

Metformin in early pregnancy and abortions



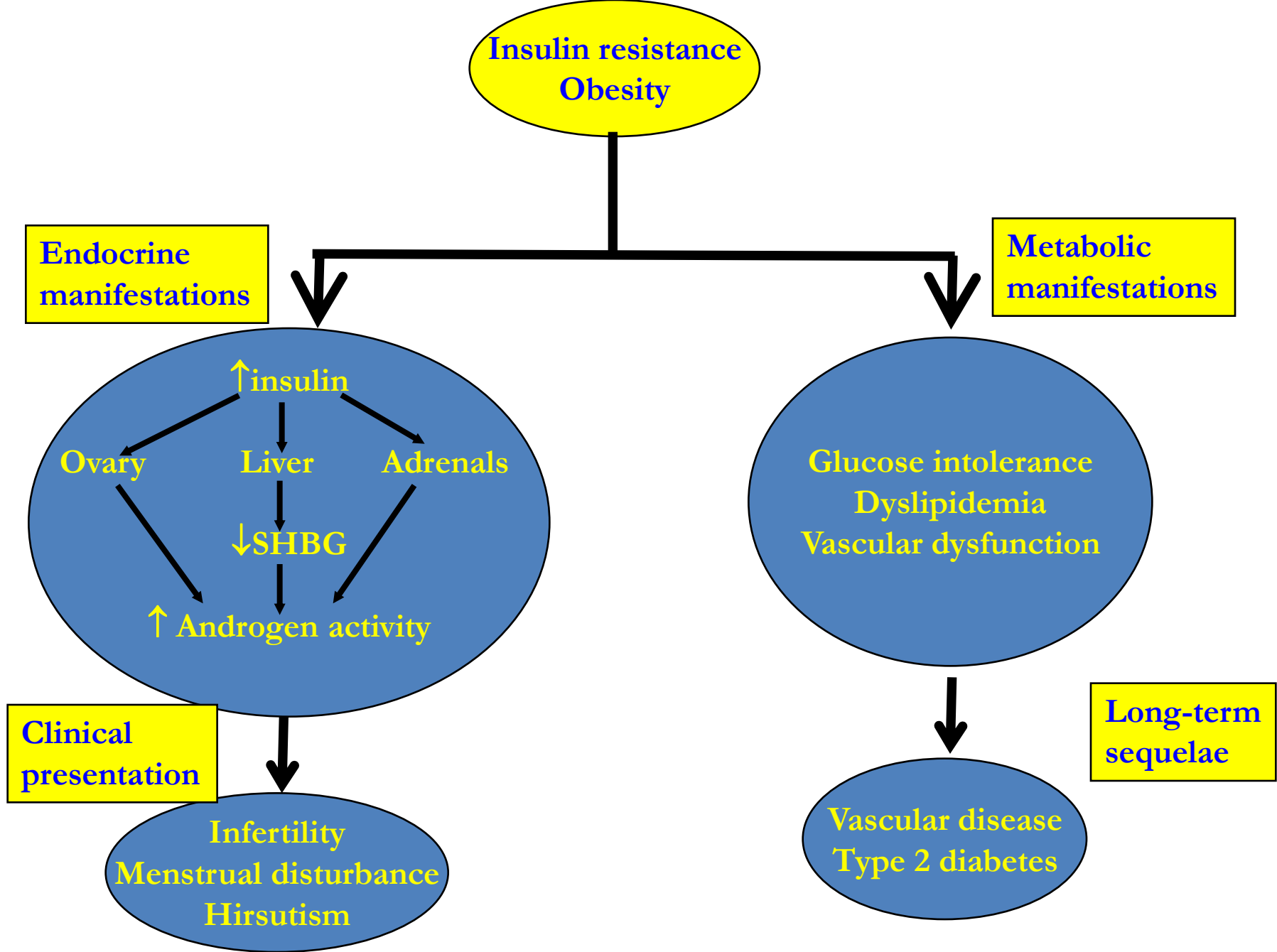
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- PCOS and miscarriage risk
- Metformin and miscarriage risk in PCOS
- Results of the Finnish RCT

PCOS and miscarriage risk

The polycystic ovary syndrome (PCOS) is associated with

- Anovulatory infertility: 30% of the causes of infertility
- Insulin resistance, especially in obese women
 - Hyperinsulinaemia ja hyperandrogenism
 - Key factors in the etiology of anovulation
 - Role in the increase of the miscarriage risk?



after Harborne et al 2003

PCOS and miscarriage risk

- ↑3-4x risk: **30-50%** vs. **10-15%** in the general population
- PCOS diagnosed in 40-80% of women with recurrent miscarriages

(Balen 1993, Homburg 1998, Regan 1990, Watson 1993, Regan 1989, Gray 2000, Jakubowicz 2002 and 2004)

- No increase of the risk
 - in studies with patients matched for BMI and etiology of infertility
 - or in population based studies

(Wang 2001, Winter 2002, Koivunen 2008)

Causes for miscarriage in PCOS

Decrease of the receptivity of the endometrium?

- Dysregulation in the control of apoptosis mechanisms in the endometrium

(Avellaira Hum Repr 2006)

- *In vitro* studies: direct inhibitory effect of androgens on the endometrial cell growth and secretory activity

(Tuckerman Fertil Steril 2000)

Endometrium


R Koivunen, 2006

POSITIVE CORRELATION

NEGATIVE CORRELATION

WITH INSULIN RESISTANCE


PAI-1

- 
- placentation
 - vascularisation of the intervillous area
 - marker of the endothelium dysfunction
 - increased in PCOS ?

LH

- increase androgen synthesis
- ↑⇒ implantation problems?

Glycodelin

- 
- secretory/decidualised endometrium
 - effect on the immune endometrium reaction
 - lower level during the 3rd to 8th weeks of pregnancy if miscarriage

IGFBP-1

- adhesion process
- low level → impairment of the endometrium function?
- lower level during the 9th to 11th weeks of pregnancy if miscarriage

(Homburg 1988, Vrbikova 2002, Kilicdag 2005, Yilmaz 2005, Palomba 2005, 2010)

(Jakubowicz 2001, 2004)

A problem of the oocyte?

- Different gene expression profiles by microarray and PCR analysis in PCOS oocytes compared to controls
 - ↓ developmental competency of PCOS oocytes?
 - Role of hyperandrogenism?

(Wood JR et al JCEM, 2007)

Metformin in PCOS

Effect on miscarriage rate

Treatment of anovulation

Metformin: mechanism of action

- Antihyperglycaemic drug, not a “true” insulin sensitizer
- Mechanism of action still unclear

METFORMIN

LIVER

↑ AMPK activity in hepatocytes
⇒ ↑ insulin sensitivity
⇒ gluconeogenesis ↓
+ hepatic glucose output ↓

**MUSCLE
FAT**

↑ glucose transport
⇒ ↑ insulin sensitivity

INTESTINE

⋮ intestinal absorption of glucose
↓

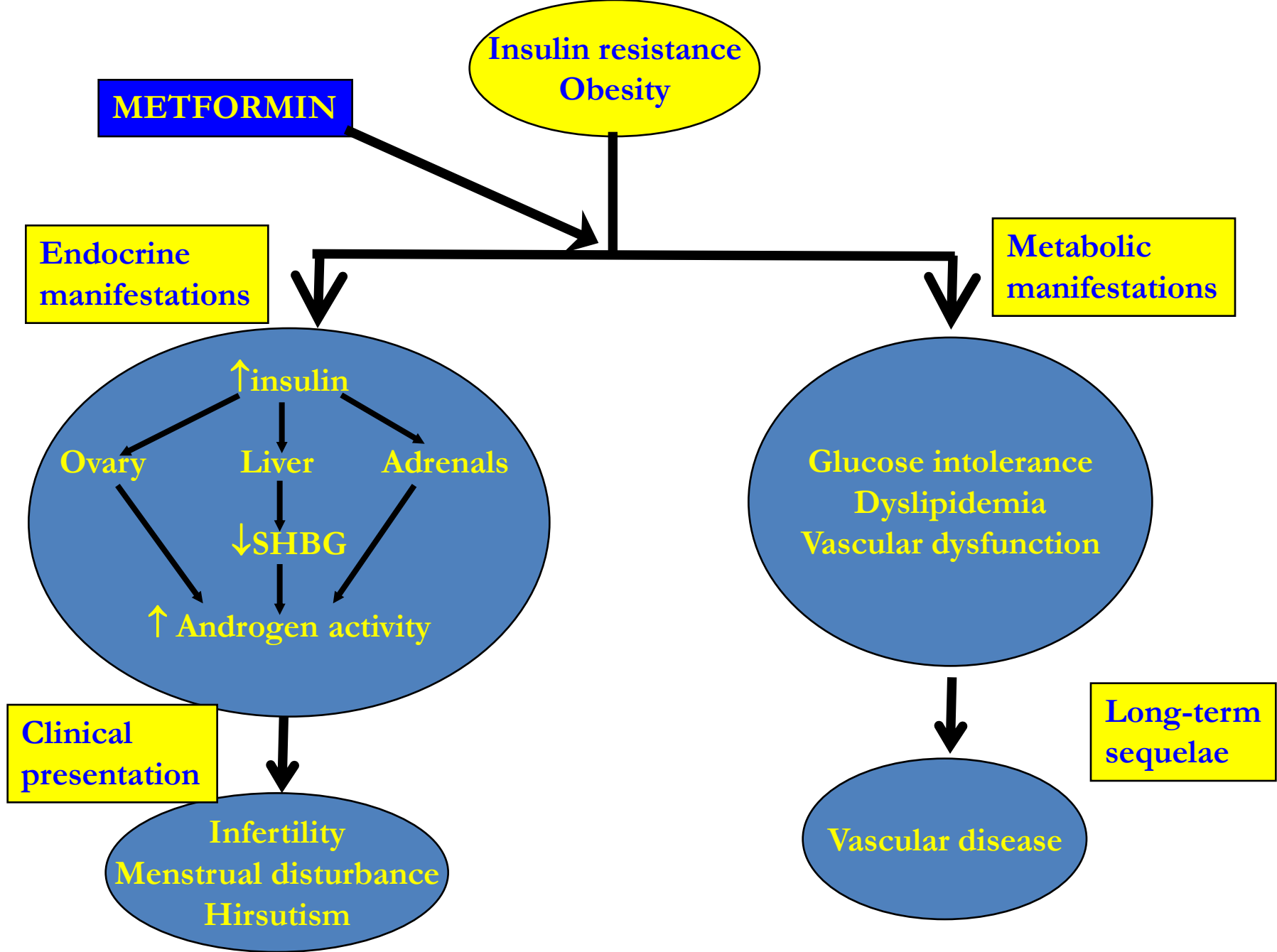
PANCREAS

no direct effect on insulin secretion
⇒ SAFE!

OVARY

? ⋮ androgen secretion
↓

*(Zhou 2001,
Natali and Ferrannini 2006)*



after Harborne et al 2003

Metformin and risk of miscarriage

- Retrospective studies
 - Metformin reduces miscarriage rates from **70%** to **10%** *(Glueck et al 2001)*
 - Decrease of PAI-I only in the women with live births *(Palomba et al 2005)*

Metformin and risk of miscarriage: RCTs

- Lower miscarriage rates in women who received metformin (**8.8%** vs. **41.9%**)

(Jakubowicz et al 2002)

- 100 nonobese women randomised
 - Metformin + PLA vs. CC + PLA
 - Miscarriage rate **9.7%** (MET) vs. **37.5%** (PLA)
 $P=0.045$
 - Cumulative PR **68.9%** (MET) vs. **34.0%** (PLA) $P<0.001$
(Palomba et al 2005)
- In women with IGT, miscarriage rate **15%** (MET) vs. **55%** (PLA), $P=0.03$ *(Zolghadri et al 2007)*

Metformin and risk of miscarriage

Mechanisms of action?

- ↓ body weight, insulin and androgen levels
- Improvement of the uterine artery blood flow

(Jakubowicz et al, JCEM 2001)

- *in vitro* in mice: activation of AMPK

- in granulosa cells → ↓ steroidogenesis?

(Sonntag et al, F&S 2005)

- in blastocysts → improvement of insulin signaling and pregnancy outcome?

(Eng et al Diabetes 2007)

Mechanisms of action: endometrium


R Koivunen, 2006

POSITIVE CORRELATION

WITH INSULIN RESISTANCE

NEGATIVE CORRELATION

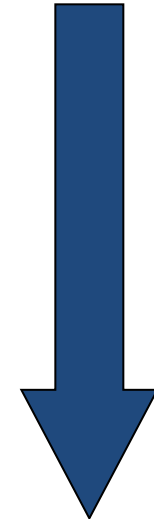
PAI-1

- 
- placentation
 - vascularisation of the intervillous area
 - metformin \Rightarrow \downarrow PAI-1?
 \Rightarrow \downarrow miscarriage risk??

LH

- Increase androgen synthesis
- increased in PCOS
- \uparrow \Rightarrow implantation problems?
- metformin \Rightarrow \downarrow LH
- \Rightarrow \downarrow miscarriage risk??

Glycodelin

- 
- secretory/decidualised endometrium
 - effect on the immune endometrium reaction
 - normalisation of level (metformin)
 \Rightarrow \downarrow miscarriage risk??

IGFBP-1

- adhesion process
- \uparrow miscarriage risk and impairment of the endometrium function
- normalisation of level (metformin)
 \Rightarrow \downarrow miscarriage risk??

(Homburg 1988, Vrbikova 2002, Kilicdag 2005, Yilmaz 2005, Palomba 2005, 2010)

(Jakubowicz 2002, 2004)

No benefit from the combination of metformin to CC (*Moll et al 2006*)

	CC + MET (n= 111)	CC + PLA (n= 114)	P-value
BMI	28.5 kg/m ²	27.8kg/m ²	
ovulation rates	64%	72%	NS
ongoing pregnancy rate	40%	46%	NS
miscarriage rate	12%	11%	NS
discontinuation (side-effects)	16%	5%	5-16%

CC better than metformin, no benefit from the combination (*Legro et al., NEJM 2007*)

	CC + PLA (N=209)	MET + PLA (N=208)	Combination (N=209)
BMI	36.0 kg/m ²	35.6 kg/m ²	34.2 kg/m ²
ovulation	49%	29%	60.4%
conception	29.7%	12%	38.3%
pregnancy	23.9%	8.7%	31.1%
live birth	22.5%	7.2%	26.8%
pregnancy loss	8.3%	20.8%	9.2%

Cochrane review (*Tang T 2010*)

- Metformin vs. CC
 - CC better for ovulation and clinical PR
 - **No effect on miscarriage rate**
 - No difference for LBR
- Metformin + ovulation inducing agent vs. placebo + ovulation inducing agent
 - Improvement of ovulation and clinical pregnancy rates
 - **No effect on miscarriage rate**
 - No effect on live birth rate

PCOS, metformin and miscarriage risk

Meta-analysis (*Palomba et al Fertil Steril 2010*)

- 17 studies included: **NO DECREASE OF RISK**
 - whole population OR=**0.89** (CI 0.65 to 1.21)
 - CC-treated patients OR=**1.02** (CI 0.59 to 1.75)
 - gonadotropin treated patients OR=**0.84** (CI, 0.24 to 2.95)
 - IVF-treated patients OR=**0.96** (CI 0.40 to 2.34)

Indications for metformin? (ESHRE/ASRM 2008)

- CC is the first-line treatment of anovulation in PCOS
 - Metformin alone less effective than CC in ovulation induction
- No indication for the prevention of miscarriage
- Metformin can be used
 - In patients with glucose intolerance
 - Could be useful
 - if BMI > 35kg/m² (?)
 - and/or CC-resistant women

Metformin improves pregnancy and live birth rates in women with polycystic ovary syndrome – a multicentre, double blinded, randomised clinical trial

Laure Morin-Papunen, M.D., Anni Rantala Med Student, Leila Unkila-Kallio M.D., Aila Tiitinen M.D., Maritta Hippeläinen M.D., Helena Tinkanen M.D., Antti Perheentupa M.D., Aimo Ruokonen M.D. and Juha Tapanainen M.D.
University Hospitals of Oulu, Helsinki, Kuopio, Tampere and Turku, Finland

Subjects and methods

We recruited women with PCOS and anovulatory infertility sent for infertility treatment to some of the five University Hospitals in Finland ●



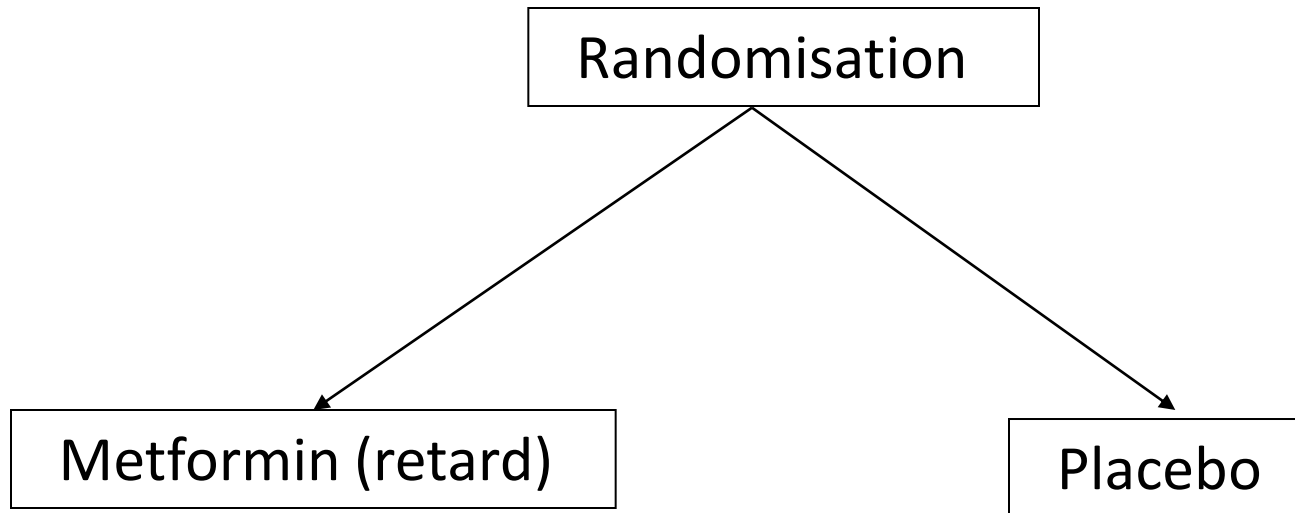
Aims of the study

- 1. To investigate whether metformin decreases first trimester miscarriage rate
- 2. To clarify whether it improves pregnancy rate (PR) and live birth rate (LBR)

Subjects and methods

- Inclusion criteria
 - age < 40 years at entry
 - BMI ≥ 19 kg/m² and < 40kg/m²
 - Criteria for PCOS as defined by ESHRE/ASRM
 - At least 6 – 12 months anovulatory infertility
- Exclusion criteria
 - Diabetic subjects
 - Alcohol users
 - Active liver disease (ALAT > 2 SD the upper normal value i.e. >100IU/L)
 - Hormonal drugs
 - Past or present cardiac failure (NYHA I-IV)
 - Liver or renal failure (S-Creatinine above the normal value ie. > 124 μ mol/l)
 - Pregnancy or lactation
 - Hypersensitivity to metformin

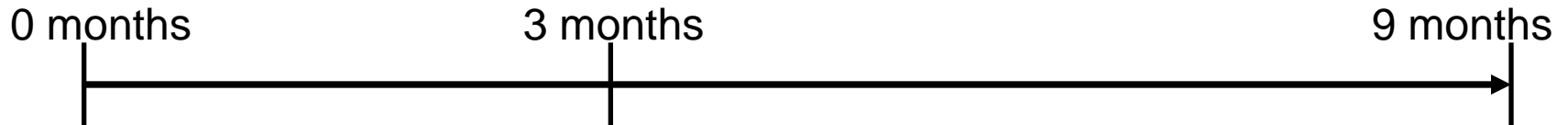
Subjects and methods



Obese (BMI $\geq 27\text{kg/m}^2$): 1g + 1g/day

Non-obese women (BMI $< 27\text{kg/m}^2$): 1g + 0,5g/ day

Protocol of the study

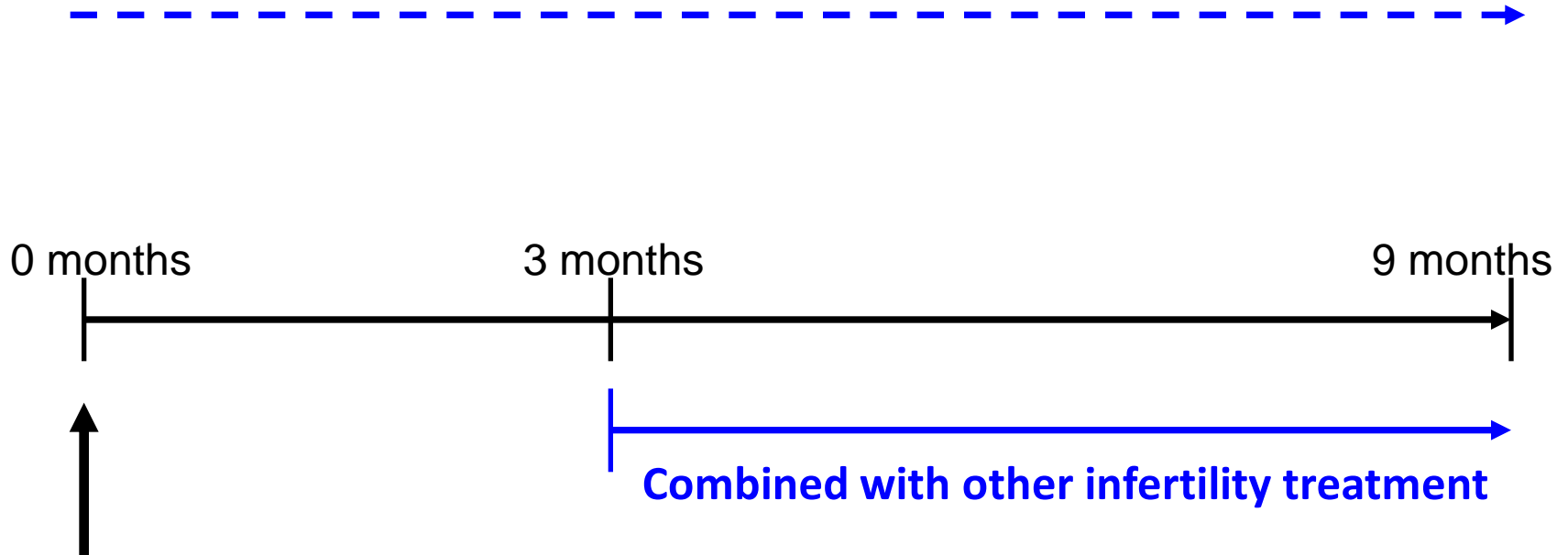


Randomisation: metformin / placebo

- up to the 12th week of pregnancy
- or up to a total duration of 9 months

Protocol of the study

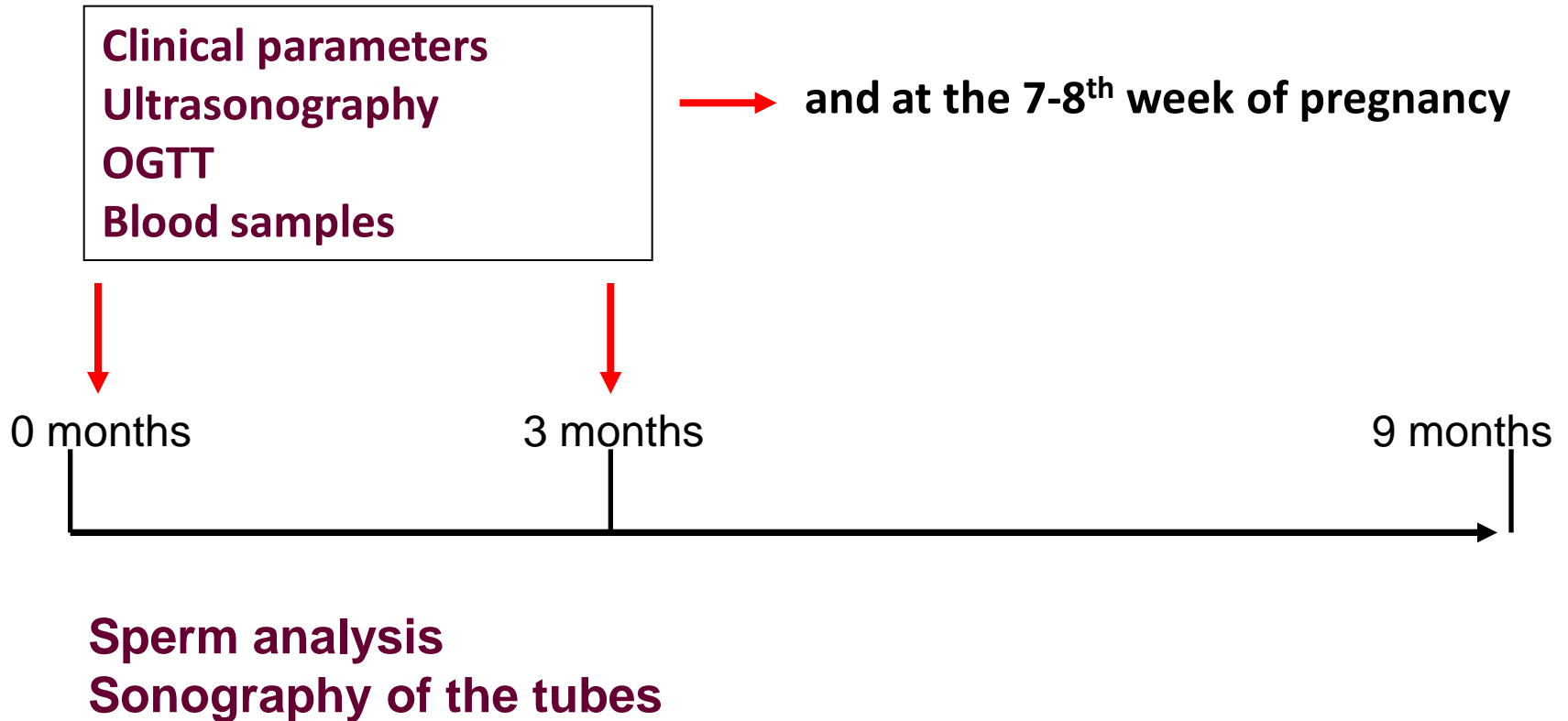
Metformin/Placebo



Metformin / placebo

- up to the 12th week of pregnancy
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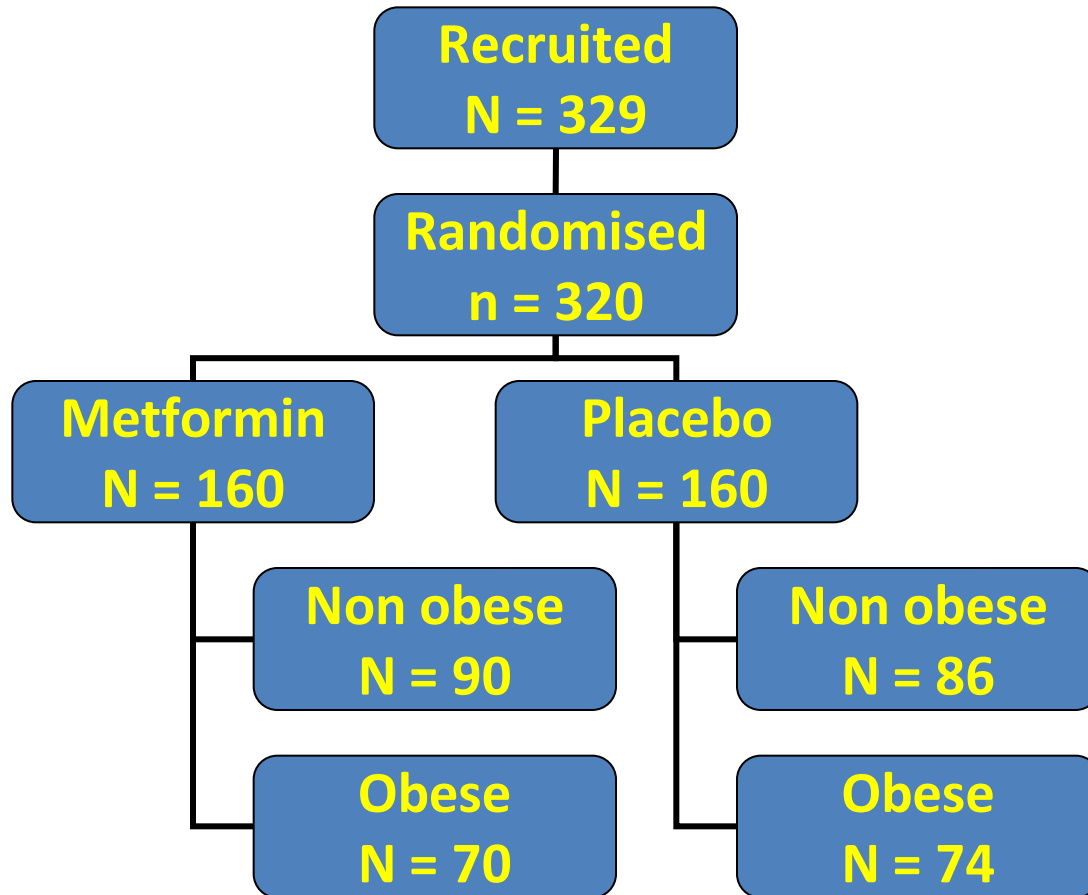
Examinations



Statistical analyses

- Power analysis
 - **Miscarriage rate**: 60 pregnant women needed in each group to show a decrease of miscarriage rate from 45% to 15%
 - **Pregnancy rate**: 120 patients needed in each group to show a 50% increase in the metformin group
 - > sample size of **300 subjects** needed
- Pregnancy rate
 - analysed as an intent-to-treat analysis with a Kaplan-Meier estimation curve
- Miscarriage and live birth rates
 - percentages calculation and χ^2 -test

Study chart



Results

To be published

Conclusions

- First trimester miscarriage rate was not increased in this PCOS population
- Metformin did not decrease miscarriage rate
- Metformin improved PR and LBR in women with PCOS

Conclusions....

- Obesity decreased PRs and LBRs in the placebo group
- The difference between the obese and non-obese disappeared during metformin therapy
→Especially obese women seemed to benefit from combining metformin with other infertility treatments