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Pregnancy in PCOS Women and their History of Diabetes

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Abstract

Objective: Evaluation of the incidence of gestational diabetes in PCOS women treated with metformin before and during early pregnancy and to ascertain their family history of diabetes.

Design: Follow-up on all women with PCOS and infertility who received treatment with metformin prior to pregnancy (=index pregnancy) during 10 years. Data on diabetes was retrieved by questionnaire and hospital charts. Main outcome measures: Incidence of gestational diabetes, pregnancy outcome, and fetal size

Results: In 18 % of the women GDM was diagnosed at some stage. The clinical and obstetrical outcome of the women showed no association with family history of diabetes or GDM. No neonatal anthropometric feature was different with respect to family history of diabetes or GDM and no fetal malformations were found

Conclusion: GDM and family history of diabetes seem not to be associated with unfavourable pregnancy outcome in PCOS women.

Keywords: Metformin; Pregnancy; Pregnancy loss; Malformation; Polycystic ovarian syndrome

Abbreviations:

DHAS: Dihydroepiandrosterone sulphate; GDM: Gestational diabetes; PCOS: Polycystic ovary syndrome; SHBG: Sexual hormone binding globulin; FAI: Calculated free androgen index; IUI: Intrauterin insemination; IVF: *In-vitro* fertilization

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of fertile age with an estimated prevalence of up to 5-10%. Hyperandrogenism and insulin resistance are cornerstones of PCOS, even though not mandatory according to the consensus criteria [1]. Metformin improves metabolic, endocrine, and ovulatory parameters, probably improving fertility in women with PCOS. Pregnancy and PCOS are variably associated with higher risk of developing gestational diabetes (GDM), pregnancy-induced hypertension, preeclampsia, and preterm birth; however, the contribution of obesity to the prevalence of obstetrical morbidity is unresolved [2]. Several retrospective and non-randomized studies have reported beneficial effects of metformin on pregnancy complications, but this is not supported by a randomized, double-blinded controlled trial [3].

In this study we sought to evaluate the incidence of gestational diabetes, pregnancy outcome, and fetal size in women treated with metformin before and during early pregnancy and to ascertain their family history of diabetes.

Materials and Methods

We examined the records of all women with PCOS and infertility who received treatment with metformin prior to pregnancy (=index pregnancy). They were referred to the Department of Gynecology at Herning and Holstebro Hospital, Denmark, during from 1999 to 2010. We defined our PCOS inclusion criteria as presence of amenorrhea, oligomenorrhea or irregular menstruation with anovulation and concomitant elevated plasma-testosterone (>1.8 nmol/l). Oligomenorrhea was defined as cycle duration between 35 days and 6 months and amenorrhea as the absence of menstruation for more than 6 months. Exclusion criteria were type 1 and 2 diabetes mellitus. A total of 117 women fulfilled our criteria. The study was approved by the Danish Data Protection Agency (no. 2013-41-1998) and conducted in accordance with the Helsinki Declaration and the guidelines for Good Clinical Practice. Questionnaires do not need approval by the Danish Ethical Committee system according to its regulatory law.

Through our records we obtained information about age, BMI, former pregnancies, former infertility treatment, and menstrual cycle pattern as well as information about conception method and consumption of medicine, tobacco, and alcohol. Our records also included plasma levels of LH, FSH, testosterone, dihydroepiandrosterone sulphate (DHAS), sexual hormone binding globulin (SHBG), thyroid stimulating hormone, prolactin (measured in early follicular phase or at random in amenorrhic women), progesterone (measured one week before expected menstruation or at random in amenorrhic women), and a calculated free androgen index (FAI = testosterone/SHBG). A physical examination was performed at first visit including a gynecological examination and vaginal ultrasound.

We supplemented our data with a questionnaire mailed to the women; we ascertained hereby information about the first pregnancy

outcome associated with metformin use, neonatal weight and height, neonatal malformations, gestational age at birth, pregnancy complications like gestational diabetes and preeclampsia, smoking and alcohol use, medication taken during pregnancy, family history of diabetes, cardiovascular and endocrine disease, cholesterol and genetic disorders. These data in the responding women were supplemented and compared with the medical records of mother and infant. The non-responding women's data charts were scrutinized for relevant, historical obstetrical data and compared with the responders where appropriate.

The women received metformin treatment at standard dosage 850 mg twice a day. The fertility treatment consisted of first line clomiphene for six months followed by three months of intrauterine insemination (IUI). If no pregnancy was achieved the couple was referred to in-vitro fertilization (IVF) treatment. Heterologue insemination was discussed if oligospermia was found in two sperm samples. If sterility (tubal occlusion or azoospermia) was present further treatment was at the IVF clinic. If the couple had no child they were eligible for free IVF treatment. The women were told to continue with metformin treatment for no longer than the 7th gestational week where the first ultrasound could verify a viable fetus.

For statistical calculations of proportions the χ^2-test with Yates' correction for discontinuity was applied. If the expected number was less than five, Fisher's Exact test was used. For continuous variables Student's t-test, Mann-Whitney's U–test, and Wilcoxon's Signed Rank test was used when appropriate. ANOVA was performed between group variables. Post-hoc test with Newman-Keul's test was performed between group pairs. The level of significance was 0.05. IBM SPSS Statistics 20 was used as the statistical software.

Results

A total of 117 PCOS women with pregnancies and periconceptional metformin were included in the study and questionnaires were mailed to them; hereof 76 (65 %) responded. The initial blood sample was drawn on day 3 or 4 in cycle; if she had oligo-/amenorrhea testing was performed on the same day (Table 1).

	The 76 included women		In 41 non-responding women	
	Before metformin treatment	**3-6 months after treatment (n=59)**	**Before metformin treatment**	**3-6 months after treatment (n=27)**
Age at treatment (yrs)	29 ± 4		29 ± 4	
Weight kg	88 ± 21 (59,139)		83 ± 26 (47,150)	
BMI kg/m^2	31 ± 7 (18,47)		29 ± 8 (17,51)	
Testosterone (nmol/l)	2.93 ± 1.0 (1.91, 6.74) §	1.74 ± 0.7 (0.52,3.74) **	2.60 ± 0.5 (1.81,4.32)	1.63 ± 0.6 (0.57,3.32)
Testosterone > 2.4 (no.(%))	47 (62)	7 (12) **	25 (61)	0 **
DHAS(nmol/l)	5934 ± 3084 (837,15000)	4921 ± 2357 (1680,11000)	5256 ± 2151 (1956,12131)	5251 ± 2040 (2290,9828) **
SHBG(nmol/l)	44 ± 25 (9,132)	49 ± 27 (13,137) *	45 ± 27 (18,134)	56 ± 46 (16,229) **
FAI (%)	9.0 ± 6.3 (2.2,26.9)	4.7 ± 3.2 (0.9,17.0)**	7.4 ± 4.3 (1.6,24)	5.0 ± 4.1 (1.1,21) **
FAI above 97.5 percentile (FAI=7%) (no. (%))	35 (46)	9 (16) **	18 (44)	4 (15) **
FSH(IE/l)	5.6 ± 6.4 (0.4,55.9)	4.7 ± 1.8 (0.8,8.6)	4.7 ± 1.8 (1.2,8)	4.9 ± 1.8 (1.2,8.9)
LH (IE/l)	12.4 ± 7.3 (1.0,44.0)	9.3 ± 5.7 (1.6,29.6) **	11.3 ± 6.1 (1.2,27.9)	9.1 ± 6.2 (1.3,24.3)
HbA1c (%)	5.4 ± 0.3 (4.8,5.9)	5.4 ± 0.3 (5,6.3)	5.2 ± 0.5 (4.4,6.6)	5.2 ± 0.6 (4,6)
Fasting blood glucose (mmol/l)	5.2 ± 0.6 (4.0,6.1) §§	5.2 ± 0.5 (4.4,6.6)	4.6 ± 0.6 (4,5.5)	5.0 ± 0.7 (4,6)

Table 1: Paraclinical data before and after metformin treatment in 117 women (mean ± SD (range)).

We found after 3-6 months of treatment a significant drop in LH, total testosterone levels and more so in its relative level of bioavailability, the free androgen index, FAI. The non-responding women showed similar trends. The paraclinical values were similarly available in the non-responding women and differed only slightly (Table 1). The results showed no difference in any of the paraclinical results in repect to GDM or diabetes in the family history. Fifty-three of the 117 women had a BMI ≥ 30 kg/m^2 at first visit. In all, 86 (74 %) had a clinical check-up 3- 6 months after the initial visit.

Before vs. after treatment: *: p<0.05, **: p<0.01. Paired, non-parametric and t-test when appropriate, Difference between included and non-responding women: § p<0.05, §§. p<0.01

The follow-up by questionnaire in the 76 responding women was performed 5 ± 2 years after the first visit at which time the women's weight and BMI had significantly decreased (88 ± 21 to 85 ± 20 kg and 31 ± 7 to 30 ± 7 kg/m^2, p<0.02, paired, non-parametric test). Twenty-three percent had managed to decrease their BMI<30 kg/m^2.

Pregnancies

At first visit, 47 women were nulligravidae and 29 women had 50 various previous pregnancy outcomes. These historic pregnancies consisted of 26 live births, 17 spontaneous abortion, 6 induced abortions, and one extrauterine pregnancy. Further, in the index pregnancy the women were treated with metformin only, ovarian stimulation, IUI, and IVF in 22, 38, 8, and 8 of the cases, respectively. This resulted in 66 live deliveries (eight twins and 58 singletons), nine abortions and one legal abortion. The clinical results of the singleton pregnancies are shown in Table 2.

	GDM in history	No GDM in history	All	No GDM or family history of DM	Family history of DM/GDM
No.	14	62	76§	34	42
Nulligravidae	8	39	47	23	24
Metformin only	2	20	22	10	12
Ovulation induction	8	30	38	18	20
IUI	2	6	8	4	4
IVF	2	6	8	2	6
Preeclampsia	2	2	4	2	2
Family history of diabetes	8	28	42	0	42
Spontaneous abortions previously/in index pregnancy	3/2	8/7	11/9	4/3	7/6
Twins	0	8	8	6	2
Hypothyroidism pregravid	-	2	2	-	2
Hypertension at follow up	1	3	4	3	1
Singleton birth weight (n=58) (g)#	3658 ± 478	3569 ± 612	3571 ± 592	3714 ± 655	3488 ± 517
Singleton length (cm)#	52 ± 2	52 ± 2	52 ± 2.3	53 ± 3*	52 ± 2
Singleton ponderal index (g/dm3)#	27 ± 4	25 ± 3	25.2 ± 2.8	25 ± 2	25 ± 3
GDM in history	14	-	14	8	6

Table 2: The clinical data by history of GDM in 76 responding of PCOS women, § one woman had a legal, induced abortion, #: Excluding eight twins, nine abortions, and one extra-uterine pregnancy, *: p<0.03 Mann-Whitney U-test: PCOS women with DM history vs. no DM or GDM in history

In 11 of 66 deliveries GDM was diagnosed in the responding group of PCOS women and further two of 29 deliveries in the non-responding group. Three of the women who had abortions had gestational diabetes in either the previous or subsequent pregnancy; thus, at follow-up 14 % of the study group had had GDM at some stage. The clinical and obstetrical outcome of the women showed no association with family history of diabetes or GDM (Tables 2 and 3). Five women had preeclampsia; one of these women had prepregnancy hypertension. Two women had concomitantly hypothyroidism and one woman hypertension; both conditions were diagnosed and treated before pregnancy. No neonatal anthropometric feature was different with respect to family history of diabetes or GDM and no fetal malformations were found; neither in hospital charts nor in the questionnaire.

	Spontaneous abortion	Singleton delivery	Twin deliveries	Induced abortion	Extra-uterine pregnancy
No.	20	85	10**	1	1
Nulligravidae	8	50	6	0	1
Metformin only	11	27	0		0
Ovulation induction	4	36	7	1	1
IUI	4	12	3		0
IVF	1	10	0		0

Preeclampsia	-	3	1		
Family history of diabetes	6	28	2	0	0
GDM*	2	11	0	1	0
Hypothyroidism pregravid	-	2			
Hypertension at follow up	2	1	1		

Table 3: Fertility treatment and maternal morbidity by pregnancy outcome in all 117 women, *: 2 women with spontaneous abortions had subsequently a pregnancy with gestational diabetes; the woman with induced abortion had previously had gestational diabetes, **: one triplet pregnancy

Discussion

We find no association of clinical outcome with history of diabetes and GDM despite the pregravid improvement of androgen status by metformin treatment. In this study metformin is only administered preconceptional and during early pregnancy. In contrast, Glueck et el. found decreased early pregnancy loss and gestational weight gain, less GDM and decreased androgen indices in pregnancy with a study design of prospective intervention and retrospective pregnancy loss data [4,5].

A Cochrane review on this subject concludes that concomitant metformin treatment improves clinical pregnancy rates when given in the time before and the immediate beginning of pregnancy with and without fertility treatment [6]. The credit for beneficial effect is given to the improvement of insulin sensitivity markers, which is expressed in general lower blood glucose, LH, and testosterone and an increase of SHBG [7-10]. Our women improve in similar insulin resistance markers.

The obvious bias of our study is that women are treated with different ovarian stimulation regimens, which will improve success rates given that each of the regimens increases the pregnancy rate. On the other hand, if insulin resistance affects pregnancy outcome in PCOS negatively, the dose of metformin would be decisive and not the ovarian stimulation. This was indicated by Khattab et al. who discontinued metformin after conception in a control group of PCOS women [11]. The PCOS women who continued with metformin throughout reduced their incidence of GDM to an OR of 0.17 compared to the control group. Similar the women are highly motivated and may seek a healthier lifestyle, which could include un-reported smoking cessation, diet, and weight reduction, all of which also improves insulin resistance.

Metformin intake throughout pregnancy has no androgen lowering effect and, if hyperandrogenism increase risk of GDM, metformin will not likely decrease the risk by this mechanism [2,3]. The reported incidence of GDM is variable in PCOS and potential prophylaxis with metformin is, thus, questionable. Glintborg et al. show no effect of metformin in increased inflammatory markers associated with diabetes and metabolic syndrome in PCOS women [12]. Although we screened for hyperglycemia in the pre-pregnancy period we found higher rate of GDM than in the background population. This may be due to the biochemical inclusion criteria together with other potential bias like obesity, age, and diabetes family history. If diabetogenic factors were involved in the etiology of miscarriages and pregnancy outcome of PCOS women, we find the family history or the likeliness of GDM itself seem not to herald increased risk. Thus, the glucose and HbA1c values at first visit were similar with respect to subsequent GDM and diabetes history. Randomized studies of treatment effects of metformin in early pregnancy showed that obese PCOS have more benefit of treatment; this is suggestive for environmental factors' causative effect, i.e. body weight as well as the pregnancy's insulin resistant milieu [10].

To be included in our study group only the first two of the consensus criteria had to be fulfilled, namely oligo- and or an ovulation and clinical and/or biochemical signs of hyperandrogenism, excluding women diagnosed due to polycystic ovaries only [1]. Thus, our inclusion criteria were stricter and perhaps only included the most severe case of PCOS. Similarly, women with ovaries of polycystic morphology (PCO), without any other features of PCOS, show no effect of metformin treatment in a randomized study [13]. We, therefore, recommend the careful selection of study population, as it should limit some of the clinical heterogeneity of PCOS regarding disease phenotype like the ultrasound appearance of ovaries, obesity, hyperandrogenemia, and glycemia.

The varying association of PCOS with GDM depends on the population studied due to genetic factors where the metabolic syndrome in parents and their siblings seems to be fundamental to the pathogenesis of PCOS [14,15]. Franks et al. conclude that PCOS is inherited on an oligogenic basis and the co-morbidity and phenotype are due to the interaction of a small number of key genes with environmental and nutritional factors [16].

Selection bias of those who participated in the questionnaire part of the study is not likely as the non-responding women had comparable BMI, testosterone, and HbA1c as to the responding women. Nearly half of women (45%) in our study are obese and 47 % had a family history of diabetes mellitus. Further, our incidence of GDM in 14 % of the women seems reasonable compared with other studies in similar populations [2,3,15].

We have no reason to believe that the women were disfavored by commencing on metformin. On the contrary, we even find that the women lost weight since the initial visit five years previously which suggests that the women are motivated and have focus on the weight issue after pregnancy. Whether metformin has any long-term effect on diabetes prevention, weight reduction, and hyperandrogenism in PCOS remains unsolved.

To date only sparse data are available regarding the effect of metformin on a large scale when administered throughout the pregnancy [17]. Vanky et al. show in their randomized study that metformin administered from third month and throughout pregnancy

is not associated with any improved outcome in terms of neonatal and maternal complications, i.e. GDM; preeclampsia, preterm delivery [3].

In conclusion, GDM and family history of diabetes is not associated with unfavorable pregnancy outcome in PCOS women.

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