

Metformin in PCOS pregnancies

Implications for the children

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Conclusion

- Children exposed to metformin in utero had increased risk of obesity and central adiposity
- The metformin effect was more pronounced when mothers had high pre-pregnancy BMI
- Our results endorse cautious use of metformin in PCOS pregnancies

Background

Metformin is increasingly used in pregnancy; in polycystic ovary syndrome (PCOS), GDM and obesity
It passes the placenta, with limited information on consequences for the offspring

Aim: to explore possible effects of intrauterine metformin exposure on metabolic health, in children of women with PCOS



Method

Follow-up of 141 children from the PregMet-study¹, an RCT comparing metformin (2000 mg daily) to placebo during PCOS pregnancies

- Primary end-point: age-and-gender adjusted BMI
- Secondary end-points: other age-and-gender adjusted anthropometric measurements, bioimpedance measurements, BMI categories, blood lipids, fasting glucose, HbA1c and blood pressure

Anthropometric measurements were converted to z-scores^{2,3}

Results

Mean age at inclusion was 7.4 ± 1.2 SD in the placebo group and 7.6 ± 1.3 SD in the metformin group

Metformin exposed children had higher BMI z-score, waist-to-height ratio z-score and waist circumference z-score

There was no difference in biochemical analyses or blood pressure

The effect of metformin on offspring BMI z-score increased by 0.05 SD (95% CI 0.00 to 0.11, $p=0.052$) with every unit increase in maternal pre-pregnancy BMI

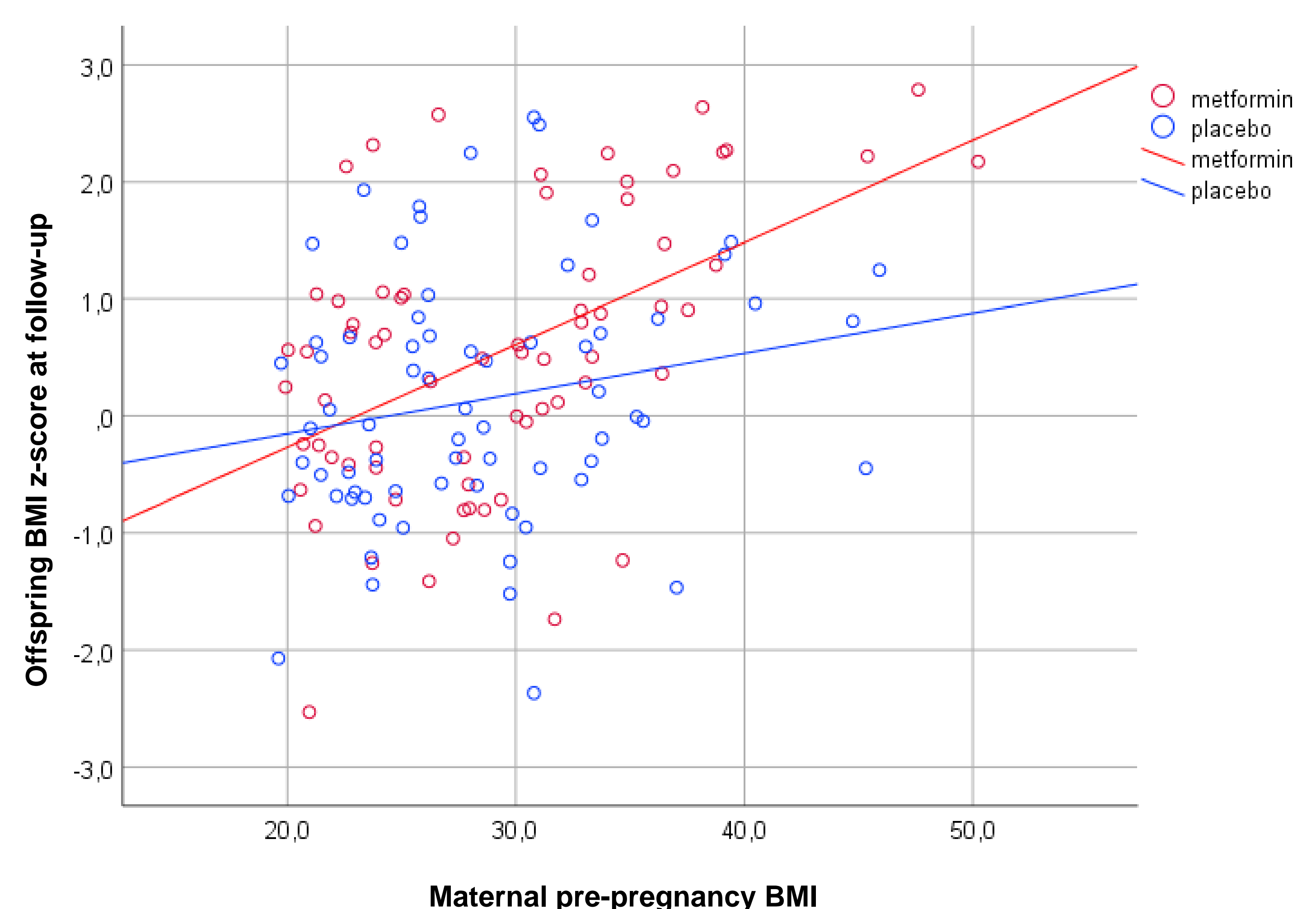
Body composition, biochemical markers and blood pressure of metformin and placebo exposed offspring

	Metformin, n=69 Mean (95% CI)	Placebo, n=70 Mean (95% CI)	P
Anthropometry			
BMI z-score	0.54 (0.26-0.83)	0.14 (-0.12-0.39)	.03
Waist-to-height ratio z-score	0.81 (0.57-1.06)	0.45 (0.27-0.64)	.02
Waist circumference z-score	0.83 (0.59-1.08)	0.43 (0.23-0.64)	.01
Weight z-score	0.53 (0.25-0.80)	0.10 (-0.18-0.38)	.03
Height z-score	0.19 (-0.05-0.42)	0.03 (-0.23-0.28)	.36
Bioelectrical impedance			
Muscle mass (kg)	11.13 (10.2-12.1)	10.50 (9.8-11.2)	.29
Body fat (kg)	6.84 (5.3-8.4)	5.05 (4.2-5.9)	.05
Body fat (%)	21.64 (18.9-24.4)	18.59 (16.3-20.9)	.09
Biochemical analyses			
Cholesterol (mmol/l)	4.14 (3.98-4.29)	4.15 (4.00-4.30)	.91
Triglyceride (mmol/l)	0.63 (0.57-0.68)	0.60 (0.53-0.66)	.45
HDL cholesterol (mmol/l)	1.59 (1.51-1.68)	1.59 (1.49-1.70)	.97
Fasting glucose (mmol/l)	4.71 (4.59-4.83)	4.91 (4.54-5.28)	.29
HbA1c (%)	5.06 (5.01-5.10)	5.11 (4.97-5.25)	.42
Blood pressure			
SBP (mmHg)	104 (102-106)	103 (101-105)	.51
DBP (mmHg)	65 (64-67)	65 (63-67)	.76
BMI categories n (%)			
Underweight grade 2	1 (1.4)	1 (1.4)	.99
Underweight grade 1	1 (1.4)	2 (2.9)	.57
Normal weight	45 (65.2)	53 (75.7)	.17
Overweight	8 (11.6)	11 (15.7)	.48
Obesity	12 (17.4)	1 (1.4)	.001
Morbid obesity	2 (2.9)	2 (2.9)	.99
Metabolically abnormal overweight/obese n (%)	5 (8.3)	0 (0.0)	.06

Maternal baseline characteristics

	Metformin n=67 Mean±SD	Placebo n=67 Mean±SD
Age (years)	29.5 ± 3.9	30.1 ± 4.1
BMI (kg/m ²)	28.8 ± 6.8	28.5 ± 6.3
Systolic blood pressure (mmHg)	118 ± 12	118 ± 12
Fasting plasma glucose (mmol/L)	4.6 ± 0.5	4.7 ± 0.6
2 h plasma glucose (mmol/L)	5.3 ± 1.5	5.4 ± 1.7
Cholesterol (mmol/L)	4.8 ± 1.1	4.4 ± 0.7
High Density Lipoprotein (mmol/L)	1.6 ± 0.4	1.6 ± 0.3
Triglycerides (mmol/L)	1.2 ± 0.5	1.1 ± 0.5
Smoking (%)	4 (6.0)	3 (4.6)

No difference (p -value < 0.05) between the groups, except cholesterol ($p=0.009$)



Scatterplot on the association between maternal pre-pregnancy BMI and offspring BMI z-score at follow-up

¹Vanky E, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab.* 2010;95(12):E448-455

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