

Metformin treatment before IVF / ICSI in non obese PCOS women

**A Nordic, prospective, randomised,
double blind, multicentre study**

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Metformin effects in PCOS

- **Increased spontaneous ovulation rates**
- **Increased ovulation rates following Clomiphene administration**

Possible Metformin effects in PCOS?

- **Increased Live Birth Rates?**
- **Is Clomiphene always better than Metformin?**

Metformin and IVF in non obese PCOS

Does metformin treatment before and during ART cycles improve live births or pregnancy rates?

Our pilot study- 2004

**Metformin treatment before IVF / ICSI in women with polycystic ovary syndrome;
a prospective, randomized, double blind study**

Kjøtrød, von Düring and Carlsen
Human Reproduction 2004

Main issues in ART

- **A healthy live birth**
- **Preferably singleton birth**
- **As inexpensive as possible**

**Patient tailored treatment
algorithms**

Does one size fit all PCOS patients??



Aim of the study

Primary endpoint

**Clinical pregnancy rate in non obese
PCOS**

Aim of the study

Secondary endpoints

- **Number oocytes and embryo quality**
- **Days and doses of gonadotrophin**
- **Safety**
- **Live birth rates**

Inclusion criteria

PCOS according to Rotterdam criteria:

- Cycle length ≥ 35 days
- Hyperandrogenism;
 - S-testosterone ≥ 2.5 nmol/L
 - s-SHBG < 30 nmol/L
 - or a need to remove facial hair weekly
- PCO-ovaries:
 - at least 12 AF in one ovary
 - and/or volume ≥ 10 ml in one ovary

Inclusion criteria

- \geq one year infertile PCOS planned for ART
- First or second cycle of IVF / ICSI
- Age $<$ 38 years at inclusion
- **BMI $<$ 28 kg / m²**
- Written informed consent
- If previously on metformin; one month washout
- PCOS according to Rotterdam criteria

**Diet / Lifestyle
advice**

**Metformin / Placebo 1g bid
4-5 months**

hCG

Pregn.test



GnRH-analogue



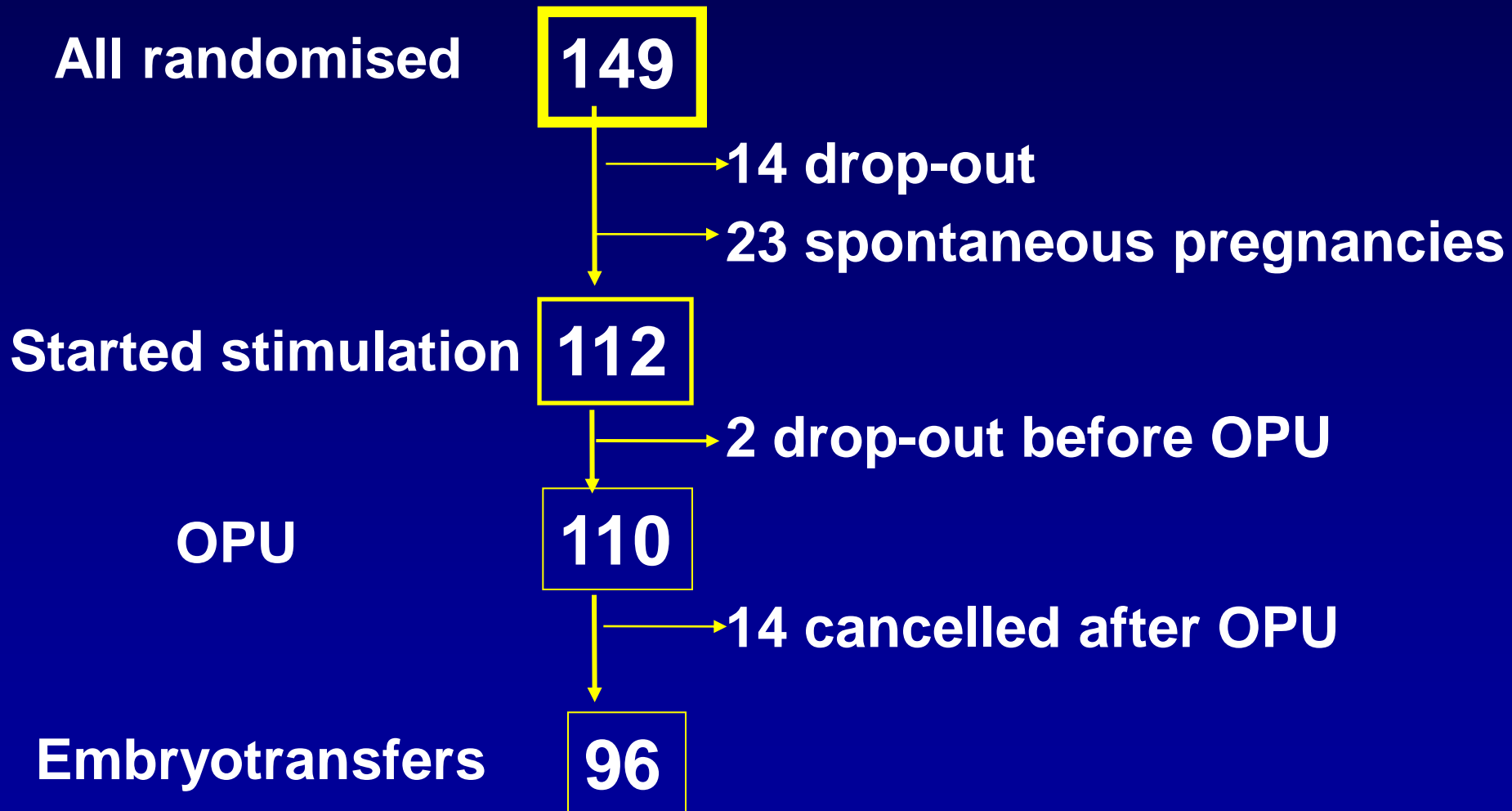
r-FSH 112.5 IU



Luteal support



Study group



Analysis

149

Intention to treat



112

Per protocol



96

Analysis

149

Intention to treat

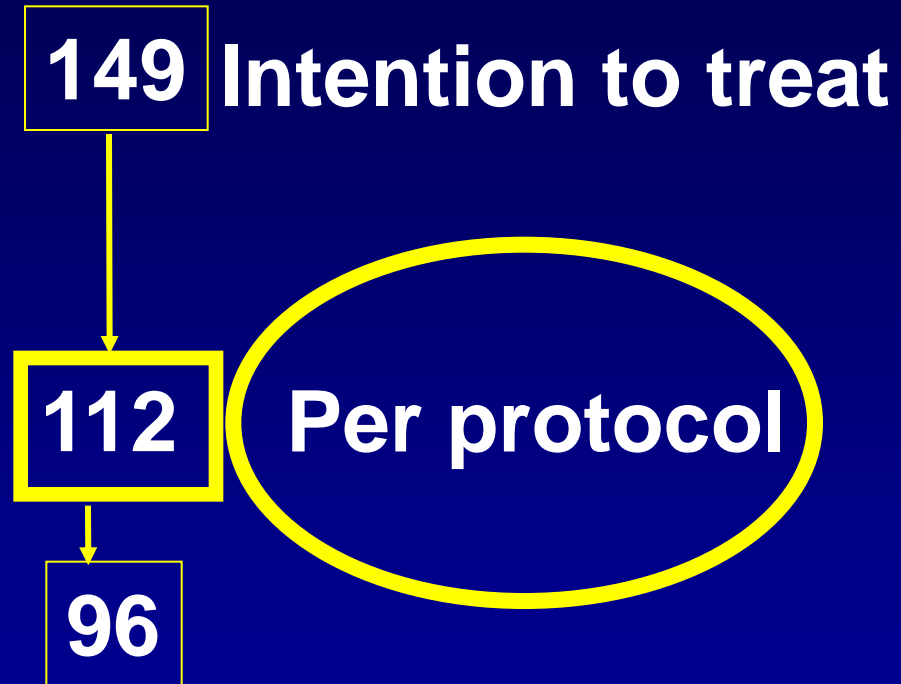
112

Per protocol

96



Analysis



Patient characteristics

	Placebo n=75	Metformin n=74	±SD
Age (yrs)	29.5	29.6	±3.6
Duration of infertility (yrs)	2.8	2.6	±1.8
Gravida 0	87%	91%	
Para 0	80%	82.0%	

Means, Mann Whitney test, CHI square test

PCO-ovaries at baseline

	Placebo n=75	Metformin n=74	p
Tot no. antral follicles	32.3	33.5	0.6
Total ovarian volume (ml)	21.0	20.0	0.4
S-AMH (ng/ml)	8.7	10.1	0.3

Means, Mann Whitney test

Baseline hormones

	Placebo n=75	Metformin n=74	p
Free testosterone index	0.33	0.39	0.1
Androstenedione (nmol/L)	8.9	8.3	0.2
DHEAS ($\mu\text{mol/L}$)	5.1	5.5	0.3
HOMA-index	2.6	2.3	0.4

Means, Mann Whitney test

Patient characteristics

	Placebo n=75	Metformin n=74	p
Previous Clomiphene	59(79%)	59(80%)	
Mean no. CC treatments	3.5	3.7	
Previous elektrokoagul.ov	10(13%)	4(5%)	0.1
Previous on metformin	10(13%)	12(16%)	
Previous IVF or ICSI	8(11%)	9(12%)	

Mann Whitney test

Results

Primary endpoint:

- **Clinical pregnancy rate**

Secondary endpoints:

- **Days and doses of gonadotrophin**
- **Number oocytes and embryo quality**
- **Safety**
- **Live birth rates**

Primary endpoint

	Placebo n=75	Metformin n=74	p
Clinical pregnancy rate	25 / 33%	37 / 50%	
	Mean difference 16.67(1.06-32.27)		0.04

Pearson chi square

Clinical pregnancy rates (per protocol)

	Placebo	Metform	p
Per protocol pop(PP)	(17/56) 30%	(25/56) 39%	0.3
Spont pregnancy rate(pre-treatment)	(8/75) 11%	(15/74) 20%	0.1

Pearson chi square

Results

- **Primary endpoints**
 - Clinical pregnancy rate
- **Secondary endpoints**
 - Days and doses of gonadotrophin
 - Number of oocytes and embryo quality
 - Safety
 - Live birth rates

Gonadotrophin doses

	Placebo n=56	Metformin n=56	p
Total FSH used (IE)	1531	1553	0.9
Number of days FSH treatment	12.1	12.4	0.6

Means, t-distribution

Results

- **Primary endpoints**
 - Clinical pregnancy rate
- **Secondary endpoints**
 - Days and doses of gonadotrophin
 - Number of oocytes and embryo quality
 - Safety
 - Live birth rates

Fertilisation / Embryo Quality

	Placebo N=56	Metformin n N=56	p
Number of oocytes	13.4 (7.2)	11.6 (6.1)	0.2
Fertilisation rate	0.54 (0.25)	0.53 (0.28)	0.8
Number of transferred embryos	1.1 (0.3)	1.2 (0.4)	0.1
Number of good embryos (frozen or transferred)	3.6 (3.0)	3.5 (3.2)	0.9

Means, SD

Results

- **Primary endpoints**
 - Clinical pregnancy rate
- **Secondary endpoints**
 - Days and doses of gonadotrophin
 - Number of oocytes and embryo quality
 - **Safety**
 - Live birth rates

Gastrointestinal side effects

Placebo
N=75

Metformin
N=74

p

Gastrointest.
side effects

11(14%)

27(37%)

Withdrawn
due to side
effects

3

2

CHI square test

Metformin and Body Weight

	Placebo N=75	Metformin N=74	p
BMI at inclusion	23.8	24.0	0.8
Difference in BMI	+0.4	- 0.3	0.0001
Difference in weight	+1.0	- 0.8	0.0001

Means, Mann Whitney test

Ovarian hyperstimulation syndrome (OHSS)

	Placebo N=56	Metformin N=56
Coasting performed	12	8
Cancelled IVF	3	1
Outpatient follow-up	2	3
Hospitalisation	3	2

No multiple pregnancies



Results

- **Primary endpoints**
 - Clinical pregnancy rate
- **Secondary endpoints**
 - Days and doses of gonadotrophin
 - Number of oocytes and embryo quality
 - Safety
 - Live birth rates

Live birth rates (ITT)

	Placebo n=75	Metformin n=74	p
Live birth rate	24 (32%)	36 (49%)	
	Mean difference 16.65 (1.12-32.18)		0.04

Pearson chi square

Live birth rates (per protocol)

	Placebo	Metform.	p
IVF / ICSI popul.	16/56 (29%)	21/56 (38%)	0.3
Spon.live birth rate (pre-treatment)	8/75 (11%)	15/74 (20%)	0.1

Pearson chi square

Conclusions

**In non obese PCOS women
4 months Metformin
before and during IVF / ICSI
improves clinical pregnancy rates**

Conclusions

**However,
more data are needed to clarify the effect of
metformin in IVF per se.**

Conclusions

Overall: Metformin is demonstrated as an easy, safe and cheap addition to increase live birth rates in **non-obese PCOS women.**

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