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Maria Othelie Underdal MD, Solhild Stridsklev MD PhD, Ingrid Hennum Oppen MD, Kristin Høgetveit MD, Marianne Skovsager Andersen MD PhD DMSciand Eszter Vanky MD PhD

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Maria Othelie Underdal MD[1,2], Solhild Stridsklev MD PhD[1,2], Ingrid Hennum Oppen MD[4], Kristin Høgetveit MD[4], Marianne Skovsager Andersen MD PhD DMSci[3*] and Eszter Vanky MD PhD[1,2*]

*[1]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway and [2]Department of Obstetrics and Gynecology, St. Olavs Hospital, University Hospital of Trondheim, Trondheim, Norway, [3]Department of Internal Medicine, Odense University Hospital, Odense, Denmark and [4]Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway *Shared last authorship*

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ORCID ID: https://orcid.org/0000-0002-9027-558X

Context

Worldwide, metformin is prescribed in an attempt to improve pregnancy outcome in PCOS. Metformin may also benefit future health by modulating the increased metabolic stress during pregnancy.

Objective

To investigate if metformin during pregnancy modified future metabolic health in women with PCOS.

Design

Follow-up study of a randomized controlled trial, which compared metformin to placebo in women with PCOS. Mean follow-up period was 8 years (5-11).

Setting

Three university hospitals, seven local hospitals, and one gynecological specialist practice.

Participants

Women with PCOS according to Rotterdam criteria, all former participants in the PregMet study.

Intervention

Metformin 2000 mg daily or placebo from 1st trimester to delivery in the original study. No intervention in the present follow-up study.

Main outcomes and measures

Main outcome measure was weight-gain in the follow-up period. Weight, body mass index, waist and hip circumferences and blood pressure were registered. Body composition was assessed by bioelectrical impedance analysis, and fasting lipids, glucose and insulin were analysed.

Results

131 out of 239 (55%) invited women participated in the follow-up. Weight gain was similar in women given metformin (2.1±10.5) and women given placebo (1.8±11.2) at 7.7 years follow-up after pregnancy (p-value=0.834). No difference was found between those treated with metformin and placebo during pregnancy in BMI, waist/hip ratio, blood pressure, body composition, lipids, glucose and insulin levels or prevalence of metabolic syndrome at follow-up.

Conclusion

Metformin treatment during pregnancy did not influence the metabolic profile in women with PCOS at 7.7 years of follow-up.

Women with PCOS have increased risk of metabolic disturbances. Treatment with metformin during pregnancy did not alter metabolic parameters in this high risk group at 8 years postpartum. .

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in young women (1). The prevalence of PCOS using the Rotterdam criteria is estimated to 10-14 % in the general population (2, 3). Implications of the syndrome are multifaceted and PCOS is associated with metabolic impairment and increased risk of pregnancy complications. Data from meta-analyses show a threefold increase in gestational diabetes mellitus (GDM) among women with PCOS (4-6).

Pregnancy entails metabolic and homeostatic alterations and a physiological increase of insulin resistance, particularly during the third trimester. In a large cohort of women, a history of pregnancy complications such as preeclampsia, gestational diabetes and giving birth to a small for gestational age infant, were indicators of an increased risk of cardiovascular disease later in life (7). Awareness of these trajectories provides an opportunity for early identification of women at risk. Excessive weight gain in pregnancy has a negative impact on obstetric outcome (8-10). Women with high gestational weight-gain have a threefold increased risk of being overweight at first prenatal visit in a consecutive pregnancy compared to women with normal or low gestational weight gain (11). Excessive post-partum weight retention at the end of the first year post-partum is a predictor for being overweight 15 years later (12). We have previously reported that women with PCOS randomized to metformin 2g/day gained less weight during pregnancy (13).

Insulin resistance, although not a criteria for PCOS, affects the majority of women with the syndrome. Among hirsute women with PCOS in a Danish cohort, increased fasting insulin was found in 28% of women with body mass index (BMI)≤25, and 74% of women with BMI>25 (14). Hyperandrogenism seems to worsen insulin resistance in PCOS; with insulin resistance found in 43% of hyperandrogenic compared to 14% of normo-androgenic women (15).

Metformin is a multipotent drug which exerts its effect on several tissues sensitive to insulin, such as liver, skeletal muscle and adipose tissue. The Endocrine Society guideline on PCOS suggests lifestyle interventions such as physical exercise and weight loss as primary treatment of overweight and obesity in PCOS. Metformin is recommended as second line treatment when type 2 diabetes mellitus (DM) or impaired glucose tolerance (IGT) is present and lifestyle intervention is insufficient to improve metabolic dysfunction. In addition, metformin is recommended in women with PCOS for menstrual irregularity, where treatment with hormonal contraceptives are contraindicated or not tolerated (16). Worldwide, metformin is prescribed in first trimester and onwards in an attempt to improve pregnancy outcome in PCOS. Metformin may also benefit future maternal health by modulating the increased metabolic stress during pregnancy

To our knowledge, prospective data regarding post-partum metabolic health in women with PCOS, has not been published. In the present study, we aimed to explore possible effects of metformin treatment in pregnancy on long-term metabolic health.

2. Materials and Methods

The present study is a follow-up of a randomized, controlled, double blind, multicenter trial. Eligible for participation in the follow-up were mothers who participated in “The Metformin in Pregnant PCOS women study” (the PregMet study) (17) from 2005-2009. Women with PCOS were randomized to metformin or placebo from first trimester to delivery, to assess if metformin could reduce pregnancy complications.

A. Study design

1. The PregMet study:

In all, 257 women with 274 pregnancies were included at 11 study centers in Norway: three university hospitals, seven local hospitals, and one gynecological specialist practice. Randomization, blinding and examinations are described elsewhere (17). Inclusion criteria for the PregMet-study were: 1) PCOS diagnosed according to the Rotterdam criteria (3) 2) age 18-45 years 3) gestational age between 5-12 weeks and 4) a singleton, viable fetus shown on ultrasonography. The participants received counseling on lifestyle and diet at inclusion, before randomization to metformin (2g/day) or placebo. To counteract possible metformin effects on folate or vitamin B12 levels, the participants were advised to take 0.8 mg folate and one multivitamin tablet daily, throughout pregnancy.

2. The follow-up study:

From April 2014 to July 2016, 239 women were invited to the follow-up. Inclusion criteria: participation in the PregMet study. Exclusion criteria: ongoing pregnancy and breast-feeding. (Figure 1.) Participants who dropped out (n=12), miscarried (n=3) or lost their children (n=3) were not invited. Seventeen of the women participated twice in the PregMet study. When women participated twice and were randomized equally, data from the first participation was recorded, if they were randomized once to metformin and once to placebo, the data from the metformin-exposed pregnancy was used. Non-responders received two reminders, about 1-2 months and 6-7 months, after the first letter. In all 131 (55%) women agreed to participate in the follow-up. One hundred seventeen women met for physical examination and interview, while 14 were interviewed by phone and gave self-reported data. Two medical students and a trained midwife examined the participants and collected the data. Standardized interviewer-administered questionnaires were used to obtain self-reported data on former medical and gynecologic/obstetric history, contraceptives, ethnicity, education, civil status, smoking, physical activity and current use of metformin.

Blood pressure was measured three times, two minutes apart with digital devices, with participant in sitting position after at least 15 minutes of rest in a chair. The mean of the second and third measurements was calculated. Height, waist and hip circumference were measured manually and rounded off to closest 0.5 cm. Body composition and weight were measured using bioelectrical impedance (Inbody 720, BIOSPACE, Seoul, Korea). The examination was performed with participant wearing light and snug clothes, and no shoes. InBody gives an estimate of total body fluids, proteins, minerals and fat and is validated against DEXA scan.

Blood samples were drawn from an antecubital vein between 0800 and 1100h after an overnight fast. All analyses except insulin were performed directly, using standard procedures at St. Olavs Hospital, Trondheim, Norway. Insulin was analyzed at Aker, Oslo University Hospital. Homeostatic model assessment (HOMA) index was computed as (fasting glucose mmol/L x fasting insulin concentration mU/L) ×/22.5. HOMA-beta was calculated using the following formula: 20 × fasting insulin (mU/L)/fasting glucose (mmol/L) − 3.5. The prevalence of metabolic syndrome (MetS) was estimated according to the Rotterdam consensus (3). Three out of the following five criteria are required: waist circumference >88 cm, triglycerides ≥150 mg/dL (1.7 mmol/L), high-density lipoprotein (HDL) ≤ 50 mg/dL (1.3 mmol/L), systolic blood pressure (BP) ≥130 mm Hg and/or diastolic BP ≥85 mm Hg, and fasting glucose 110–126 mg/dL (6.11–6.99 nmol/L) and/or 2-hour oral glucose tolerance test glucose ≥ 140–199 mg/dL (7.78–11.04 nmol/L). The more widely applicable guideline, National Cholesterol Education Program – Adult Treatment Panel III definition, requires the presence of at least three out for the following five criteria: waist circumference >88cm, triglycerides ≥150mg/dL (1.7mmol/L) or drug treatment for elevated triglycerides, HDL ≤50 mg/dL (1.3 mmol/L) or drug treatment for reduced HDL cholesterol, systolic BP ≥ 130mmHg and/or diastolic BP ≥ 85mmHg or treatment for elevated BP, and fasting glucose ≥ 100mg/dL (5.6 nmol/L).

Participants were asked if they were diagnosed with diabetes mellitus type 2, hypertension, coronary heart disease or depression.

B. Statistical analyses

Statistics were performed with SPSS version 24 (SPSS Inc., USA). Data were reported as mean ± standard deviation SD or absolute numbers (percentages). Differences between study groups were assessed with two-tailed t-tests for independent samples. Fisher`s exact test was used for evaluation of discrete data. To adjust for multiple testing, we considered significance as a two-tailed p-value < 0.01.

C. Ethical approval

Written informed consent was obtained from each participant before inclusion and the declaration of Helsinki was followed throughout the study. The Regional Committees for Medical and Health Research Ethics REK Midt approved the present study 04.04.2014, reference number: 2014/96.

3. Results

In all, 131 out of 239 (55%) invited participants in the PregMet study agreed to participate in this follow-up. The only difference between the metformin and the placebo group at baseline, (at inclusion in the PregMet study), was lower total cholesterol level in the placebo group (Table 1). Women who participated in the follow-up and those who declined were comparable at baseline, except for a tendency of more smokers among those who declined, 15 vs. 7 (*p=0.051*) (data not shown). In the PregMet study, 80% of the participants took more than 85% of the study medication.

Education level, civil status and parity were similar in both groups at follow-up (Table 3). We found no difference in weight-gain (from first trimester of pregnancy to follow-up), BMI, waist/hip ratio, blood pressure, body composition, fasting lipids, fasting glucose or HOMA-index when comparing metformin to placebo treated women at follow-up. Prevalence of metabolic syndrome, type 2 DM, hypertension, coronary heart disease (CVD) and depression were comparable between the metformin and placebo group. Participants with hyperandrogenism were comparable to those without hyperandrogenism regarding waist circumference, blood pressure, fasting lipids, glucose and HOMA-index (data not shown).

4. Discussion

Metformin-use from first trimester and throughout pregnancy did not modify maternal metabolic profile at 7.7 years post-partum. Postpartum yearly weight increase in women with PCOS was relatively low, independent of randomization.

A. Strengths of the study

This is the first study to prospectively assess long-term metabolic profile in a well-characterized cohort of women with PCOS after randomization to metformin or placebo treatment during pregnancy. Participants in the follow-up were representative of the original study population.

B. Limitations of the study

Participants in this follow-up were relatively young to experience serious complications of the metabolic syndrome such as CVD. Risk factors of CVD may occur at this age, and may potentially be modified by metformin intervention. A 55% participation rate is less than we hoped for, but the percentage is in accordance with other clinical follow-up studies. Further assessment of glucose tolerance by an oral glucose tolerance test (OGTT) would be preferable, but was not possible due to limited recourses and practical reasons.

C. The metformin effect

We found no difference in weight gain from first trimester of pregnancy to current follow-up according to randomization. Women randomized to metformin, gained less weight during pregnancy than those randomized to placebo. However, maternal BMI-increase from first trimester to 1 year postpartum was higher in the metformin group (13), these findings may be explained by weight homeostasis mechanisms restoring pre-pregnancy weight (18).

Interestingly, the average annual weight-gain of 0.25kg/year (0.44 kg/year when 8 cases of bariatric surgery were excluded) in the follow-up period is relatively small in the present study compared to the background population. In a Norwegian population-based cohort (HUNT), mean 11-year weight-gain was 7.0 kg (0.64 kg/year) in the age group 30-39 years (19). A higher baseline weight (mean 80.0 kg) in women with PCOS, compared to the Norwegian cohort (mean 64.1 kg) may partly explain this observation. In an Australian community-based longitudinal cohort of women with PCOS in their 20ies, a 10-year weight-gain of 6.6 kg (0.66kg/year) is reported (20). Women participating in the present follow-up were older. A relatively small weight increase by age in women with PCOS from their 4th decade of life and onward might point to a different pattern of weight-changes through life in this group of women being more susceptible to weight-gain in adolescence and early reproductive years. Another possible explanation could be that all participants (metformin and placebo group) received counseling on lifestyle and diet when entering the original study. Both the counseling itself and the timing of it, in early pregnancy, might have had a lasting effect on life style and weight management.

Contrary to our assumptions, the lower weight gain and metformin treatment as such during pregnancy, did not affect maternal metabolic risk factors or lower the trajectory of insulin resistance 7.7 years postpartum. Women with PCOS are reported to have higher gestational weight-gain compared to controls (21). In non-obese women without PCOS, measurement of maternal insulin concentration in the upper quartile in early pregnancy was associated with increased gestational weight gain and higher postpartum weight retention (22). IR is reported to remain more pronounced 18 months post partum in women with PCOS compared to non-PCOS women with GDM (23). According to the “metabolic memory”-theory, early intensive glycemic control is proposed in patients with DM2, to prevent high plasma glucose levels from triggering the known mechanisms of endothelial damage such as oxidative stress, non-enzymatic glycation of proteins, epigenetic changes and chronic inflammation. In in-vitro studies, metformin, among other pharmaceutical interventions used to prevent long-term consequence of hyperglycemia, show a strong inhibitory effect on formation and accumulation of advanced glycation end products after non-enzymatic glycation (24). One could hypothesize that metformin, in addition to lowering gluconeogenesis, increasing peripheral glucose use and delaying glucose absorption, has beneficial effects in suppressing progression of hyperglycemia induced “metabolic memory” changes also during the pregnant state.

Participants in the PregMet-study were diagnosed according to Rotterdam criteria and 72% presented with a phenotype that included hyperandrogenism. Applying the original phenotyping from the PregMet-study to subdivide in hyperandrogenic vs. normo-androgenic women, no difference in metabolic risk factors were detected at follow-up (data not shown). The prevalence of MetS, type 2DM and CVD was low in the present study, as could be expected at mean 37 years. Data on the risk of hard end-points such as cardiovascular disease in post-menopausal women with PCOS is diverging, and some studies suggest protective factors are activated prohibiting increased CVD-risk factors to translate to CVD disease (25).

5. Conclusion

At follow-up 7.7 years postpartum, weight and metabolic health of women with PCOS were not influenced by metformin use in pregnancy. Weight increase in the 4th decade of life in women with PCOS was less than in the general population.

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Reprint requests should be addressed to the corresponding author.

Correspondence: Maria Othelie Underdal, MD. Department of Obstetrics and Gynaecology, St. Olavs Hospital. University Hospital of Trondheim, Olav Kyrres gt.16, 7006 Trondheim., Telephone numbers: +47 95112509, +47 72836176., Email address: maria.o.underdal@ntnu.no

Disclosure summary:
The authors declare no conflicts of interest in this work.

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Figure 1: Flow chart on randomization, dropouts and exclusion

Table 1 Baseline characteristics of participants (N=131) at 1st trimester of pregnancy in the PregMet study

	Metformin N=66	Placebo N=65
Age (years)	29.5±3.9	30.1±4.1
Weight (kg)	79.9±19.5	80.1±17.7
BMI (kg/m^2)	28.7±6.9	28.5±6.2
Systolic blood pressure (mmHg)	118±12	118±12
Diastolic blood pressure (mmHg)	73±10	72±10
Fasting glucose (mmol/L)	4.6±0.5	4.7±0.6
2-h glucose (mmol/L)	5.3±1.5	5.4±1.7
Cholesterol (mmol/L)	4.8±1.1	4.4±0.7
HDL cholesterol (mmol/L)	1.6±0.4	1.6±0.3
Triglycerides (mmol/L)	1.2±0.5	1.1±0.5
Hyperandrogenic phenotype n (%)	48 (72.7)	46 (70.8)
Normoandrogenic phenotype n (%)	18 (27.3)	19 (29.2)

Data presented as mean ± SD or n(%) as appropriate
Abbreviations: BMI, body mass index.

Table 2 Anthropometry and endocrine characteristics of women with PCOS at 5-11 year follow-up, categorized according to use of metformin or placebo during pregnancy

	Metformin N=66	Placebo N=65	p-value
Follow-up (years)	7.6±1.4	7.7±1.2	0.696
Age (years)	37.5±4.2	38.5±4.7	0.180
Weight (kg)	82.0±19.4	81.9±18.4	0.960
BMI (kg/m^2)	29.6±6.9	29.3±6.9	0.790
Δ weight: inclusion to follow-up (kg)	2.1±10.5	1.8±11.2	0.834
Δ weight per year: inclusion to follow-up (kg)	0.30±1.40	0.20±1.48	0.711
Waist (cm)	90.7±15.5	89.9±14.4	0.748
Hip (cm)	107.3±15.5	108.4±13.1	0.664
Waist/hip ratio	0.90±0.07	0.90±0.08	0.609
Waist >88cm n(%)	38 (59)	33 (52)	0.481
Body muscle mass (kg)	28.3±4.3	28.8±3.2	0.559
Body fat (kg)	31.6±15.0	33.8±16.7	0.521
Body fat (%)	36.4±9.4	37.6±10.1	0.575
Visceral Fat Area (cm^2)	128.4±64.1	135.6±72.3	0.637
Systolic blood pressure (mmHg)	119±14	119±14	0.817
Diastolic blood pressure (mmHg)	78±10	77±11	0.555
Fasting glucose (mmol/L)	5.1±0.5	5.2±0.7	0.329
Fasting insulin (μIU/ml)	10.8±7.5	12.0±7.6	0.437
HOMA-IR index	2.4±1.6	2.9±1.9	0.155
HOMA-β	1.3±0.7	1.4±1.1	0.886
c-peptide (nmol/L)	0.67±0.34	0.77±0.37	0.148
HbA1c (%)	5.2±0.26	5.2±0.45	0.624
Total cholesterol (mmol/L)	4.7±0.8	4.6±0.7	0.234
HDL cholesterol (mmol/L)	1.5±0.4	1.5±0.4	0.850
Triglycerides (mmol/L)	1.0±0.5	1.0±0.6	0.450
	N (%)	N(%)	
Metabolic syndrome "Rotterdam" criteria	12 (18.2)	10 (15.4)	0.816
Metabolic syndrome NCEP-ATPIII 2005	15 (22.7)	12 (18.5)	0.667
Type 2 diabetes mellitus	0 (0)	3 (4.6)	0.119
Hypertension	5 (7.6)	4 (6.2)	1.000
Coronary heart disease	0 (0)	1 (1.5)	0.496
Depression	8 (12.1)	9 (13.8)	0.800

Bariatric surgery	6 (9.1)	2 (3.1)	0.274
Smoking	8 (12.3)	8 (12.3)	1.0
Current use of metformin	5 (7.6)	8 (12.3)	0.397

Data presented as mean ± SD or n(%) as appropriate

Abbreviations: PCOS, polycystic ovary syndrome; BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; NCEP-ATPIII, National cholesterol education program adult treatment panel III.

Table 3 Socio-economic measures at 5-11 year follow-up

	Metformin N=66 N(%)	Placebo N=65 N(%)	p-value
Education			0.778
10 years primary school	3 (4.6)	1 (1.5)	
High school	17 (26.2)	18 (27.7)	
College <4 years	22 (33.8)	22 (33.8)	
College=/>4years	23 (35.4)	24 (36.9)	
Civil status			0.547
Married	35 (53.8)	42 (64.6)	
Co-habitant	21 (32.3)	17 (26.2)	
Single/divorced	6 (9.2)	5 (7.7)	
Other	3 (4.6)	1 (1.5)	
Parity			0.809
Parity 1	11 (16.7)	9 (13.8)	
Parity 2+	55 (83.3)	56 (86.2)	

Data presented as numbers with percentages in ()