

Metformin and pregnancy outcome in PCOS

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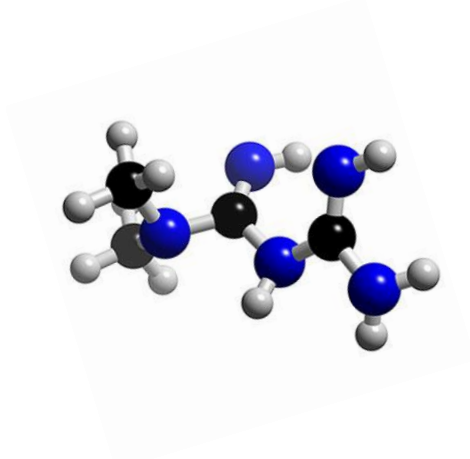
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Metformin

- ❑ Oral anti-diabetic drug
- ❑ Treatment of type 2 diabetes
- ❑ Used in Norway since the 1960's
- ❑ Guanidine; water soluble biguanid
- ❑ Excreted through the kidneys
- ❑ Does not cause hypoglycemia



French lilac – Galega officinalis

Metformin safety aspects



Passage

- Passes the placenta
- Therapeutical levels in fetal umbilical cord blood
- Some accumulation in fetal blood

Vanky et al 2004

Safety

- No teratogenic effects in therapeutic doses in animals
- No teratogenic effects reported i humans
- Does not affect fetal acid –base balance
- At intrauterine exposure no negative effect at 18 mth Glueck at al 2007
 - Height
 - Weight
 - Motor and social development

Metformin in pregnancy



Sarlis 1999

- Metformin reduced testosterone level in a hyperandrogenic pregnant women

Jakubowicz 2001

- Metformin reduced spontaneous abortions 9% vs 42% in PCOS

Glueck 2001-2008

- ↓ spontaneous abortions
- ↓ gestational diabetes
- Safe for the baby
- Safe during breast feeding

Begum 2009

- Metformin reduces gestational diabetes in PCOS women (9x)

Navaz 2010

- Reduces early pregnancy loss

Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study

E.Vanky^{1,5}, K.Å.Salvesen¹, R.Heimstad¹, K.J.Fougner², P.Romundstad³ and S.M.Carlsen⁴

Placebo group

Composite serious
complications

N = 7/22

Metformin group

Composite serious
complications

N = 0/20

P = 0.01

What did we do?





The PregMet Study

Prospective, randomized, Norwegian
multicentre study



The PregMet study

The aim of the study

Does metformin reduce pregnancy complications?

Primary outcome measures:

- Preeclampsia
- Preterm delivery
- Gestational diabetes
- "The composite of these three"



The PregMet study

Methods



Inclusion criteria

- ❑ PCOS diagnosis
(Rotterdam consensus)
- ❑ Single viable fetus
- ❑ Gestational age <13 weeks

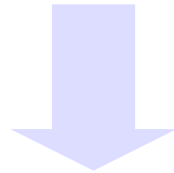
Exclusion criteria

- ❑ ALAT > 90 IU/L
- ❑ Creatinine > 130 $\mu\text{mol/L}$
- ❑ Fasting glucose > 7.0 mmol/L
- ❑ Alcohol abuse
- ❑ Drugs interfering with metformin

The PregMet study

Methods

Randomization



Diet and lifestyle

+



500 mg x 2/day the 1st week
1000 mg x 2/day until delivery



Diet and lifestyle

+

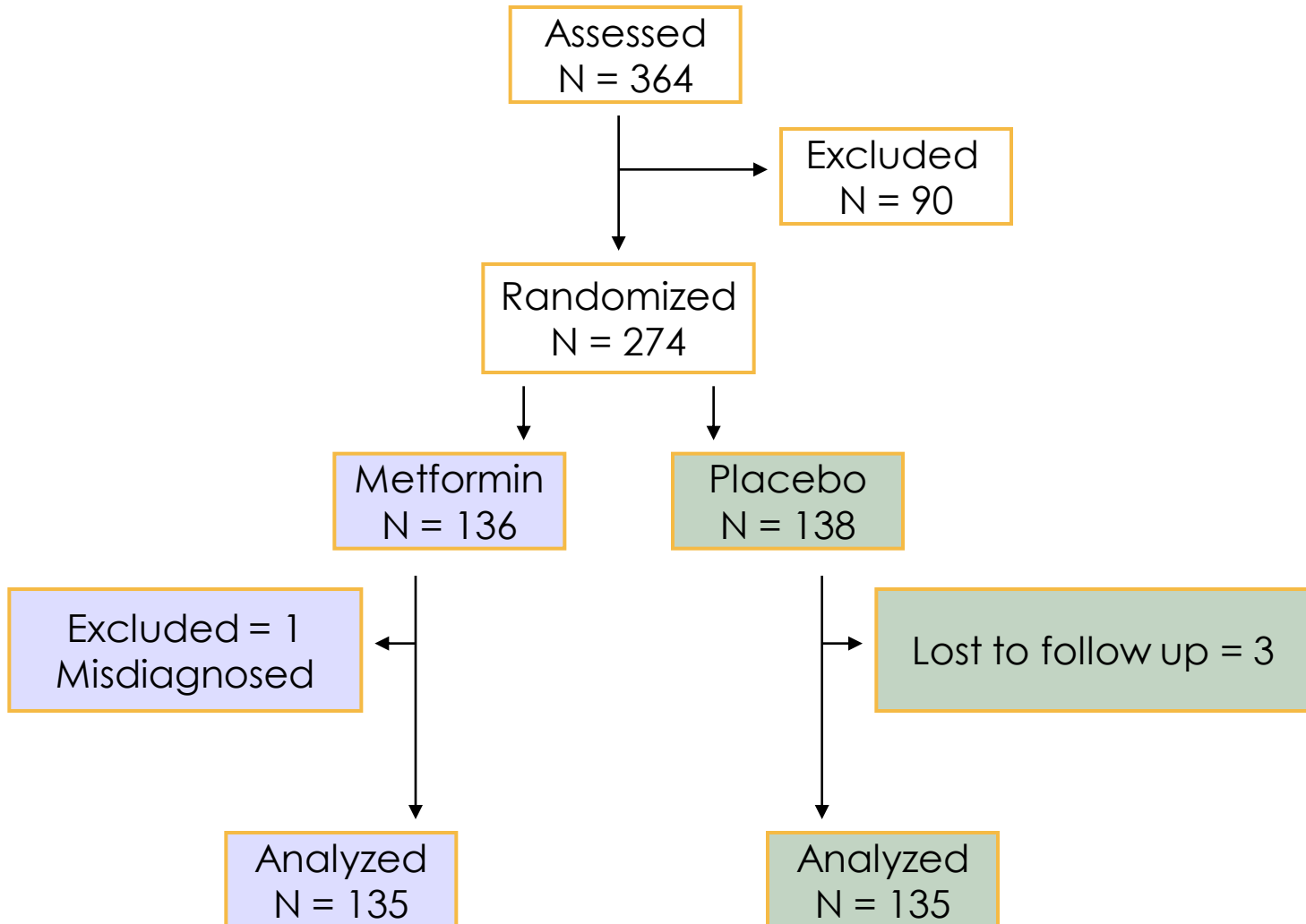


1 tablets x 2 daily for 1st week
2 tablets x 2 daily until delivery



The PregMet study

February 2005 – August 2009



The PregMet study

Results



At inclusion	Metformin N = 135	Placebo N = 138
Age (yrs)	29.6 (4.4)	29.2 (4.4)
BMI (kg/m ²)	29.5 (7.0)	28.5 (7.2)
Systolic BP (mmHg)	119 (12)	118 (11)
Diastolic BP (mmHg)	74 (12)	73 (10)
Gestational age (days)	74 (13)	75 (11)
GDM at inclusion (%)	10 (7)	13 (9)

The PregMet study

Results



	Metformin N = 135	Placebo N = 138
Metformin use at conception (%)	45 (33)	42 (30)
Mode of conception		
Spontaneous (%)	77 (57)	80 (58)
Clomiphen stimulation (%)	40 (30)	31 (23)
IVF/ICSI (%)	18 (13)	22 (16)
Parity 0 (%)	77 (57)	77 (56)
1+ (%)	58 (43)	61 (44)
NIH criteria met (%)	86 (64)	88 (64)
Only Rotterdam criteria met (%)	49 (36)	50 (36)
Smoking (%)	14 (10)	9 (7)



The PregMet study

Results – primary endpoints



	Metformin N = 135	Placebo N = 135	95% CI	P-value
Preeclampsia	10/135 (7.4)	5/135 (3.7)	-1.7 to 9.2	0.18

The PregMet study

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The PregMet study

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New GDM	22/125 (17.6)	21/124 (16.9)	-8.6 to 10.2	0.87

The PregMet study

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The PregMet study

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Not what we
expected.....



The PregMet study

Secondary end point data



	Metformin	Placebo	P -value
Labour onset			0.52
Spontaneous	97/130 (75)	91/128 (72)	
Induced	33/130 (25)	37/128 (28)	
Mode of delivery			0.76
Vaginal	94/135 (70)	94/135 (70)	
Operative vaginal	12/135 (9)	15/135 (11)	
Caesarean section	29/135 (21)	26/135 (19)	

The PregMet study

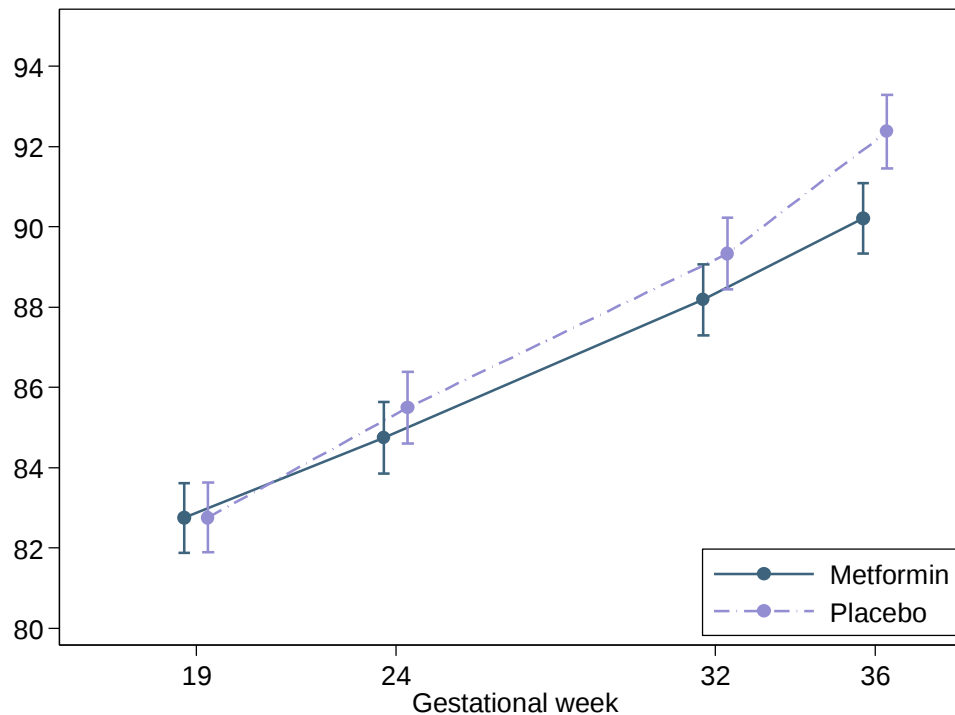
Neonatal outcomes



	Metformin	Placebo	P-value
Birth weight (g) (SD)	3550 (568)	3527 (615)	0.75
Length (cm)	50.3 (4.4)	50.0 (2.5)	0.44
Placenta weight (g)	666 (142)	673 (165)	0.74
Apgar <7 (%)			
1 min	8/135 (6)	7/135(5)	1.00
5 min	2/135 (2)	2/135 (2)	1.00
10 min	0/135 (0)	1/135 (1)	1.00
pH < 7.10 (%)	4/74 (6)	3/85 (4)	0.71
Weight			0.32
≤ 2500 (g) no.	8/135(6)	8/ 135 (6)	
2501 – 4500 (g) no.	125/135 (93)	120/135 (89)	
> 4500 (g) no.	1/135 (2)	7/135 (5)	

The PregMet study

Weight gain in pregnancy



- 2.2 kg
P = 0.001

The PregMet study

Other pregnancy outcomes



	Metformin	Placebo
Placental abruptions	1	1
Labor < 3 h	8	10
Prolonged 1 st *and 2 nd stage [†] labor	18	18
Severe perineal injuries	1	4
Post partum anemia	14	11
Post partum infections	3	3
Scar rupture	1	0
Other serious complications	3	0

The PregMet study

Other neonatal outcomes



	Metformin	Placebo
Asphyxia	3	6
Aspiration, respiratory failure	6	10
Neonatal icterus	8	13
Hypoglycemia	3	2
Cerebral irritability	1	1
Convulsions	0	2
Clavicle fracture	1	1
Neonatal sepsis	2	3
Other infections	3	4
Neonatal death	1	1

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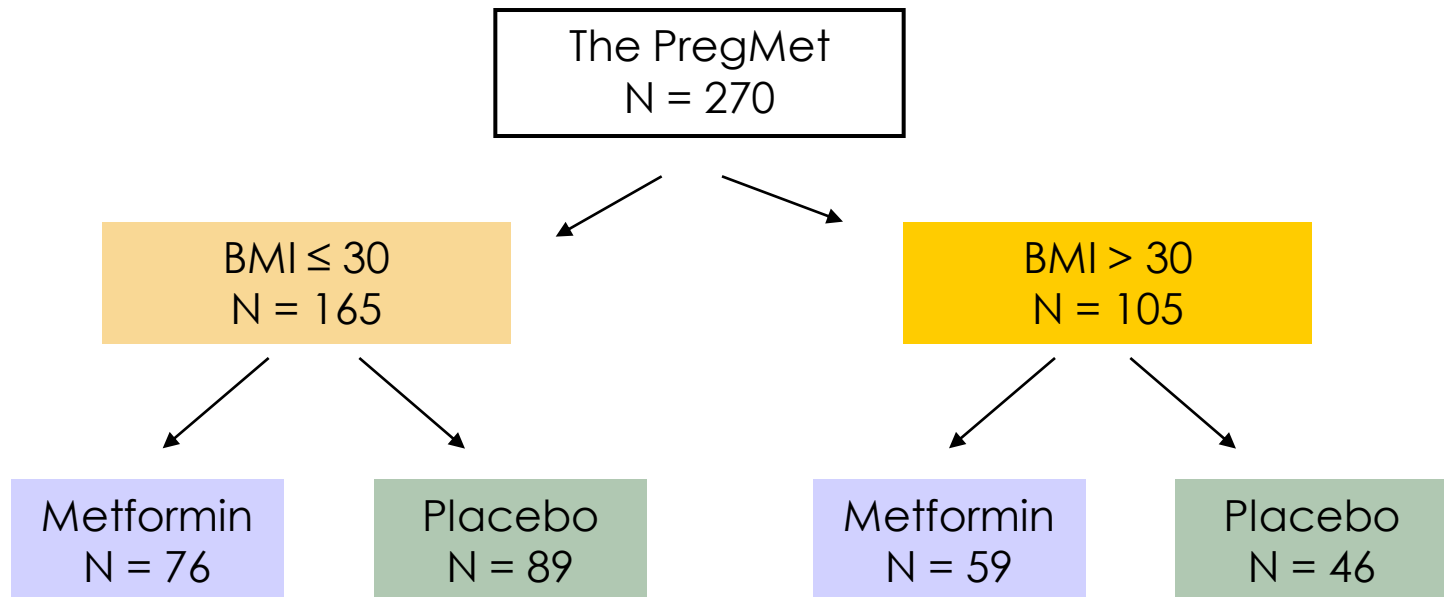
Newborn safety data



	Metformin	Placebo
Open ductus arteriosus	2	0
Pulmonary valve stenosis	1	0
VSD	1	0
ASD + VSD	0	2
Congenital foot deformities	3	0
Cryptorchidism	0	1
Hypospadias	0	1
Congenital urethral valve	0	1
Congenital ovarian cyst	0	1
Tongue tie	3	1

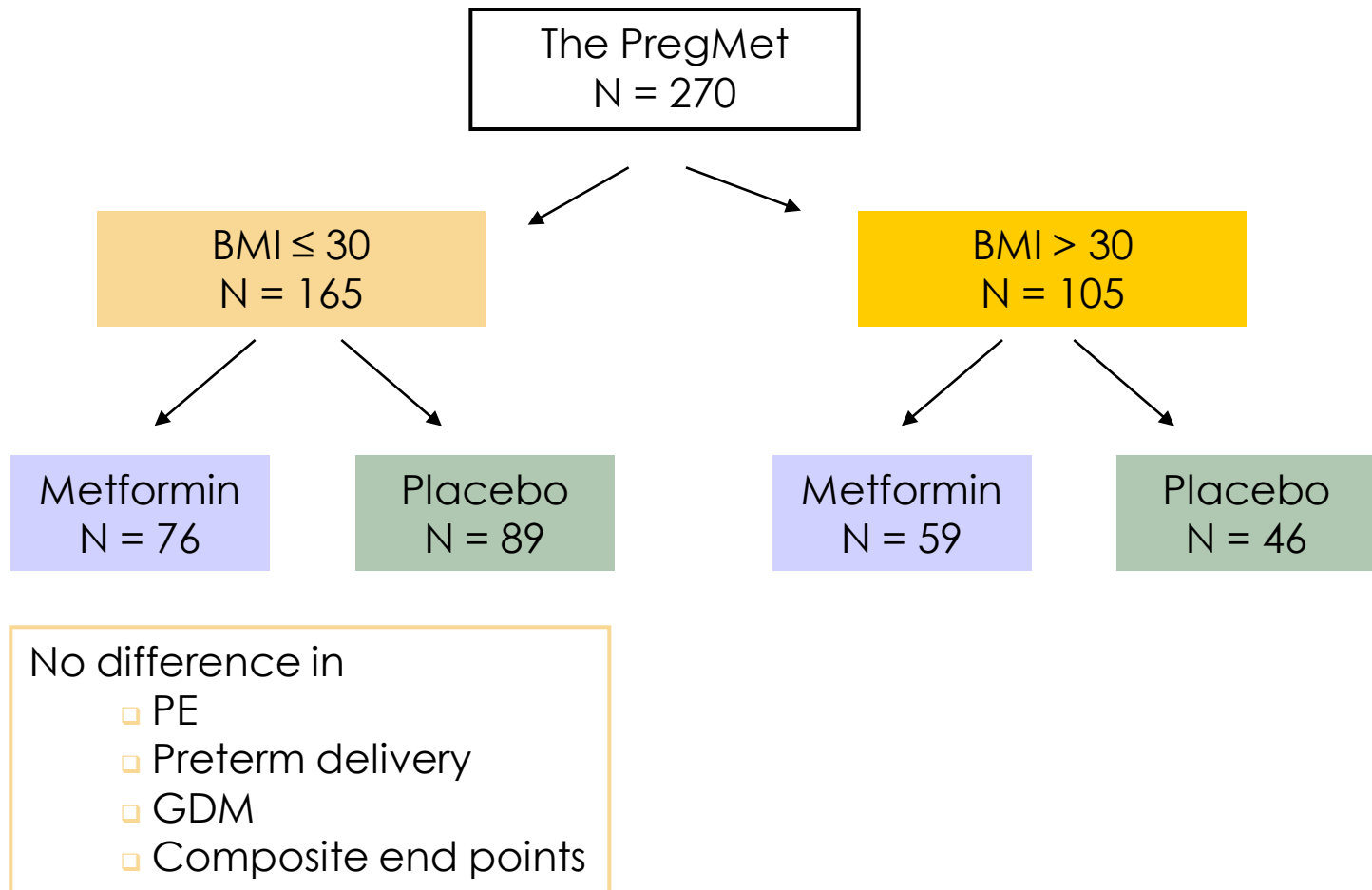
The PregMet study

Results – Subgroup analyses



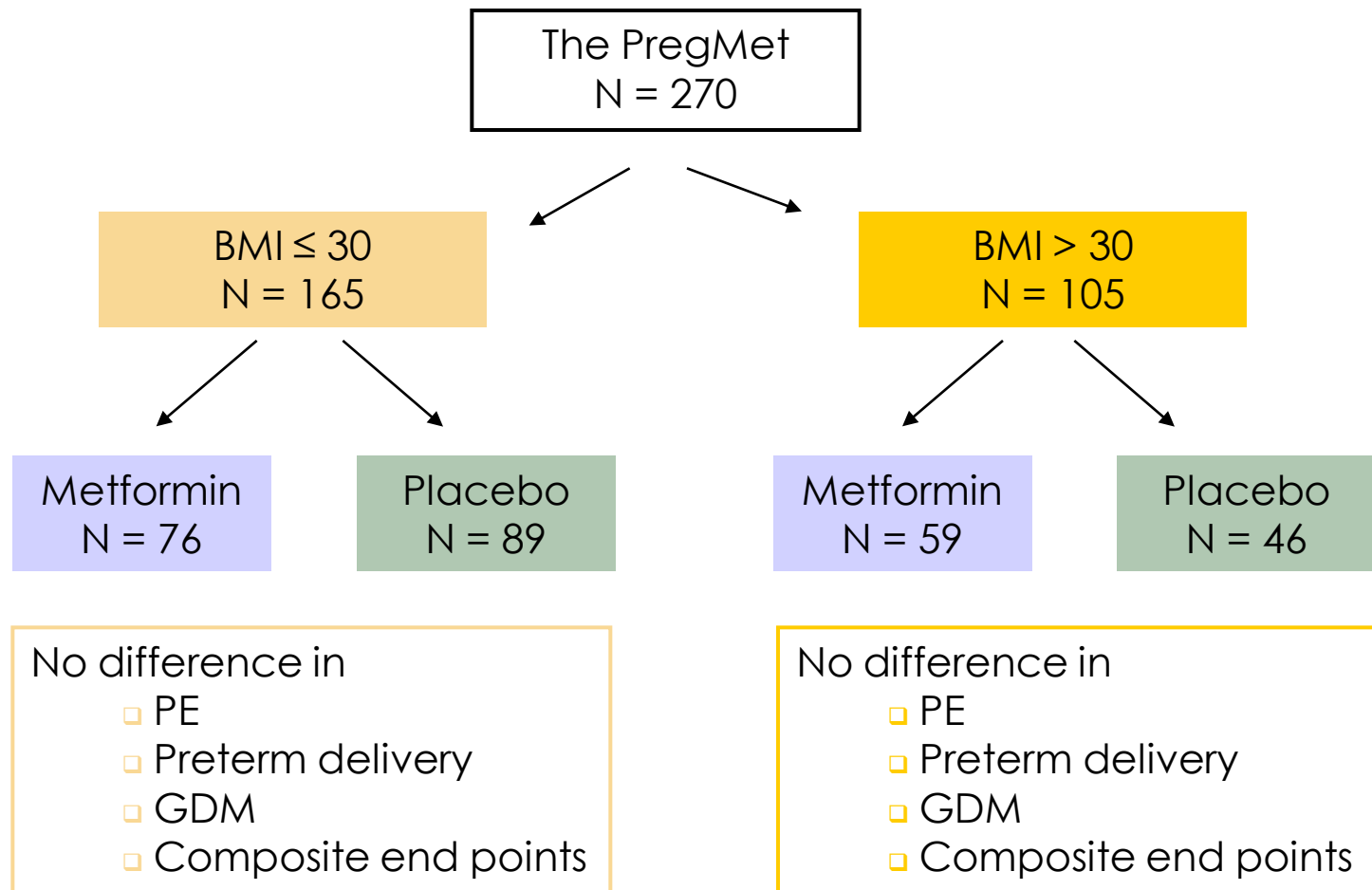
The PregMet study

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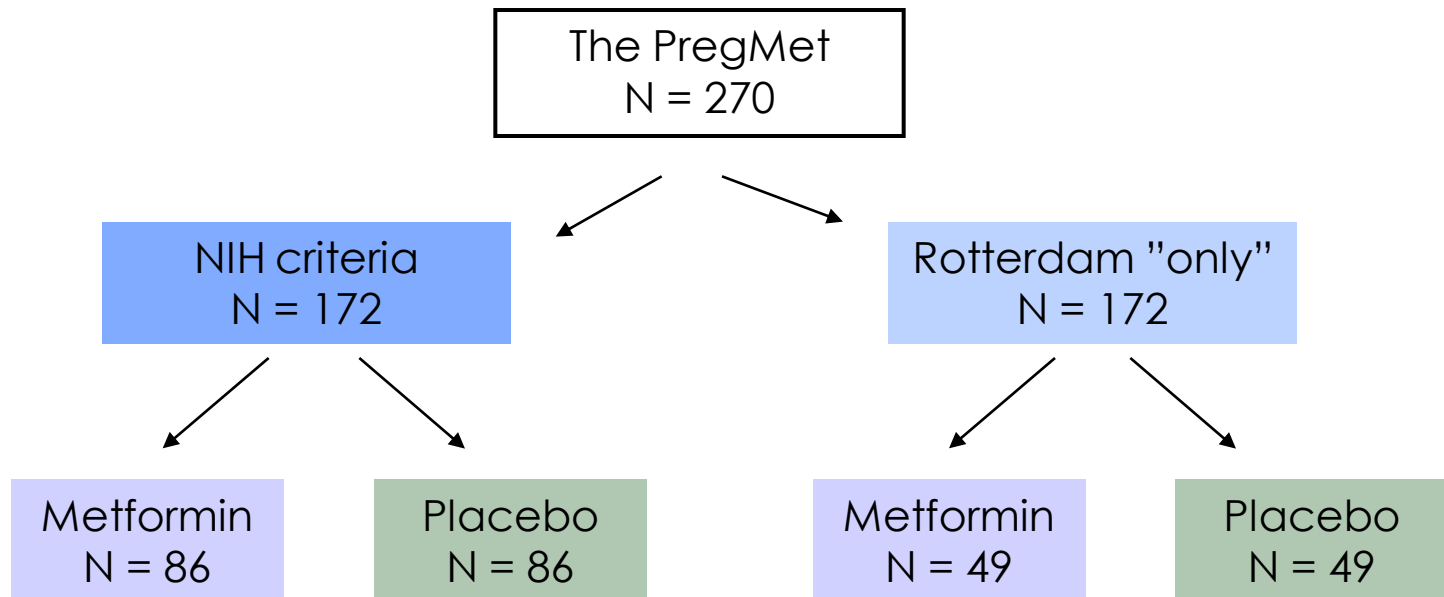
The PregMet study

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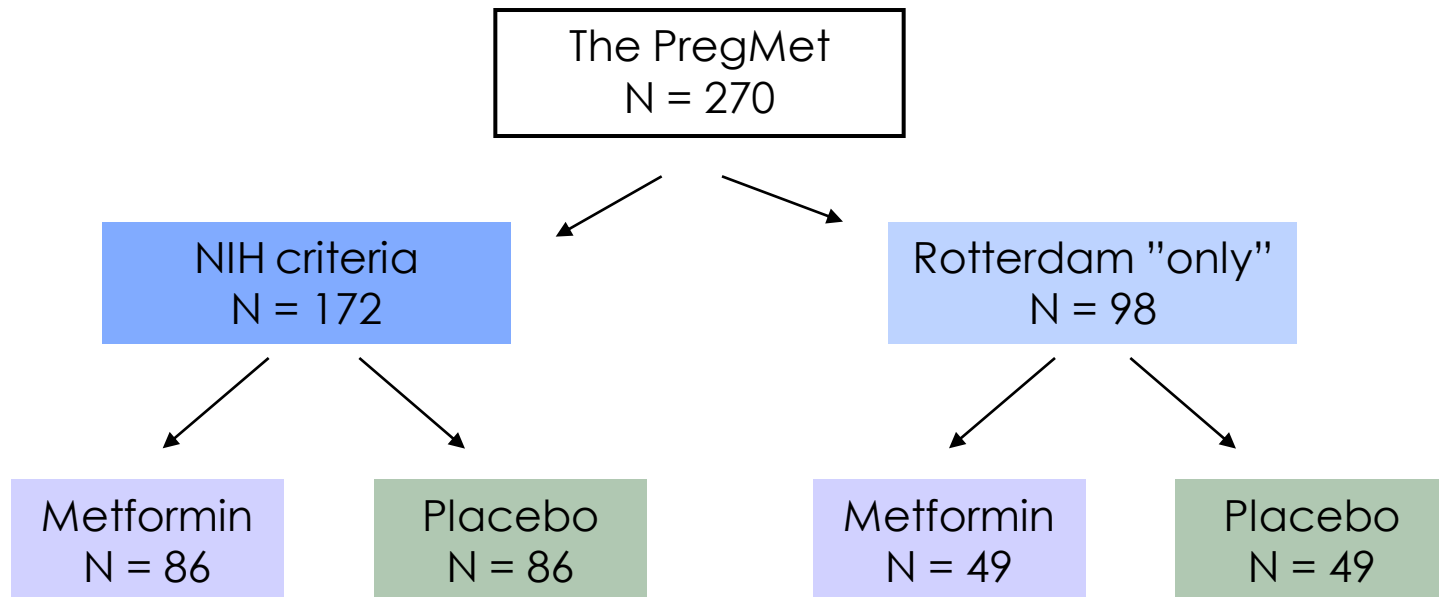
The PregMet study

Results – Subgroup analyses



The PregMet study

Results – Subgroup analyses



No difference in

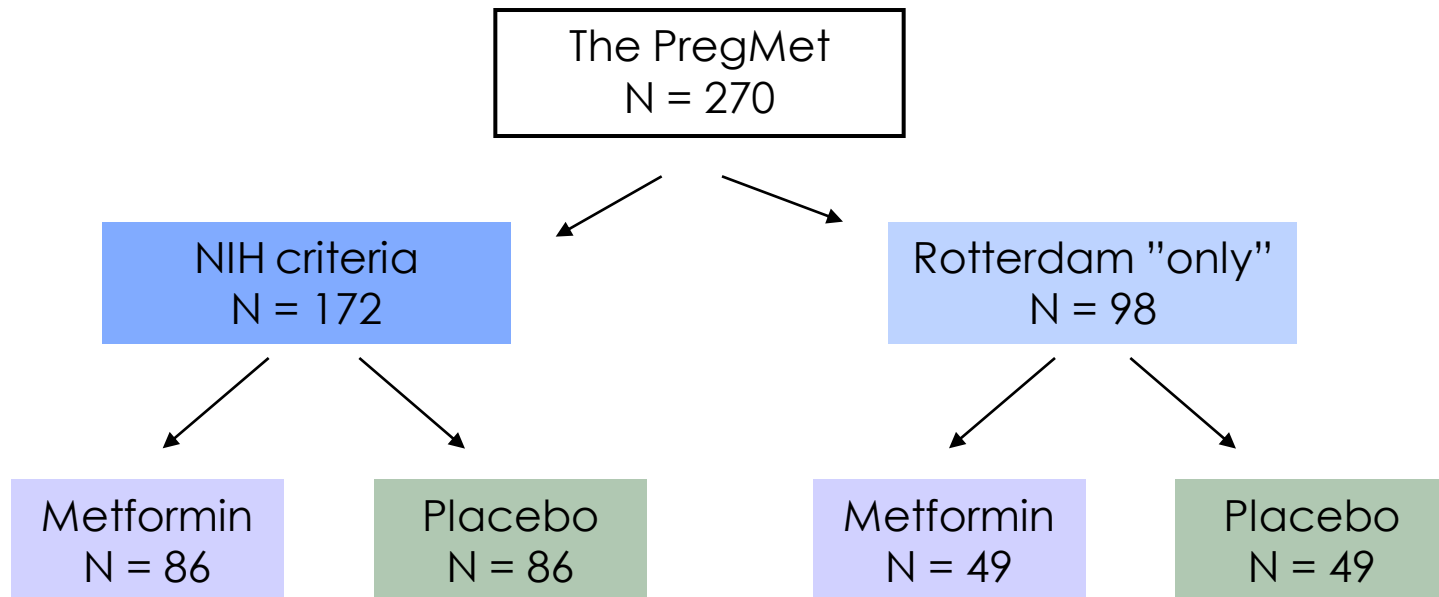
- PE
- GDM
- Composite end points

Less preterm in the metformin group

0 vs 4 P = 0.04

The PregMet study

Results – Subgroup analyses



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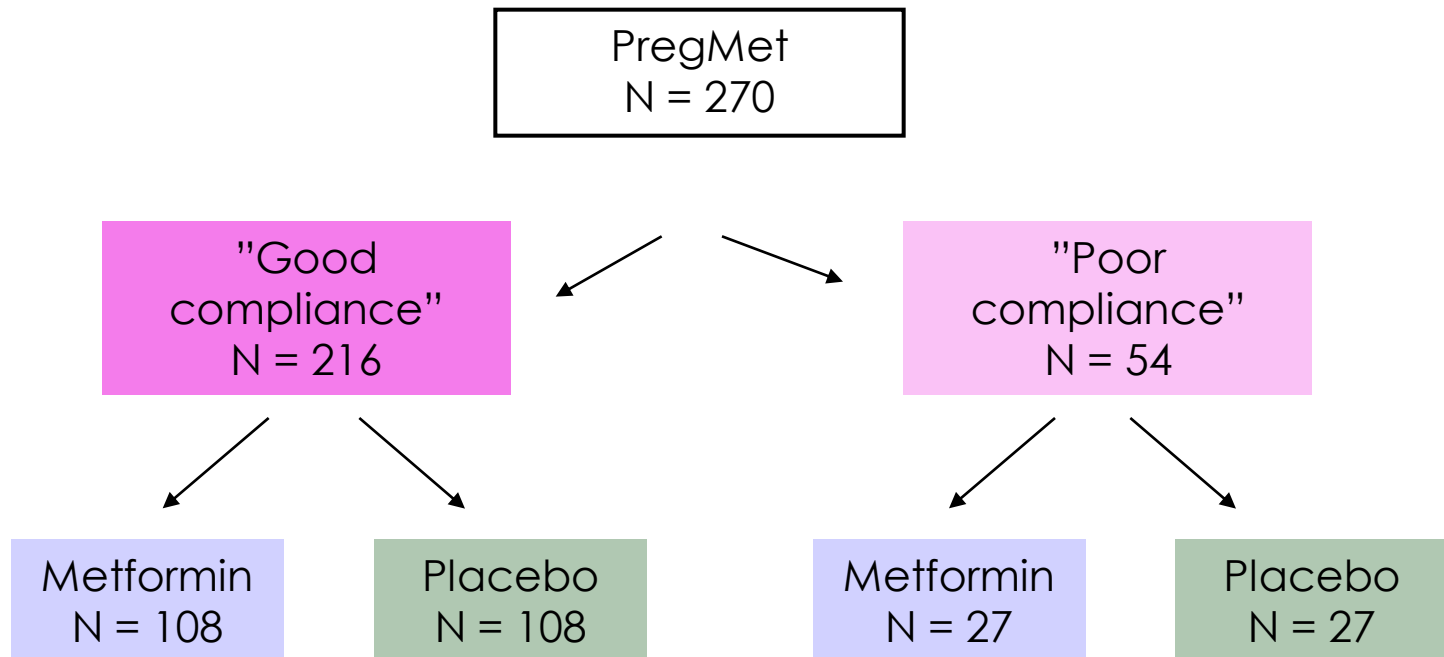
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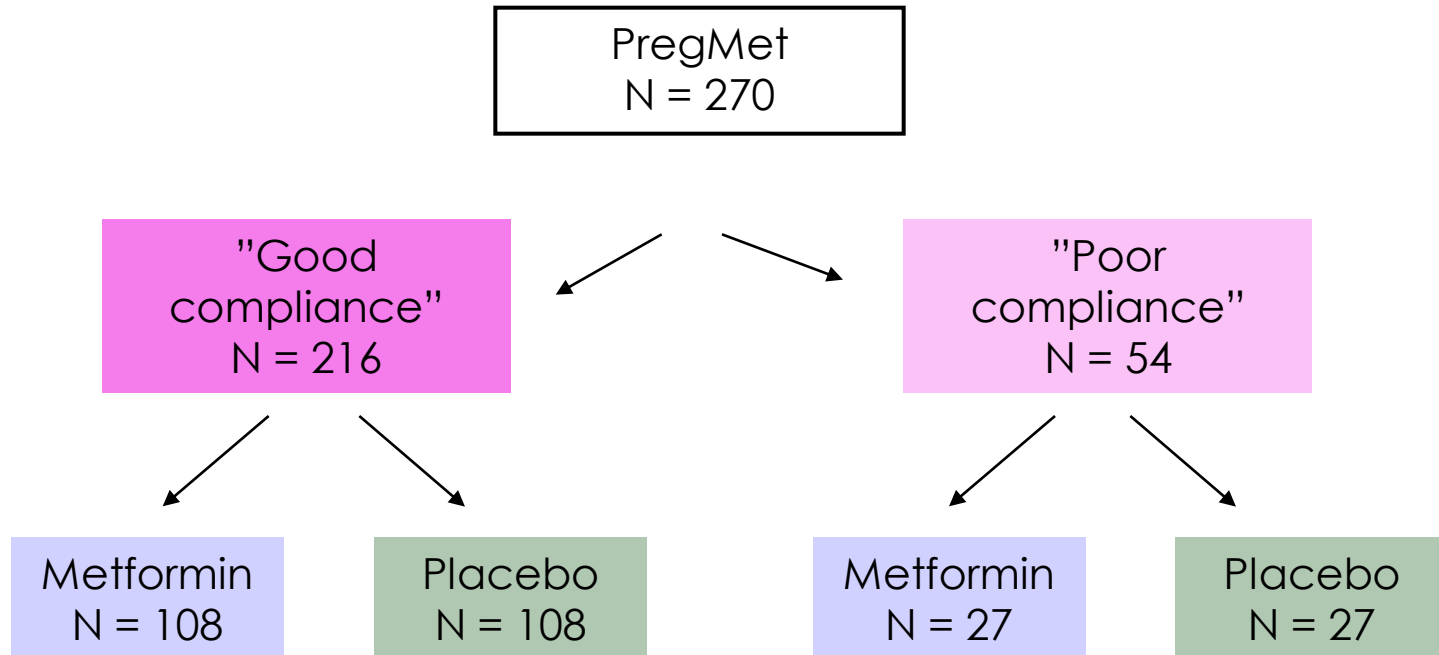
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Results – "per protocol analysis"



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Results – "per protocol analysis"



No difference in

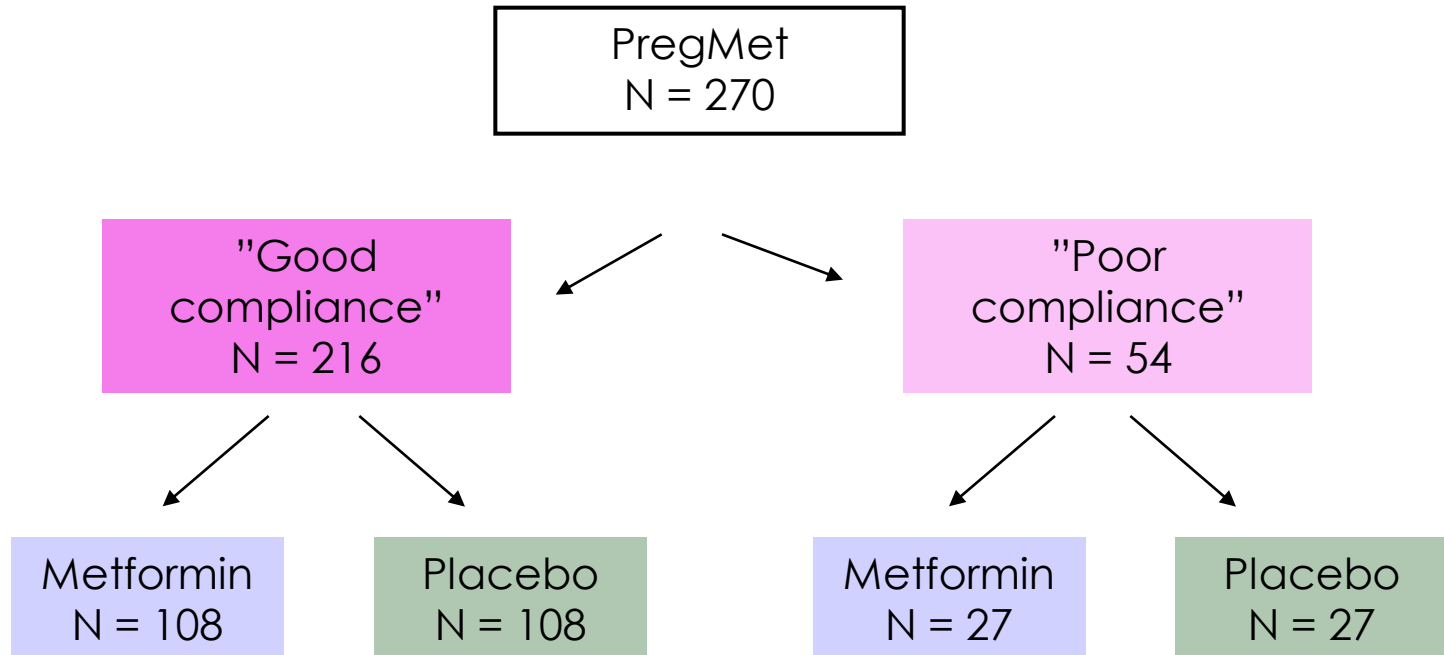
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PregMet studien

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Less preterm in the metformin group
3 vs 11 P = 0.04

No difference in

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The PregMet study

Conclusions

Metformin did not reduce the incidence of

- PE
- Preterm delivery
- GDM or
- The composite of these three

No difference between the groups in

- Secondary endpoint
- Neonatal data

Less weight gain in the metformin group

Subgroup of PCOS may benefit from metformin – more research needed



Metformin Versus Placebo from First Trimester to Delivery in Polycystic Ovary Syndrome: A Randomized, Controlled Multicenter Study

Eszter Vanky, Solhild Stridsklev, Runa Heimstad, Pål Romundstad, Kristin Skogøy, Odrun Kleggetveit, Sissel Hjelle, Philip von Brandis, Torunn Eikeland, Karin Flo, Kristin Flaten Berg, Gabor Bunford, Agnethe Lund, Cecilie Bjerke, Ingunn Almås, Ann Hilde Berg, Anna Danielson, Gulim Lahmami, and Sven Magnus Carlsen*

No evidence for metformin treatment
of PCOS women during pregnancy



How to take care of the pregnant PCOS woman - suggestions



- ❑ Weight reduction before pregnancy
- ❑ 30 min physical activity /day
- ❑ No soft drinks!
- ❑ 5 meals/day
- ❑ Weight control during pregnancy (max 8-12 kg gain)
- ❑ OGTT in the I. trimester and early III. trimester
- ❑ Growth assessment at week 32 by ultra sound

Thanks to all
co-authors and co-workers
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The PregMet study

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Anna
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Lillehammer

Gulim
Lahmami
Bergen

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Placebo – good compliance

Metformin – good compliance

- Second trimester abortions and preterm deliveries
Gestational week:

PregMet study

17
21
30
31
32
32
34
34
34
35
36
36
36

- Second trimester abortions and preterm deliveries
Gestational week:

PregMet study

35
36
36





St. Olav's Hospital, University Hospital of Trondheim
Institute of Laboratory Medicine, Children's and Women's Health



The PregMet study

Side effects

- ❑ Nausea
- ❑ Vomiting
- ❑ Diarrhea
- ❑ Bloating
- ❑ Abdominal pain
- ❑ Metal taste

In the metformin group, at
all time points:

More diarrhea
 $P < 0.003$





Incidence in The PregMet study

- Preeclapmsia = 5.6%
- Preterm delivery = 5.9%
- GDM = 24%
- Smoking = 8.4%

Parity

- 0 = 59%
- 1 = 32%
- 2+ = 9%

Incidence in Norway (Medical Birth Registry 2005-2008)

- Preeclapmsia = 3.7%
- Preterm delivery = 6.3%
- GDM = 1.1%
- Smoking = 17%

Parity

- 0 = 42%
- 1 = 35%
- 2+ = 23%

The PregMet study

Compliance

- ❑ Good compliance = 78%

Medication taken as intended

- ❑ Acceptable compliance = 6%

1-2 tablets for max of 4 weeks or

No tablets for max 2 weeks

- ❑ Poor compliance = 16%

1-2 tablets more than 4 weeks or

No tablets more than 2 weeks



The PregMet study

Summary II



No difference in the metformin and placebo group in

- ❑ Blood pressure development
- ❑ Labour onset
- ❑ Mode of delivery
- ❑ Neonatal outcomes
- ❑ Other maternal outcomes
- ❑ Safety data

No difference in serious side effect

- ❑ More diarrhea in the metformin group

PCOS - pregnancy outcome



PCOS vs normal women: meta – analysis

❑ Miscarriage	× 2 - 4
❑ Gestational diabetes	× 3
❑ Hypertention in pregnancy	× 3 - 4
❑ Preeclampsia	× 3 - 4
❑ “Small for gestational age”	× 2
❑ Preterm delivery < week 37	× 1.5 - 2
❑ Transferred to NICU	× 2 - 2.5
❑ Perinatal mortality	× 3

Boomsma CM. Hum Reprod Update, 2006

