Reduce the Fitness of Their Female Co-Twins in Contemporary Samples

Medland et al, 2008. Twin Res Hum Genet 11:481-487

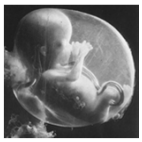
Prevalence of Polycystic Ovary Syndrome in Women from Opposite-Sex Twin Pairs

Kuijper et al, 2009. J Clin Endocrinol Metab, 94:1987-1990

18

Aim of our study:

Compare androgen (and estrogen) levels during gestation and in umbilical cord blood from children born from PCOS mothers and controls



Caanen et al submitted

19

Methods

Subjects

-Prospective, large cohort study, 523 mothers

-Hormones throughout pregnancy

-Natural pregnancy – assisted reproduction

Caanen et al submitted

20

Methods

Subjects

Cases: PCOS defined by Rotterdam criteria (N=20)

Controls (N=83):

- regular cycle (<35 days)
- no acne or hirsutism
- natural conception

Inclusion:
- age > 18
- singleton pregnancies

Exclusion:
- multiple gestations
- delivery < 32 weeks
- assisted reproduction

Caanen et al submitted

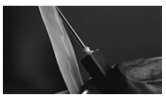
21

Methods

Time points

Maternal blood samples:
- 20 weeks of gestation
- delivery

Neonatal blood samples:
- cord blood



Hormones measured*

Estrogens:
- estrone (E1)
- estradiol (E2)
- estriol (E3)

Androgens:
- testosterone (T)
- androstenedione (ADION)
- dehydroepiandrosterone sulfate (DHEAS)

**using LCMS technology (Salt Lake City)*

Caanen et al submitted

22

Results

Baseline characteristics

	PCOS N=20 Mean (SD) or %	**non-PCOS** N=83 Mean (SD) or %	**P-value**
Age	32.0 (4.0)	33.8 (3.9)	0.061
Cycle duration (days)	140.1 (32.8)	27.7 (2.9)	0.002
BMI 20 week GA	24.2 (3.6)	25.1 (4.0)	0.375
Menarche (age)	13.3 (2.0)	13.3 (1.6)	0.911
Trying to become pregnant (months)	8.3 (9.0)	7 (13.0)	0.698
Mode of conception			0.000
Spontaneous	25%	100%	
Ovulation Induction	55%	0	
IVF	5%	0	
ICSI	15%	0	
Neonatal sex			0.090
Girl	70%	45.8%	
Boy	30%	54.2%	
Mode of delivery			0.668
Natural	70%	62.7%	
VE	5%	13.3%	
Prim SC	5%	12%	
Sec SC	20%	12%	
Smoking			0.325
Yes	45%	61%	
No	55%	39%	

Caanen et al submitted

23

Results

Regression analyses

Maternal serum levels (means) - **20 weeks**

	Girls			***Boys***		
	PCOS	Non-PCOS	P-value	PCOS	Non-PCOS	P-value
ADION (ng/ml)	**2.13**	**1.08**	**0.034**	2.60	1.24	0.084
T (ng/ml)	**1.04**	**0.507**	**0.019**	1.15	0.56	0.113
DHEAS (ng/ml)	3.12	2.76	0.788	4.18	2.58	0.654
E1 (pg/ml)	3889.3	4469.4	0.928	5433.3	3128.7	0.061
E2 (pg/ml)	6441.4	6942.2	0.559	7250.0	6074.4	0.300
E3 (pg/ml)	2213.6	2106.2	0.815	2345.0	1972.9	0.139

PCOS mothers pregnant with a girl: significantly higher ADION and T levels

Caanen et al submitted

24

Results

Regression analyses

Maternal serum levels (means) - **delivery**

	Girls			***Boys***		
	PCOS	Non-PCOS	P-value	PCOS	Non-PCOS	P-value
ADION (ng/ml)	**4.22**	**1.62**	**0.009**	4.48	2.04	0.537
T (ng/ml)	**2.79**	**0.91**	**0.004**	2.57	1.1	0.675
DHEAS (ng/ml)	9.11	6.85	0.360	5.16	6.09	0.940
E1 (pg/ml)	9786.7	8845.3	0.690	13625	7454.5	0.015
E2 (pg/ml)	8184.8	9882.3	0.979	13850	9460.0	0.208
E3 (pg/ml)	2342.3	4392.9	0.461	19922.3	7843.4	0.341

PCOS mothers pregnant with a girl: significantly higher ADION and T levels

Caanen et al submitted

25

Results

Regression analyses

Cord blood (means)

	Girls			*Boys*		
	PCOS	Non-PCOS	P-value	PCOS	Non-PCOS	P-value
ADION (ng/ml)	0.45	0.84	0.094	0.49	0.54	0.834
T (ng/ml)	0.12	0.15	0.959	0.178	0.20	0.676
DHEAS (ng/ml)	4.9	5.65	0.577	2.98	2.90	0.162
E1 (pg/ml)	**10511.1**	**22025.7**	**0.007**	14734.5	21123.9	0.718
E2 (ng/ml)	5426.1	8919.2	0.052	9601.5	9196.4	0.520
E3 (ng/ml)	57412.1	52729.2	0.836	51568	55135.1	0.378

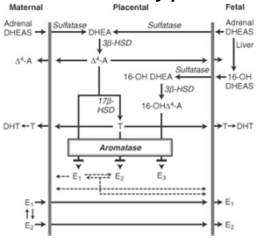
Girls from PCOS mothers: no elevated androgens

Caanen et al submitted

26

Conclusions

- **There are no indications of increased fetal androgen levels of PCOS mothers in their offspring, despite consequently elevated levels throughout the pregnancy**
- **Apparently placental aromatase sufficiently protects**



Caanen et al submitted

27

Conclusions (2)

- **There is a significant reduction of E1 levels - E2 and ADION tend to be reduced, only in the girls**
- **These gender specific differences may suggest a fetal gonadal origin of altered sex-steriodogenesis**
- **It remains to be determined if this altered setting is intrinsic to the female fetus of a PCOS mother, or of maternal origin**

Caanen et al submitted

28

Articles

Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology

A J Swerdlow, B L De Stavola, M A Swanwick, N E S Maconochie

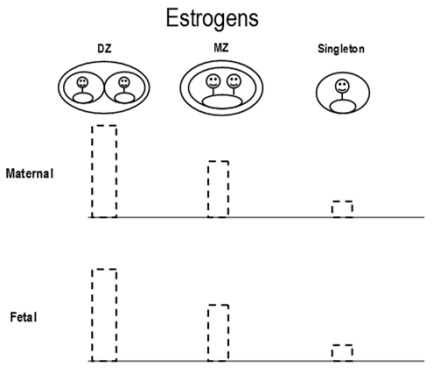
Findings We identified 500 twins with breast cancer and 194 with testicular cancer. We found a non-significantly raised risk of breast cancer in dizygotic compared with monozygotic twins younger than 30 years (odds ratio 2·3 [95% CI 0·9–5·9]) but not older. The overall risk of testicular cancer was significantly higher in dizygotic twins than in monozygotic twins (1·5 [1·1–2·2]) consequent on a risk for seminomas was high (3·2 [1·6–6·5]; p=0·001).

Interpretation The higher risks of these cancers in dizygotic than in monozygotic twins support a prenatal aetiology, and are compatible with aetiology related to raised maternal concentrations of free, unbound oestrogens. The results for twins of probands have implications for genetic aetiology; appropriate clinical action for monozygotic twins needs consideration.

Lancet 1997; **350:** 1723–28

29

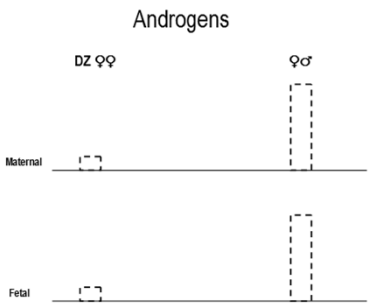
Endocrine assumptions in twins



Kuijper et al 2014 submitted

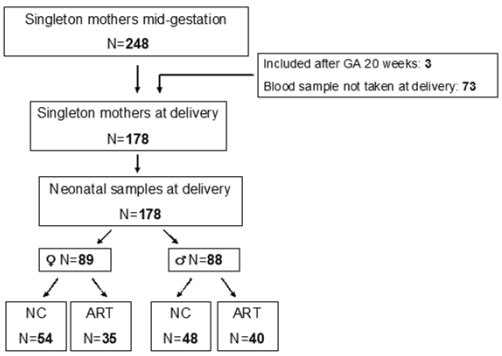
30

Endocrine assumptions; opposite sex twin girls



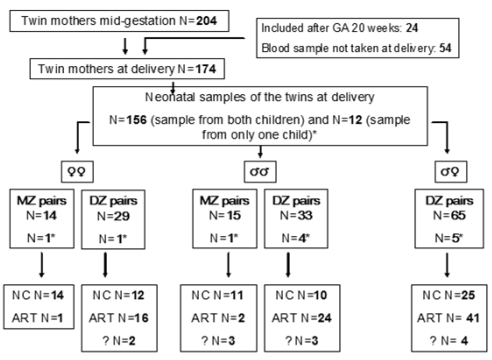
Kuijper et al 2014 submitted

31



Kuijper et al 2014 submitted

32



Kuijper et al 2014 submitted

33

Baseline characteristics children

Neonatal characteristics at birth (mean (± SD) or %))	
Zygosity	
Singleton	51.4 %
MZ twin	9.0 %
DZ twin	39.6 %
Gestational age	
Singleton	39.6 (1.8)
MZ twin	36.9 (1.7)
DZ twin	37.0 (1.6)
Birth weight	
Singleton	3424.0 (638.2)
MZ twin	
First twin child	2635.4 (435.5)
Second twin child	2540.7 (469.9)
DZ twin	
First twin child	2662.5 (420.2)
Second twin child	2597.0 (501.3)
Natural delivery	
Singleton	48.6 %
MZ twin	25.6 %
DZ twin	25.5 %

Kuijper et al 2014 submitted

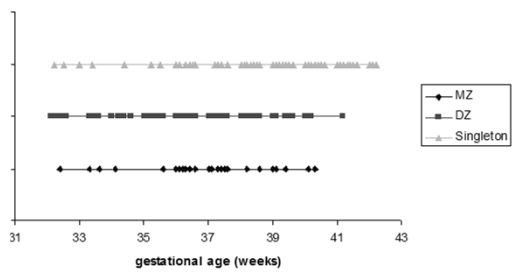
34

Baseline characteristics mothers

	All	Singletons	MZ twins	DZ twins
Age	33.6 (4.1)	33.9 (4.1)	32.2 (4.6)	33.4 (3.8)
Parity				
0	53.6 %	52.1 %	56.1 %	55.0 %
1	34.0 %	34.2 %	26.8 %	35.5 %
> 2	12.4 %	13.7 %	17.1 %	19.5 %
Ethnicity				
Caucasian	86.8 %	84.8 %	95.0%	87.5 %
Asian	1.8 %	2.2 %		1.8 %
Hindustani	0.9 %	1.3 %		0.6 %
Mediterranean	5.5 %	5.6 %	5.0%	5.4 %
Creole	3.9 %	4.8 %		3.6 %
Other	1.1 %	1.3 %		1.1 %
BMI	25.5 (4.2)	25.0 (4.3)	26.2 (3.4)	25.9 (4.3)
Smoking				
Never smoked	41.7 %	41.8 %	41.9 %	41.5 %
Ever smoked	58.3 %	58.2%	58.1 %	58.5 %
1 year before pregnancy				
No	69.3 %	70.9 %	65.1 %	68.1 %
Yes	30.7 %	29.1 %	34.9 %	31.9 %
During pregnancy				
No	84.6 %	86.9 %	79.1 %	83.0 %
Yes	15.4 %	13.1 %	20.9 %	17.0 %

Kuijper et al 2014 submitted

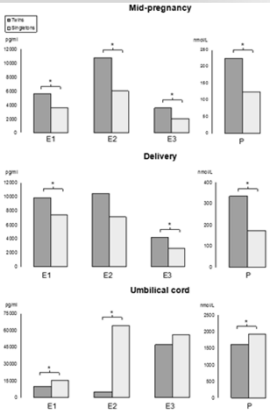
35



Kuijper et al 2014 submitted

36

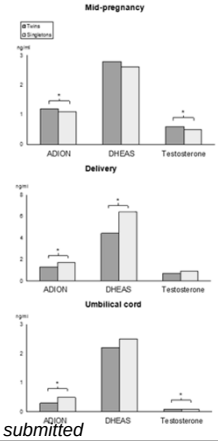
Estrogens & Progesterone



Kuijper et al 2014 submitted

37

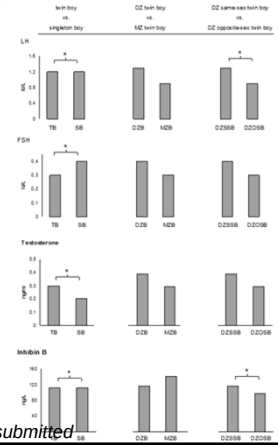
Androgens



Kuijper et al 2014 submitted

38

Same sex twin boys vs opposite sex twin boys



Kuijper et al 2014 submitted

39

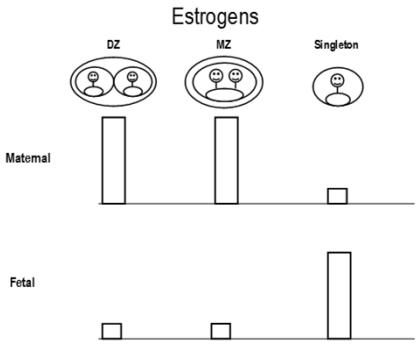
MZ versus DZ

- Overall no differences
- No differences between MZ boys and DZ boys
- DZ girls versus MZ girls
  - Higher Estriol
  - Lower FSH

Kuijper et al 2014 submitted

40

Endocrine facts in twins

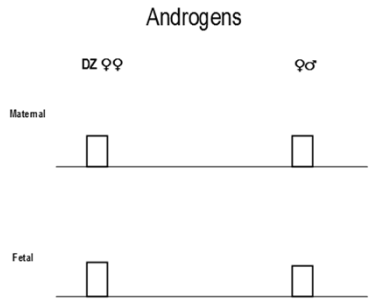


Kuijper et al 2014 submitted

41

Same sex twin girls vs opposite sex twin girls

No indications for androgen over exposure



Kuijper et al 2014 submitted

42

Conclusions (3)

- **Estrogen and progesterone concentrations are higher in mothers of twins compared to singletons**
- **In contrast to what is generally assumed opposite-sex twin babies are not overexposed to sex steroid hormones at birth**
- **In opposite-sex twins we found no distinct androgenic effects of boys on their female co-twin**
- **DZ girls experience a higher estrogenic milieu compared to MZ girls**
- **The hypothalamic-pituitary-gonadal axis in male newborns with a female co-twin is partially suppressed since these boys have lower LH and inhibin B levels compared to same sex dizygotic twin boys**

43

Genetic Aspects of Early Pregnancy Success

Priv. Doz. Dr. med. Tina Buchholz

Gyn-Gen-Lehel MVZ
Institut für Humangenetik, TUM, München

Learning Objectives

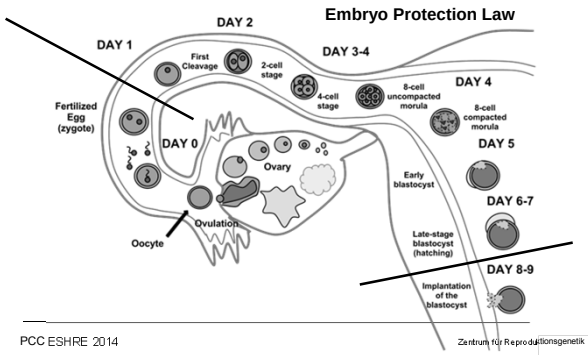
Early pregnancy success depends:

Genetic and chromosomal constitution of the embryo
- Pedigree
- Maternal age

Environmental factors -
As early as zygote, blastocyst, implantation embryo
- Endocrine function
- Implantation and placentation function

No conflict of interest

Human Embryonic Development



Genetic counselling

Personal and familiy history and pedigree
Clinical examination, dysmorphological examination
Background of genetic diseases

Diagnostic options
cytogenetic, biochemical oder molecular genetic diagnostics

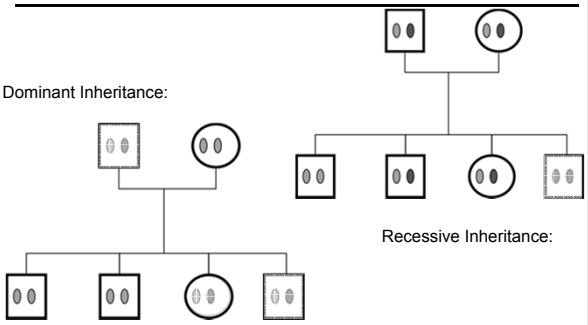
Counselling and/or examination of further family members
Interdisciplinary counselling

Individual risk estimation, recurrence risk
Basic risk 2 - 5 %

Therapeutic options
Information – non-directive counselling

Monogenetic Disorders

Dominant Inheritance:



Recessive Inheritance:

Recessive - Dominant

• gene dosage effect

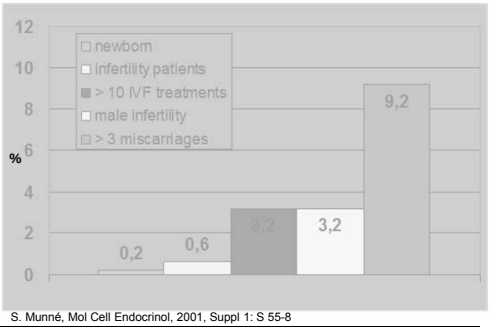
• 2 copies (allels) or 1 allel sufficient for gene product functioning
Vice versa
1 allel missing or impaired already disease causing
or both allels missing or impaired needed

• for metabolic disorders 1 allel mostly enough
(perhaps only 50% enzyme activity)

• for structural defects 1 disfunctioning allel
leads to structural abnormalities

recessive genes – enzyme proteins
dominant genes – structural proteins

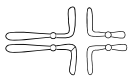
Prevalence of translocations



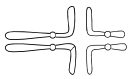
S. Munné, Mol Cell Endocrinol, 2001, Suppl 1: S 55-8

Segregation

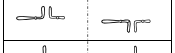
- In translocation carriers during meiosis I segregation forms
  - regular homologue chromosomal pairing
  - quadrivalents (in reciprocal translocation) or trivalents (in Robertsonian translocation)



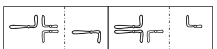
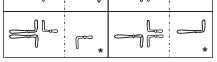
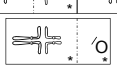
Segregation Pattern



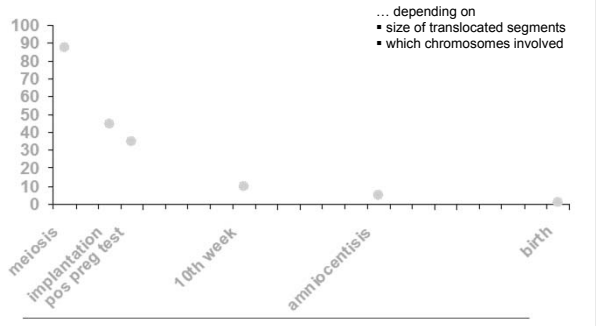
2:2

alternate		balanced
adjacent 1		unbalanced (translocated seg. small)
adjacent 2		unbalanced (centric seg. small)

3:1 (quadrivalent asymetrical)

tertiary trisomy/ monosomy		unbalanced
interchange trisomy/ monosomy		unbalanced
4:0	 * not viable	unbalanced

Theoretical Rate of Unbalanced Constitutions



Learning Objectives

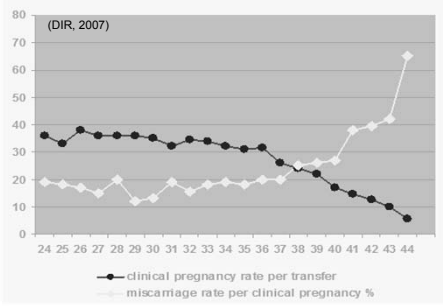
Early pregnancy success depends:

Genetic and chromosomal constitution of the embryo
- Pedigree
- Maternal age

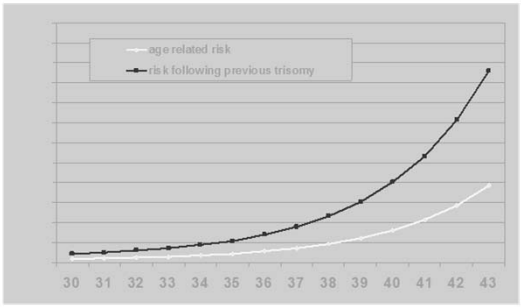
Environmental factors -
As early as zygote, blastocyst, implantation embryo
- Endocrine function
- Implantation and placentation function

No conflict of interest

Pregnancy Rates



Risk of Aneuploidies
following previous trisomy



Genetic counselling – reproductive genetics

Prior to infertility treatment

Elevated risk for chromosomal abnormalities
According to pedigree associated with monogenetic disorders

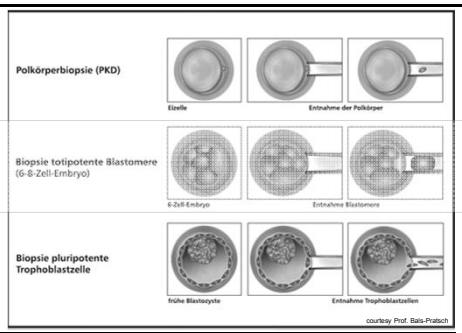
Diagnostics

Genetic counselling prior to preimplantation genetic diagnosis

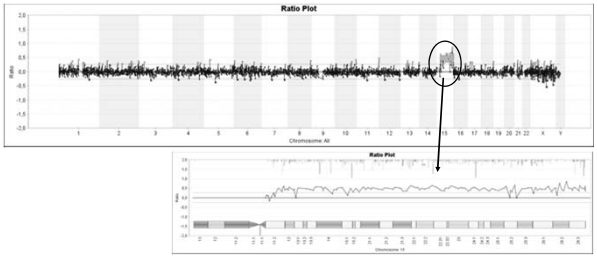
Known translocation
Known monogenetic disorder, known mutation - carrier

Therapy

Preimplantation Genetic Diagnosis - PGD



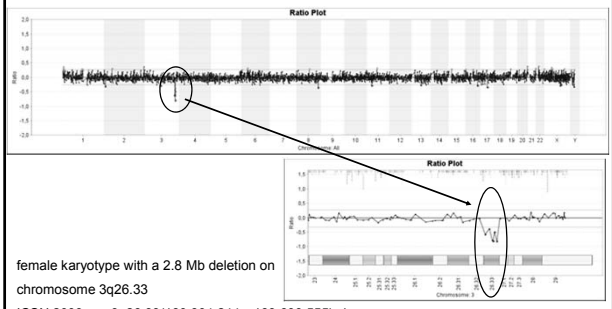
ArrayCGH Results shown as Ratio Plots



Male karyotype with a trisomy 15

ISCN 2009: arr 15q11.2q26.3(21,414,203->100,564,651)x3

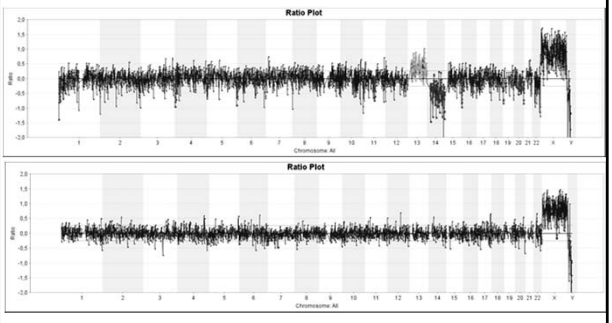
ArrayCGH Results shown as Ratio Plots



female karyotype with a 2.8 Mb deletion on chromosome 3q26.33

ICSN 2009: arr 3q26.33(180,804,244→183,600,555)x1

ArrayCGH – results



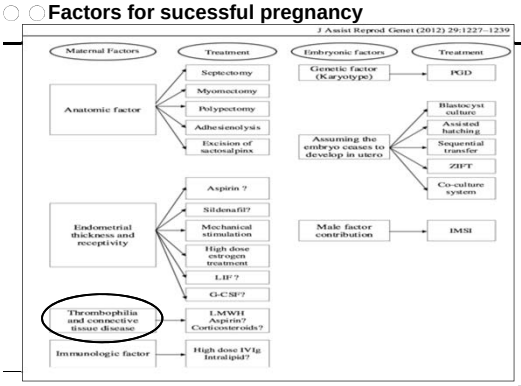
Postimplantation – Prenatal Testing

prenatal diagnostic (PND)

Non invasiv PND	**Molecular non invasiv PND**	Invasive PND
• sonographic • biochemical	• **Massive parallel sequenzing of cffDNA from maternal plasma**	• CVS • AC
+ no risk + indirect testing	+ **no risk** + **direct testing**	+ direct testing + full karyotype
- Odds ratio, no result	**Trisomy 21, 13 and 18**	- Complication rate 0,2-1%

Trisomie 21 seit August 2012
Trisomie 13 und 18 seit Februar 2013

Factors for sucessful pregnancy



Learning Objectives

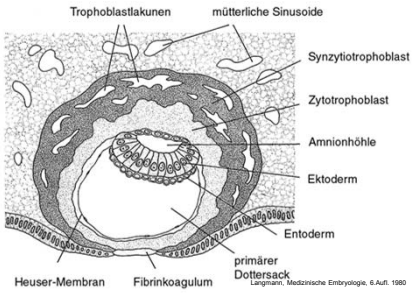
Early pregnancy success depends:

Genetic and chromosomal constitution of the embryo
- Pedigree
- Maternal age

Environmental factors -
As early as zygote, blastocyst, implantation embryo
- Endocrine function
- Implantation and placentation function

No conflict of interest

Implantation

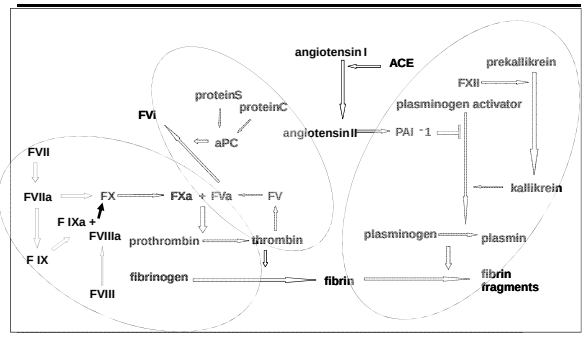


Thrombophilia – Fetal Risk

- Placental perfusion deficiencies
  -> miscarriages
  -> intrauterine growthretardation
  -> placental abruption
  -> placental insufficiency
  -> preeclamsia

- Implantation failure

Coagulation



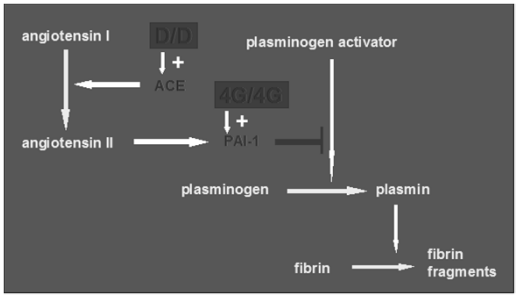
Thrombophilia - Summary

	Factors	Alteration	Effect
Pro-coagulatory Factors	FV	G1691A	continious Prothrombin activation
	PT (FII)	G21210	enhanced Plasma-thrombin activation
Anti-coagulatory Factors	Proteine C	deficiency	enhanced FV und FVIII activation
	Proteine S	deficiency	impaired Proteine C activity
	AT III	deficiency	enhanced Plasma-thrombin activation
Fibrinolytic Factors	PAI1	4G/4G polymorphism	impaired fibrinolysis
	ACE	D/D polymorphism	reduced fibrinolysis
	FXIII	mutation	reduced fibrin stability
	FXII	polymorphism	reduced fibrinolysis

Thrombophilia – Risk for Thrombosis

	mutation	Prevalence in general (in EU)	Prevalence in thrombosis patients	RR
F-V-mutation	G1691A	5 %	Bis 40 %	7-fold
Prothrombin-mutation	G20210A	2 %	10 %	3-fold
Protein C/S-deficiency, ATIII	multiple	0,1 %	Up to 5 %	11-fold – Prot C 10% - Prot S 40% - ATIII
PAI1	4G/4G	20 %	25 %	2-fold
Antiphospholipid-syndrome		0,1 %	5 %	50 %
Hyperhomo-cysteinämia	MTHFR-mutation	2 %	Up to 15 %	to determine

Fibrinolysis – Synergism of PAI-1 & ACE



Results - ACE & PAI-1 combined

	PAI-1	5G/5G		4G/5G		4G/4G	
ACE	RSA (n= 184) Kontrollen (n= 127)	n	%	n	%	n	%
I/I	RSA	10	5.4	19	10.3	13	7.0
	Kontrollen	6	4.7	8	6.3	12	9.5
	p	0.78		0.22		0.45	
D/I	RSA	17	9.2	32	17.4	34	18.5
	Kontrollen	12	9.5	36	28.3	23	18.1
	p	0.95		0.02		0.93	
	RR (CI)			0.6 (0.39-0.95)			
D/D	RSA	10	5.4	24	13.0	25	13.6
	Kontrollen	10	7.9	14	11.0	6	4.7
	p	0.39		0.59		0.01	
	RR (CI)					2.87 (1.16-7.69)	

Buchholz et al., Hum. Reprod., 2003

Thrombophilia - Implantation

		IVF failure (n=90)	Pregnancy following 1. IVF (n=90)	Pregnacy spontanously (n=100)
FV	heterozygote	10 %	1,1%	2%
	homozygote	4,4 %	0 %	0 %
MTHFR	heterozygote	7,8 %	8,9 %	9 %
	homozygote	14,4 %	3,3 %	2 %
PT	heterozygote	5,6 %	3,3 %	3 %
	homozygote	1,1 %	1,1 %	0 %
Proteine C deficiency		2,2 %	1,1 %	0 %
Proteine S deficiency		3,3 %	2,2 %	3 %
AT III deficiency		1,1 %	0 %	1 %
Lupus Antikoagulans		8,9 %	2,2 %	2 %
Anticardiolipin-AK		10 %	2,2 %	3 %
combined defects		35,6 %	4,4 %	3 %

Hussein S.Qubla et al. Hum Reprod 2006

Cooperation

profertilita

Dr. Dagmar Gutknecht
Dr. Angelika Eder
Prof. Dr. Monika Bals-Pratsch

Zentrum für Pränataldiagnostik und Humangenetik
Kurfürstendamm 199
BG Berlin-Genetics GmbH
Berlin

PD Dr. Markus Stumm
PD Dr. Tina Buchholz

Katrin-Janine Heiliger
Dr. Caroline Adelfalk
PD Dr. Tina Buchholz

Gyn-Gen-Lehel
Zentrum fuer Reproduktionsgenetik
München

Thank you for listening …. !

Center for Reproductive Genetics

www.gyn-gen-lehel.de

Debate
Is there a need for early pregnancy progesterone supplementation?
No

Anders Nyboe Andersen
Professor, MD
The Fertility Clinic, Copenhagen University Hospital, Rigshospitalet, Denmark

anders.nyboe.andersen@regionh.dk

Declarations of potential conflicts of interest

Anders Nyboe Andersen has:

Received ph.d. grants, other study supports, honoraria's for lectures and ad hoc advisory functions and have been part in phamaceutical industry driven research projects involving the 3 companies

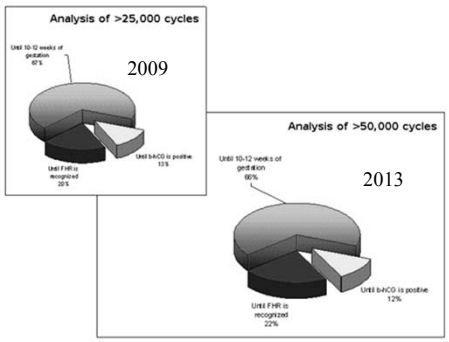
MSD
Ferring
Merck Serono

Learning objectives

Luteal supplementation with progesterone after ART should be withdrawn two weeks after transfer when hCG is positive, because:

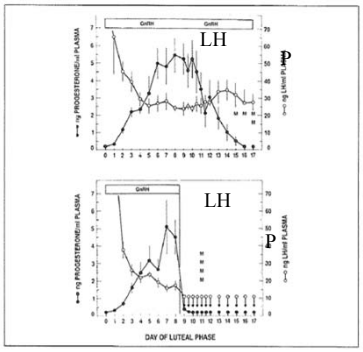
- There is no biological rationale for this practise, because inadequate progesterone secretion is caused by low LH/hCG stimulation and this is solved when endogenous hCG from the gestation stimulates the corpora lutea of early pregnancy
- Randomised controlled trials (RCT's) after agonist and antagonist protocols show no benefits of prolonging the luteal support
- Several non-RCT provides additional support for the early withdrawal of progesterone

Practise on progesterone prolongation. www.ivf-worldwide.com



Criteria	25,000 cycles	50000 cycles
Until b-hCG is positive	12%	13%
Until FHR is recognized	20%	22%
Until 10-12 weeks of gestation	67%	66%

The LH dependence of Progesterone –
Experiments in pituitary stalk-resected monkeys



Zeleznik and
Hutchison, Endocrinology 1985

The Corpus Luteum of the Primate Menstrual Cycle Is Capable of Recovering from a Transient Withdrawal of Pituitary Gonadotropin Support*

JAMES S. HUTCHISON† AND ANTHONY J. ZELEZNIK

Departments of Physiology and Obstetrics and Gynecology, The University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

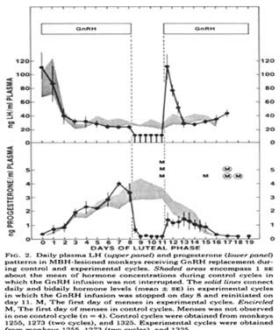
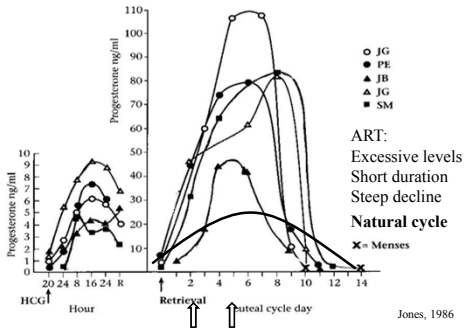


FIG. 2. Daily plasma LH (*upper panel*) and progesterone (*lower panel*) patterns in MBH-lesioned monkeys receiving GnRH replacement during control and experimental cycles. *Shaded areas* encompass 1 SE about the mean of hormone concentrations during control cycles in which the GnRH infusion was not interrupted. The *solid lines* connect daily and bidaily hormone levels (mean ± SE) in experimental cycles in which the GnRH infusion was stopped on day 8 and reinitiated on day 11. M, The first day of menses in experimental cycles. *Encircled* M, The first day of menses in control cycles. Menses was not observed in one control cycle (n = 4). Control cycles were obtained from monkeys 1255, 1273 (two cycles), and 1325. Experimental cycles were obtained from monkeys 1255, 1273 (two cycles), and 1325.

Zeleznik and
Hutchison, Endocrinology 1985

The luteal phase concern after ART

Progesterone in the luteal phase after controlled ovarian stimulation for ART

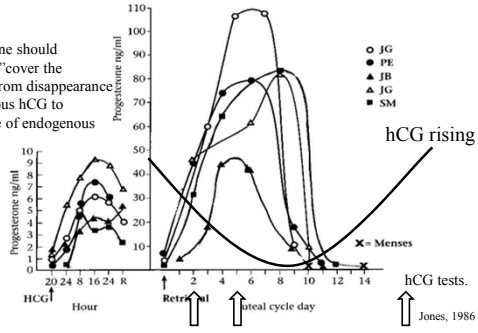


ART:
Excessive levels
Short duration
Steep decline
Natural cycle

Jones, 1986

Progesterone in the luteal phase after controlled ovarian stimulation for ART

Progesterone should be used to "cover the window" from disappearance of exogenous hCG to appearance of endogenous hCG



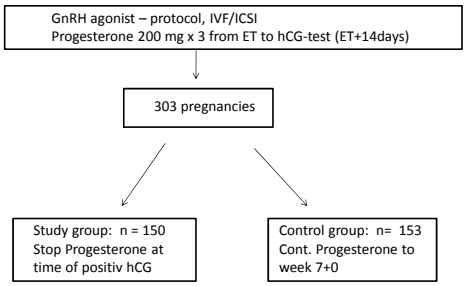
hCG rising

hCG tests.

Jones, 1986

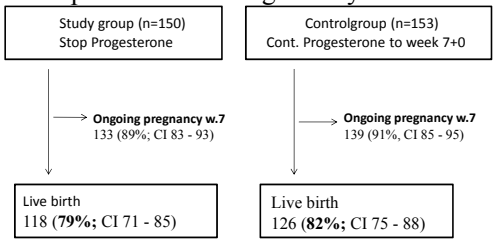
RCT's on early withdrawal of progesterone

A RCT on duration of Progesterone after positive hCG in agonist cycles.



Nyboe Andersen 2002

A RCT on duration of Progesterone after positive hCG in agonist cycles.



Nyboe Andersen 2002

A RCT on duration of Progesterone after positive hCG in antagonist cycles.

Antagonist – protocol, IVF/ICSI
Progesterone 200 mg x 3 from ET to hCG-test (ET+16days)

↓

200 pregnancies

↙ ↘

Studygroup: n = 100
Stop Progesterone at time of positiv hCG

Controlgroup: n= 100
Cont. Progesterone to week 7+0

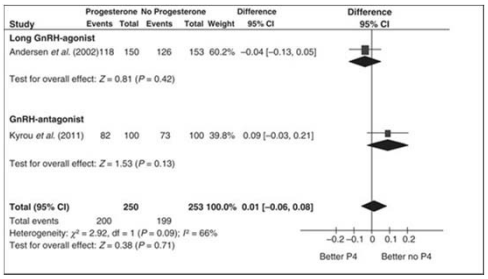
Kyrou 2011

A RCT on duration of Progesterone after positive hCG in antagonist cycles.

Study group Stop Progesterone	Controlgroup Cont. Progesterone to week 7+0
→ Abortion < week 7: **9%**	→ Abortion < week 7: **12%**
→ Abortion > week 7: **8%**	→ Abortion > week 7: **10%**
→ Bleeding episodes: **14%**	→ Bleeding episodes: **19%**
Ongoing pregnancy > 12.w **82%**	Ongoing pregnancy > 12. w **73%**

Progesterone (Utrogestan)
Kyrou 2011

Even a meta-analysis……



Griesinger 2011

Is it time to abandon progesterone supplementation of early pregnancy after IVF?

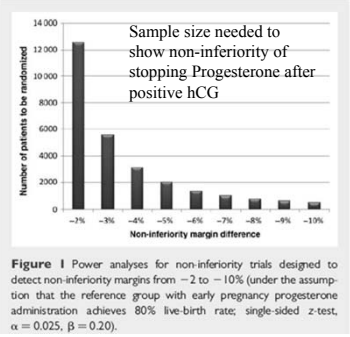


Figure 1 Power analyses for non-inferiority trials designed to detect non-inferiority margins from −2 to −10% (under the assumption that the reference group with early pregnancy progesterone administration achieves 80% live-birth rate; single-sided z-test, $\alpha = 0.025$, $\beta = 0.20$).

Griesinger 2011

Why so few RCT on duration of progesterone?

- No interest for the Pharmaceutical industry
- In our country the Medicines Agency have demanded that we paid all medication (30.000 €)
- The fees for registrations (Data Protection, Ethical Committee, Medicine agency (2.500 €)
- The fees for GCP monitoring may reach (25.000 €)
- The study would take at least 12 month of "paper work" – incompatible with normal clinical work (12 month salary …..€)

So – Can we achieve supportive informations without the RCT……?

Progesterone in early pregnancy

Evidence through
comparisons of prospective studies designed for other purposes

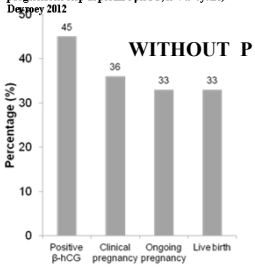
A comparison of live birth rates with (MERIT) or without (MEGASET) continuation of Progesterone

Positive βhCG:	Positive serum βhCG test 13-15 days after transfer
Clinical pregnancy:	Transvaginal ultrasound showing at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer
Ongoing pregnancy:	Transvaginal ultrasound showing at least one viable fetus 10-11 weeks after transfer
Live birth:	At least one liveborn neonate

Pregnancy and Live Birth Rates
per Cycle with Transfer (MEGASET and MERIT)

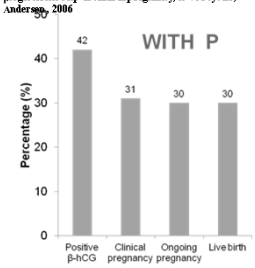
MEGASET

(GnRH antagonist, transfer of 1 blastocyst on day 5, progesterone stop at positive βhCG, n=749 cycles) Devroey 2012



MERIT

(long GnRH agonist, transfer of 1-2 embryos on day 3, progesterone stop at clinical pregnancy, n=731 cycles) Andersen, 2006



12% loss from pos. hCG to live birth in both studies

Duration of progesterone therapy

Evidence through retrospective studies

Autunm 1997 (Control group)

200 pregnant IVF/ICSI patients (hCG >5 iu/l) 14 days after ET who all continued Progestan 200 mg x 3 daily for 3 weeks during early pregnancy.

vs

Spring 1998 (Study group)

200 pregnant IVF/ICSI patients (hCG >5 iu/l) 14 days after ET who all stopped all Progestan treatment at the day the hCG was positive (ET day 14).

Schmidt, Andersen 2001

Results – observational study
Duration of progesterone therapy

	Study (stop P)	**Control (continue P)**
Positive hCG	200	200
Ongoing (w 7)	132 (66%; CI 59 - 73)	138 (69%, CI 62 – 75)
Delivery	126 (63%; CI 56 – 70)	128 (64%; CI 57 – 71)

Schmidt, Andersen 2001

An American study

Uncontrolled trial of 172 pregnancies

		Live births	
Study	(stop all P at day of hCG)	n = 116	77%
Control	(continued P til w.12)	n = 56	75%

Proctor 2006

Progesterone withdrawal earlier than week 10-12 or in selected patients

- **Week 5**
  A RCT (n=220) of supplementation to week 5 vs. 8.
  No difference in outcome (Kohls et al.2012)
- **Selected patients, at time of positive hCG**
  A RCT (n=97) of supplementation (s-Prog > 15 ng/ml at the time of positive hCG) to weeks 8 vs immediate withdrawal.
  No difference in outcome (Goudge et al. 2010)

National register data (2007)

The Netherlands and Belgium used progesterone into early pregnancy whereas the Nordic Countries did not. (Similar twin birth rates - 12.7% vs 11.2%)

	Transfers	Births/transfer
• NL + B	30.259	22.6%
• Nordic	32.922	22.1%

ESHRE, EIM 2012

Let’s stop using ”adjuvant therapy”
with evidence of no effects.

We could also use prednisolone, aspirin, beta-mimetics, post-retrieval doxycycline for 7 days and acupuncture for all….?

Thank you for your attention

References

Nyboe Andersen A, Popovic-Todorovic B, Schmidt KT, Loft A, Lindhard A, Hojgaard A, et al. Progesterone supplementation during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial. Hum Reprod 2002;17:357-61.

Kyrou D, Fatemi HM, Zepiridis L, Riva A, Papanikolaou EG, Tarlatzis BC, et al. Does cessation of progesterone supplementation during early pregnancy in patients treated with recFSH/GnRH antagonist affect ongoing pregnancy rates? A randomized controlled trial. Hum Reprod 2011;26:1020-4.

Griesinger G. Editorial commentary: is it time to abandon progesterone supplementation of early pregnancy after IVF? Hum Reprod 2011;26:1017-9.

Goudge CS, Nagel TC, Damario MA. Duration of progesterone-in-oil support after in vitro fertilization and embryo transfer: a randomized, controlled trial. Fertil Steril 2010;94:946-51.

Kohls G, Ruiz F, Martinez M, Hauzman E, de la Fuente G, Pellicer A, et al. Early progesterone cessation after in vitro fertilization/ intracytoplasmic sperm injection: a randomized, controlled trial. Fertil Steril 2012;98:858-62.

Schmidt KL, Ziebe S, Popovic B, Lindhard A, Loft A, Andersen AN. Progesterone supplementation during early gestation after in vitro fertilization has no effect on the delivery rate. Fertil Steril 2001;75:337-41.

Stovall DW, Van Voorhis BJ, Sparks AE, Adams LM, Syrop CH. Selective early elimination of luteal support in assisted reproduction cycles using a gonadotropin-releasing hormone agonist during ovarian stimulation. Fertil Steril 1998;70:1056-62.

Devroey P, Pellicer A, Nyboe AA, Arce JC. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. Fertil Steril 2012;97:561-71.

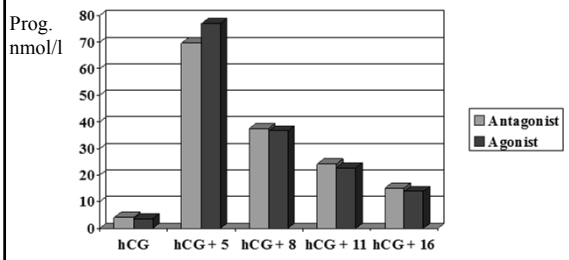
Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod 2006;21:3217-27.

ESHRE EIM. Assisted reproductive technology in Europe, 2007: results generated from European registers by ESHRE. Hum Reprod 2012;27:954-66.

Toner J P. The luteal phase: Luteal support protocols. In Gardner, Weisman, Howles and Shoham. Textbook of Assisted Reproductive Techniques. Laboratory and Clinical Aspects. Martin Dunitz Ltd, United Kingdom 2001.

Extra slides for discussion

No difference in serum progesterone after antagonist versus agonist cycles



Adapted from Fiedler et al. RBMOnline, 12, 2006, 27-32

Is there a need for early pregnancy progesterone supplementation?

Georg Griesinger
University of Lübeck
Department of Gynecological Endocrinology and Reproductive Medicine

Disclosure

Advisor for
Merck Serono, MSD, Ferring, IBSA, Glycotope, ReprodWissen GmbH

Travel invitations
Merck Serono, MSD, Ferring, IBSA

Honorarium for lectures
Merck Serono, MSD, Ferring, IBSA, ReprodWissen GmbH

Learning objectives

- To understand the rationale, design and interpretation of non-inferiority trials in the context of withdrawing early pregnancy progesterone supplementation

If we want to withdraw progesterone…

We need to have a high level of confidence of not doing harm

Task is to prove that stopping progesterone with a positive pregnancy test is non-inferior to continuing progesterone in terms of live birth achievement.

Is it non-inferior to withdraw progesterone?

What difference in live birth rate would justify using progesterone in your opinion?

Difference in live birth rate:

1% 3% 5% 7%

Or: how many women are we prepared to unnecessarily treat with progesterone to save one pregnancy from aborting?

Non-inferiority trial design

- In order to demonstrate non-inferiority, the recommended approach is to pre-specify a margin of non-inferiority
- After study completion, a one-sided 97.5% interval for the true difference between the two treatments is constructed. This interval should lie entirely on the positive side of the non-inferiority margin with special note on the lower limit of the confidence interval, which represents the degree of inferiority to the reference that can be excluded

Trial methodology pitfall

(Andersen et al., Hum Reprod 2002)

n = 303 patients randomized (150 + 153 patients)

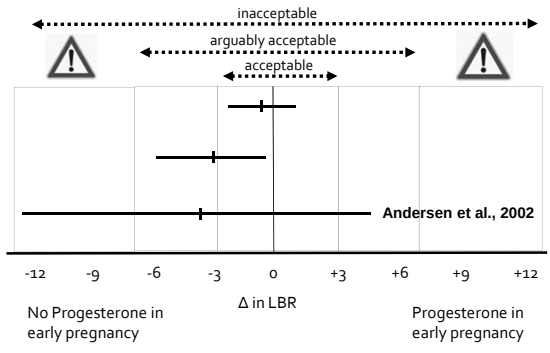
Study group: 3x200 mg vaginal P (Utrogest) for 3 weeks if hCG positive

Control group: no further progesterone

Live birth rate:
78.7 % without progesterone vs. 82.4 % with progesterone **p>0.05**

Authors conclusions: Prolongation of progesterone supplementation in early pregnancy has no influence on the miscarriage rate, and thus no effect on the delivery rate. Progesterone supplementation can safely be withdrawn at the time of a positive HCG test.

The concept of equivalence



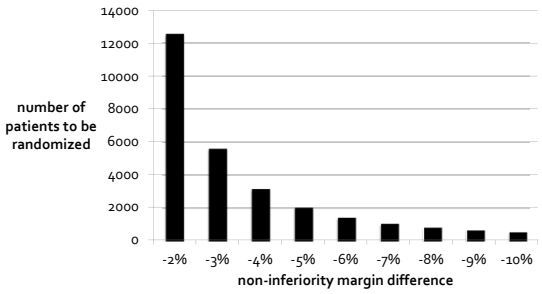
lack of superiority ≠ equivalence

‚lack of evidence of difference'

is *not synonymous* with

'evidence of a lack of difference'

Sample size for a conclusive study



Griesinger, Hum Reprod 2011

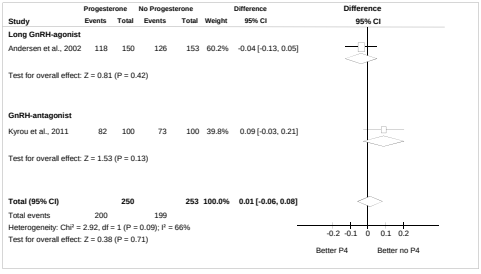
Combined analysis of 2 RCTs

Lower limit of 95% CI

-13%

-3%

-6%



Griesinger, Hum Reprod 2011

A patient finally gets pregnant after IVF…

Crinone 8%®

…when pregnancy is confirmed, **continue therapie for up to 30 days**

… pregnancy occurs treatment may **continue for up to 10-12 weeks**

…if you become pregnant, your doctor may decide to continue treatment for **up to 10 to 12 weeks**

Utrogestan®

… the recommended dosage is 600 mg/day, in three divided doses, from the day of embryo transfer **until at least the 7th week of pregnancy** and not later than the 12th week of pregnancy

Lutinus®

…the administration of Lutinus should be **continued for 30 days,** if pregnancy has been confirmed

True burden…

Approximately one positive pregancy test per 2-8 woman treated with IVF or ICSI (age dependent)!

Costs

Progestan® Weichkapseln
Rp ATC: G03DA04
Zus.: 1 Weichkps. enth.: Progesteron 100 mg
Sonst. Bestandteile: Raffiniertes Sonnenblumenöl, Gelatine, Glycerol, (3-sn-Phosphatidyl)cholin (aus Sojabohnen), Titandioxid (E 171)

30 Weichkps. (N1)		16,51	PZN 02178920
90 Weichkps. (N3)		29,04	PZN 02178937

LUTINUS® 100 mg Vaginaltabletten
Rp ATC: G03DA04
Zus.: 1 Vaginaltbl. enth.: Progesteron 100 mg
Sonst. Bestandteile: Hochdisp. Siliciumdioxid, Lactose $1H_2O$, vorverkleist. Stärke (Mais), Povidon K 29/32, Adipinsäure, Natriumhydrogencarbonat, Natriumdodecylsulfat, Magnesiumstearat (Ph. Eur.)

21 Vaginaltbl. (N1)		45,51	PZN 06129611
90 Vaginaltbl. (N2)		158,91	PZN 10073218

Crinone® 8% Vaginalgel
Rp ATC: G03DA04
Zus.: 1,125 g enth.: Progesteron 90 mg
Sonst. Bestandteile: Sorbinsäure 0,9 mg, Glycerol, dünnflüssiges Paraffin, hydriertes Palmölglycerid, Carbomer 974P, Polycarbophil, Natriumhydroxid, gereinigtes Wasser

6 Einmaldosen-Appl. (N1) à 1,125 g		42,04	PZN 08819024
15 Einmaldosen-Appl. (N2) à 1,125 g		87,36	PZN 08819030

…and risks?

External validity of the existing studies

- Patients with early bleeding?
- Patients with endometriosis?
- Patients with abnormal cycles?
- Patients with endocrine abnormalities?

A patient finally gets pregnant after IVF…

Thank you for your attention!

griesing@uni-luebeck.de

UPCOMING ESHRE EVENTS

// ESHRE CAMPUS EVENTS

ESHRE's 30th Annual Meeting

www.eshre2014.eu

Munich, Germany
29 June - 2 July 2014

Epigenetics in reproduction

www.eshre.eu/lisbon

Lisbon, Portugal
26-27 September 2014

Endoscopy in reproductive medicine

www.eshre.eu/endoscopyoct

Leuven, Belgium
15-17 October 2014

Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering **www.eshre.eu/thessaloniki**

Thessaloniki, Greece
31 October-1 November 2014

From gametes to blastocysts – a continuous dialogue

www.eshre.eu/dundee

Dundee, United Kingdom
7-8 November 2014

Controversies in endometriosis and adenomyosis

www.eshre.eu/liege

Liège, Belgium
4-6 December 2014

Bringing evidence based early pregnancy care to your clinic

www.eshre.eu/copenhagen

Copenhagen, Denmark
11-12 December 2014

An update on preimplantation genetic screening (PGS)

www.eshre.eu/rome

Rome, Italy
12-13 March 2014

For information and registration: www.eshre.eu/calendar
or contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES